THE ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

IN-PERSON/WEBINAR

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Welcome and Roll Call

DR. CALONGE: If everyone could try to find their seat, we will get started. I'd like to welcome you all to the second meeting on the Advisory Meeting on Heritable disorders in Newborns and Children in 2023.

OPERATOR: Recording in progress.

DR. CALONGE: This is our first in-person meeting this year and it really is great to see so many folks in the room and I forgot my slide.

As we gather in person at 5600 Fishers Lane, I would like to open the meeting by acknowledging that the land and water on which we are meeting is taking--where our meeting is taking place was and still is inhabited and cared for by the Susquehanna Tribe and Piscataway Tribe peoples—the Piscataway peoples including the Piscataway-Conoy Tribe and the Choptico band of the Piscataway Indian Nation.

We are grateful for their past and continued stewardship of this land, and we pay our respects to Maryland's indigenous community and their elders, both past and present as well as future generations.

I'm also excited to welcome a new member who is joining us virtually today and we look forward to when she can join us in person. Dr. Christine

Dorley is the Assistant Director of the Newborn Screening Laboratory for the Tennessee Department of Health Division of Laboratory Services. She has been with the laboratory for 28 years, serving in different capacities. Dr. Dorley has been instrumental in migrating the NBS laboratory to a 7-day work week, with a significant decrease in turnaround time.

Under her leadership, the laboratory has been an early adopter of screening for disorders under the Recommended Uniform Screening Panel. She is a member of the Association of Public Health Laboratories, serving on several Committees including new steps in hemoglobinopathies laboratory workgroup.

She received the APHL Everyday lifesaver award in 2021. She is also a contributing faculty member at Waldon University, teaching masters and doctorate level students courses on epidemiology and public health. We welcome her and can't wait for her to be sitting at the table with us.

I also want to acknowledge and welcome a new Organizational Representative, but I want to start by thanking Dr. Gerald Barry for serving on the Org Rep for this Society for Inherited Metabolic Disorders and welcome Dr. Sue Berry as the new Organizational Rep for SIMD. She will be joining us in person tomorrow and virtual today. She is a Professor of Pediatrics at the University of

Minnesota and a member of the Division of Genetics and Metabolism.

She is a Fellow of the American Academy of Pediatrics and a Founding Fellow of the American College of American Genetics and Genomics. She is a current President of the SIMD and a member of the Steering Committee for the newborn screening translation research network. She is a member of the Board of Directors for the National Organization for rare disease and for the National PKU Alliance and is currently PI of their PKU patient registry. She has been a longstanding liaison to the Newborn Screening and Genetics and Public Health Committee for the Association of Public Health Laboratories and was honored to receive the clinician champion award in newborn screening from that organization at their 2022 annual symposium.

She has a particular interest in providing management for persons with inborn errors in metabolism and has a longstanding interest in improvement in their care through early diagnosis and treatment and so we welcome her and glad you are joining us virtually today and Susan I look forward to seeing you in person tomorrow. With that, I'm going to turn things over to Leticia for the rollcall.

MS. MANNING: Good morning everyone. So, I'm going to start off with the roll-call. From the

Agency for Healthcare Research and Quality, Kamila Mistry, I believe she's virtual.

DR. MISTRY: Yes, I'm here. Thank you.

MS. MANNING: Kyle Brothers?

DR. BROTHERS: Here.

MS. MANNING: Michele Caggana?

DR. CAGGANA: Here.

MS. MANNING: Ned Calonge?

DR. CALONGE: Here.

MS. MANNING: Carla Cuthbert?

DR. CUTHBERT: I'm here.

MS. MANNING: Jannine Cody?

DR. CODY: I'm here.

MS. MANNING: Jane DeLuca?

DR. DELUCA: Here.

MS. MANNING: Christine Dorley, I believe she's virtual.

DR. DORLEY: Here.

MS. MANNING: From the Food and Drug administration, Kellie Kelm?

DR. KELM: HERE

MS. MANNING: From the Health Resources and Services administration, Michael Warren?

DR. WARREN: Here

MS. MANNING: Jennifer Kwon?

DR. KWON: Here.

MS. MANNING: Ashutosh Lal?

DR. LAL: Here.

MS. MANNING: Shawn McCandless?

DR. MCCANDLESS: Here.

MS. MANNING: From the National Institution of Health, Melissa Parisi?

DR. PARISI: Here.

MS. MANNING: Chanika Phornphutkul? I think she's not here.

And for our organizational representatives. From the American Academy of Physicians, Robert Ostrander? I believe he's virtual.

Dr. OSTRANDER: Here.

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

DR. FREEDENBERG: Here.

MS. MANNING: From the American College of Medical Genetics, Marc Williams. He's notified me he will be attending later this morning. From the American College of Obstetricians and Gynecologists, Stephen Ralston.

(No Response.)

From the Association of Maternal andChild Health Programs, Karin Downs?

MS. DOWNS: Here.

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

DR. TANKSLEY: Here.

MS. MANNING: From the Association of State and Territorial Health Officials, Scott Shone.

DR. SHONE: Here.

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

(No response.)

From the Child Neurology Society, Margie Ream.

DR. REAM: Here.

MS. MANNING: From the Department of Defense, Jacob Hogue.

DR. HOGUE: Here.

MS. MANNING: From the Genetic Alliance, Natasha Bonhomme.

MS. BONHOMME: Here.

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

DR. DOLAN: Here.

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

MS. VOCKLEY: I'm here.

MS. MANNING: And for the Society of Inherited Metabolic Disorders, Sue Berry. All right. Thank you for bearing with me through rollcall.

Okay, I just want to go over, just as a reminder for folks around Ethics and Conflicts of Interest. Please remember we are Advisory to the Secretary of HHS and if you receive inquiries about-- you may receive inquiries about the Committee and so

you have to consider when to recuse yourself and in all matters likely to affect the financial interest of any organization with which you serve as an officer, a director, trustee, or general partner, unless you are also an employee of the organization, or unless you have received a waiver from HHS authorizing them to participate.

So that's just a reminder for folks. Okay. In regards to meeting participation, all Committee meetings are public and open to the public, meetings and agenda and topics are announced in the Federal Register so that the public has the opportunity to participate in meeting discussions. If the public wishes to participate, they can do so by following the instructions within the Federal Register. Only with advanced approval of the Chair or DFO may public participants question Committee members or other presenters. Public participants may submit written statements. Also, public participants should be advised that Committee members are given copies of all written statements submitted by the public.

As a reminder, it is stated in the FRN as well as the registration website that all written public comments are part of the Official Meeting Record and are shared with Committee members. Any further public participation will be solely at the discretion of the chair and the DFO, the Designated Federal Official.

So now I'm going to do, you know, kind of the visitor's talk for those of you that are physically here in the building at 5600 Fishers Lane. Please note that you only have access to this room, the pavilion area outside of this room, the restrooms and if there's any meeting rooms which we won't be using today, okay.

So, don't try to go up the elevators or wander around the building. You are permitted to stay within this vicinity. If you need to leave, outside of the building, outside--you will be required to go through security screening again and you'll require a HRSA escort. We do have HRSA staff that are here to help you. They have the escort badge that they're wearing but please allow for time to get back into the building because it may take now up to 15 minutes to go through security and come back in within the building.

Okay, visitors are not allowed to take any video or photography in the building. In case of an emergency please exit through the front door from which you came in. Cross the street and there's a parking lot and there will be an area where we will be meeting to make sure, you know, everyone is safely out of the building. Please do not take any nonessential items with you if there is an evacuation, as it could delay your reentry into the building. But you will need to take that ID so you can get back in, so remember that.

Okay and this is just a map of the building.

There's that parking lot and you'll just cross over to the parking lot but you'll see all of us. We'll all be going in the same place.

So, this slide maybe should have been presented earlier but I can see that you all figured out how to work the mics so very good. Remember when you're speaking, turn it on and speak at the nearest microphone on the table. I believe everyone has their tent cards. And we do have folks participating in virtually and so we will be looking for raised hands during Committee discussion and we'll call on you during that time. A reminder for those folks that are participating virtually, the audio will come through your computer speakers. There's no call in option, unless it was sent via the email. If you are unable to access the audio or microphone through your computer, a conference line has been sent to you through your email.

Please speak clearly. Remember to state your name to ensure proper recording for the Committee transcript and minutes. Please remember to use the "raise your hand" feature when wanting to make comments for questions. If you're having technical difficulties, please reopen the webinar using a different browser and we also have wonderful folks that are handling, I say that the special hands behind the screen and so if you are having technical issues, please feel free to reach out to them via the

email that was sent to you.

Okay, this is just a reminder, all right. I do want to take a moment to remind folks of future meetings. They are posted on the website. Our next meeting is scheduled for August 10th through the 11th. It will be virtual for all participants. In November, November 2nd-3rd it will be in-person with telecast options so similar to what we are doing today. And then in February of 2024, I know you guys are like "2024!" February 8th-9th it will be virtual, and you can find that on our Committee website. And now, I'm going to turn it back over to Ned.

DR. CALONGE: Thanks, Leticia. I'm going to go through Committee business quickly and give you a preview of today's meeting. Just to remind you, in February's meeting the Committee voted on whether to recommend to the Secretary to include Krabbe disease on the RUSP. I wanted to acknowledge this was a difficult vote and ultimately the Committee did not recommend including Krabbe on the RUSP at this time. I've had the opportunity to meet with the Krabbe disease nominators to discuss the items in the Chair letter. The Chair letter is available in your packet and briefing book and in the ACHDNC website. Also, at our last meeting the Committee voted whether to move DMD to full evidence review and did not recommend that full evidence review at this time.

I also had the opportunity to meet with the

DMD nominators to discuss the items identified in the chair letter. The additions to the Muscular Dystrophy Chair Letter can be found in your briefing book and on our website. In each of the Chair Letters to our nominators and on our calls, information was provided on the process to resubmit nominations and what is needed to inform future votes. The Krabbe disease nominators or the DMD nominators choose to resubmit the Committee's evidence review group with a nomination prior authorization workgroup will be reconvened to review the new evidence and tomorrow we will talk a little bit about what an expedited review process might look like when a number of items in the requests looks like they could be completed within a

As far as the minutes for the meeting, I want to thank the Committee members and organizational reps for reviewing the February 2023 minutes. We've made--we've had some Committee members provide some comments which we are working to include in the minutes, and we will review those and vote on them tomorrow. So, I wanted to announce a National Academy of Science, Engineering, and Medicine Meeting.

On June 7th there will be a meeting workshop on next generation screening, The Promise and Perils of DNA Sequencing of Newborns at Birth. This will be a hybrid workshop that will examine the utilization of DNA sequencing as a supplement to newborn screening for treatable but not clinically evidence

conditions in the newborn phase. The overarching goals of the workshop are to explore the current use of newborn DNA sequencing as well as the known expected benefits, potential harms, ethical and data security and ownership issues and equity and access to screening. The workshop is open to the public. Registration is required and in your briefing book is a link to the workshop registration.

To look at today, this morning we're going to look at some broad newborn screening topics, including research and policy implications that can improve our work. We're going to talk about newborn screening and intervention and research on benefits and harms from uncertain results. And after lunch we'll focus on a federal agency collaboration to improve newborn screening data integration including a discussion of the sickle cell data collection program, a talk on implementing the blueprint and implications on newborn screening and then CDC's Ed3N Project, Enhancing Data-Driven Disease Detection in Newborns Project. And we'll end the day with public comments which we think will be a great segue to tomorrow's discussions.

Tomorrow our goal will be to address a variety of Committee policies and procedures that have arisen in the last year or so, including an update from the Prioritization and Capacity workgroup. We're going to revisit and discuss our

changes to the ACHDNC Decision Matrix. We're going to talk about ad hoc topic group ideas as this is where we're moving from standing workgroups to more task-oriented workgroups and discuss where we want to put our efforts that could include, or should include conflict of interest, work, and then topics that were identified by the Committee at previous areas and then we will finish with new business.

Newborn Screening and Early Intervention

So, we're going to start our day learning about newborn screening and early intervention and we're pleased that Dr. Don Bailey, a former Committee member and Dr. Elizabeth Reynolds, both of whom are from RTI International, are going to describe how early intervention and newborn screening have similar goals and the benefits of integration and coordination of the two systems.

Dr. Bailey is a distinguished fellow at RTI International where he is a member of RTI's Genomics Translational Research Center. Prior to joining RTI in 2006, he was on faculty at the University of North Carolina in Chapel Hill. From 2011 to 2017, he served as a voting member on the ACHDNC. He has a significant record of publications on a variety of topics related to disability, early identification, early intervention, newborn screening, and family support and currently his work focuses on the future

of newborn screening, having published several papers recently on how newborn screening can prepare for a future of transformative treatments and genome sequencing.

He and his team have developed a partnership with the North Carolina State Laboratory of Public Health and their signature initiative is Early Check, a statewide research project to help prepare newborn screening for new conditions and new technologies with a current focus on whole genome sequencing.

Then Dr. Elizabeth Reynolds is a research public health analyst in the Genomics and Translation Research Center at RTI where her interests include rare diseases, patient registries and early developmental outcomes. She leads a project examining linkages between early intervention and newborn screening and contributes to projects related to rare disease databases, electronic health record integration and longitudinal follow up.

She is also the founder of the CHAMP Foundation. This is a patient advocacy group focusing on supporting research to find treatment and care for single, large-scale mitochondrial DNA deletion syndromes, such as Pearson Syndrome. She received her PhD in Applied Developmental Science from the University of North Carolina at Chapel Hill and I will turn things over to Dr. Bailey and Dr. Reynolds.

DR. BAILEY: Okay, thank you so much, Ned and

it's really great to see everybody here again. It was a pleasure and honor serving on the advisory Committee a number of years ago and that was some of the highlights of my career. I very much appreciate the work that this Committee is doing and all the advocates who are supporting and challenging the Committee. It's really great work.

So we're going to be talking about a topic here related to early intervention and newborn screening and we don't, we're not used to calling each other Dr. Reynolds and Dr. Bailey. So we may say Elizabeth and Don but I think that will work okay.

So our goals are to, first of all we're going to provide a brief overview of what early intervention in the United States is all about. So we're going to use early intervention in two ways. There's a lower case early intervention which refers to you know, anything that you're doing in an organized kind of way to help support early development of children. And I'm going to use a capitalized Early Intervention to refer specifically to what's called a "Part C" program which is a component of Individuals with Disabilities Education Act and I'll describe some more about that program in a minute. We’re going to present findings from a study that we've partially completed now because there are several components of it and here to determine which current newborn screening conditions

should be eligible for Early Intervention and in what states. And then we're going to suggest some next steps for you know, how this might be relevant both to newborn screening, to early intervention programs and actually to this Committee.

So this work was all funded by the John Merck Fund. The John Merck Fund is a private family, a small family foundation that has really been very supportive of our work over the years. Woops, whoa, hello. Any questions?

Let's see. How are we getting back here. Somebody else will do it for us, okay.

Okay, great. Is this the next slide? So we have a good project team, so Elizabeth and I collaborated with this group in doing this project and so I just want to make the point that three of us have a background in either early childhood special education or applied developmental sciences so we're really focused on early development of young children and how that development can be impacted by a variety of different factors.

And then we have two physicians on the team as well, Pranesh Chakraborty who's from Canada and very much an integral part of the Newborn Screening Program there, Elizabeth Jalazo who is a professor and UNC Chapel Hill and is a pediatric geneticist and so we had both perspectives here as we were working on this project.

All right, maybe I need to do something else here. All right, so I'm going to couch this discussion and we're going to couch it in the context of net benefit because that's really something that the Committee talks about a lot and I just want to make a point that net benefit is really thought about in a lot of different ways. It's not in just this Committee. You can look at the FDA has a net benefit. You can look at Social Security and figure out what your net benefit is--benefits are. You can look at financial decisions and so forth. So net benefit is a broad construct that usually brings in a variety of different factors. Some of them are very specific like Social Security benefit is a formula, we know exactly what that is and how to get to it.

Other kinds of net benefit are much more complicated and that's certainly the nature of this Committee's work. So I can go back and look at the matrix and where I've highlighted net benefits throughout the just, in every category of discussion here and it's up to you to decide. There’s no formula for you, right, to determine net benefit. So each of you, in your own minds need to think about well okay, what is the net benefit. Weighing the pros and cons and the data that Alex and his group had brought in. What’s the net benefit of the screening? And you can make an individual decision about that and then you collectively have to make a decision, a Committee

decision about how that is.

So I've actually, we've been thinking about early intervention as a potential newborn screening benefit for a long time. In 2005, 18 years ago I published a paper called "Newborn Screening for Developmental Disabilities, Reframing Presumptive Benefit" and I've talked about a variety of different things, beyond just a dietary medical treatment for children.

Just to back up a minute and give a little bit of personal history, so when I first started studying Fragile X Syndrome, found out from my interviews with parents about how long it took them to get a diagnosis, I very naively said "well, we can fix that through newborn screening.” I really didn't know the newborn screening system at all. I really didn't know what the criteria were for including and so people would tell me “Well there's no treatment". And as an early childhood special educator I'd say "well of course we have a treatment. We have early intervention programs.” And I was always told well, do you have evidence, specific evidence that early intervention makes a difference in the lives of children with Fragile X Syndrome, and would it make a difference if you identified them earlier and providing that kind of service.

So that's why I wrote this particular paper but in the meantime I've kind of immersed myself in

the newborn screening world and we've thought about it in every frame, I'm thinking, a good bit here but we're coming back to it now.

So what I earlier mentioned--is important we can think about it from a broad perspective. You know, this is an older publication but from the National Institute of Medicine on "From Neurons to Neighborhood" and this was a big argument. Melissa, I see you're nodding your head on this. This was a very well-known document that came out that really made the pitch going from brain development to actually functional early childhood development, a variety of things impact early development but it made the point here that the first three years maybe not be a critical period in the biological stance, but they are especially formative in that time. They are foundational time in human development.

And of course during this time parents provide essential care and support for their children and advocate for their children but there are also formal and more informal programs that can support families and children by providing access to specialized interventions and therapies. And so early intervention and provide an additive benefit to medical or dietary treatments. And so I'll just give this one--this is an old study, but it makes a point I think.

So this is a study of stunting and what you

can help to prevent stunting in children. And so there was one treatment that was a dietary supplement as you could imagine would be necessary there. As a second treatment there is an early childhood stimulation program but without the dietary supplement and our third group got both.

And you can see that an additive effect of the stimulation program to nutritional program. And that's the point we're trying to make here is that early intervention without the supplemental diet didn't make much difference, it wasn't different. But combined of those two things it did make a big difference.

So a couple years ago I wrote a paper called "Early Intervention in Newborn Screening Parallel Roads or Diversion Highways" and I was trying to decide, you know, how are these two programs different and alike. So they all start with the basic--they both have the same basic assumption. That is if you identify children early and you provide services for them they're going to be better off than if you wait. It's kind of a simple colloquial way of saying it.

They both are longstanding. They are both state-based programs with guidance--you know, guidance from the Federal Government. Both have well-established ways to identify children and provide services otherwise fundamentally different,

differences in of course, as you can imagine, approaches and services and so forth. And from what we've been able to garner now from interviews that we're doing which we will report on another time, two programs operate in virtual independent spheres and so one of our questions is well would there be some benefit, some synergy in some collaboration among these two programs.

So for those of you who aren't familiar with the early intervention in the United States, there's Federal legislation that provides guidance to statewide, voluntary statewide programs called Part C and a program as part of the Individuals with Disabilities Education Act, there's a voluntary program that every state now has bought into it.

So the Federal Legislation provides guidance to states and a lot of money to states if you provide parts of these services. So based on a per capita basis. To get into services, you have to have a doc-- and I will go into more detail about this in a minute. You must have a documented developmental delay or an established condition likely to lead to a delay.

Over 400,000 babies are currently enrolled in this, what's called a birth to 3 year early intervention program. The services are determined by what they call an individualized family service plan, so this is a set of goals and objectives that drive

what's happening in early intervention programs. This is intentionally called an Individualized Family Service plan because it realizes--it recognizes that children, especially very young children, they all live in the context of their families. And family context is critical to early childhood development so it's not only about supporting children and providing things like occupational therapy or physical therapy that are now family support as well. So but--only about a third of the children in early intervention programs enter before age-- before 12 months of age.

So because most of them enter because of this criteria for having an established condition. I'm not going to go through this slide, this is in the paper--the first paper that we published but it shows that these two programs differ both in history and entering eligibility characteristics models outcomes family components and so forth.

The eligibility categories for early intervention is just as important for the rest of our discussion and I'll just focus on these first two. You can get under early intervention primarily in two ways. You have a developmental delay. It's actually documented through a test. You're behind development in some--in some way. But the Federal Government doesn't tell you what the definition is for developmental delay so every state has its own criteria.

So here's some examples of states, in one state we'd have two standard deviations below the mean in one area of development. Another state has one and a half standard deviations below the mean in two or more areas of the illness. So there's not great consistency across states in developmental delay but they are required to come up with a specific definition. Most disorders that we're-- you're discussing in newborn screening and also the ones that would offer to start early intervention at birth, they don't have a developmental delay.

So you either have to wait until they prove they are having a problem or that someone recognizes it and does some developmental assessments. So the legislation added a second category called established conditions. So this would be a disorder that a child doesn't test. They're hard to test a week-old baby anyway in terms of developmental delay. But you don't have a documented developmental delay, but you have a condition that's likely to lead to developmental delay.

And so the legislation describes some broad categories like chromosomal abnormalities or genetic conditions, hearing or vision impairment, fetal alcohol syndrome. Those would be examples that were there but also, we'll make the point that every state is to decide what their established condition list is. So some of them have very specific categories,

they name exactly the disorder that are on there. Some might have a broader category like a chromosomal disorder. Some of them will have even broader categories and some may not have any at all and they leave it up to local providers to help make that, make that determination.

So from our perspective, we think we all collectively should be interested in the intersections between newborn screening and early intervention because we believe, or at least we did before we started this study and now, we firmly believe that many children identified through newborn screening could benefit from early intervention but the path from getting to newborn screening to early intervention is really not clear. And that's the point of the second study that we're doing that we won't be able to report on today, but typically newborn screening labs don't see that as their job to refer children directly to early intervention programs, it's often the pediatrician that does that.

So the linkages, how we make those linkages happen could be interesting. So parents obviously are caught in the middle, they may feel like their children need early intervention services but the medical system doesn't always link them to those services and early intervention doesn't always link them to medical programs. So we think that integration and coordination of those services could

enable faster entry into early intervention assure families of the system's level support. But we didn't know that for sure and so this series of projects that we're engaging in have tried to add some information about that.

So I'm going to turn it over to Elizabeth. She's the one who really ran the project, did all of the core work to make it happen and so she's going to describe what we actually did and then I'll come back at the end and get some wrap-up comments. So handing over the baton to you.

DR. REYNOLDS: All right. Thank you very much. Okay so even after children with newborn screening conditions are diagnosed and receive appropriate medical clear, many children can still experience developmental delays, but the rates—we don't know necessarily, even the frequency and processes by which these children are then enrolled into early intervention. And the exception here is hearing loss. So if a child is identified with hearing loss during newborn screening, the National Early Hearing Detection and Intervention Program facilitates the link between newborn screening, diagnostic evaluation, early intervention referral, and enrollment into early intervention. But conversely this is not known whether this is true for the other conditions and whether there is a national program, policy or guideline to streamline the refer--the

identification, referral or eligibility for the other dried blot-spot conditions.

Our team at RTI conducted a series of projects to examine these two programs that share a common goal and we set out to examine these—the linkages with four projects. In the first project, our team examined each condition to determine the extent it was included on the state's early intervention established conditions list which auto-qualified children for early intervention.

Next, we examined whether a condition should be on a state's automatically eligible established conditions list because they put children at a high probability of resulting and developmental delay. Our second project is a survey study of state early intervention coordinators and newborn screening coordinators and the third project was--is a caregiver study that's ongoing and the 4th project aims to develop a template of benefit to assess whether early intervention could be considered as part of the net benefit equation.

So as part of the first project, we wanted to know which one of the newborn screening conditions are on state's established conditions list. And early intervention--and we explored each state's list and specifically counted the number of RUSP conditions that are included. This table shows the results or the number of times each RUSP condition was included

on state's established conditions list. And you can see that spinal muscular atrophy was included the most frequently on 29 states' lists and MPS and Maple Syrup Urine Disease were the next frequently included conditions and were included on 25 states' lists. Holocarboxylase Synthetase Deficiency and SCID were included the least frequently and were included on only two states' lists and the states that included these conditions were Michigan and North Dakota and these were the only two states that explicitly said all children that were diagnosed with a newborn screening disorder were automatically eligible for early intervention.

So here's a map that shows how many newborn screening conditions are included on states' established conditions lists and at the time of analyses most states did have established conditions lists but you can see that there are some states that did not necessarily include any newborn screening disorder. Thirteen states have between 1-5 conditions, nine states have between 6-10 conditions, another nine have between 11 and 15 conditions and six states have 16 or more. Georgia had 23. Virginia and Maine had 29 and Michigan and North Dakota again listed all 34 RUSP dried-blood spot conditions that we were examining.

So after we had conducted which conditions were on states' established conditions lists, we

wanted to know which conditions should be on states' lists because they have a high probability of resulting in developmental delay. But we recognized pretty early on that there were significant challenges for defining and rating conditions on probability of resulting and developmental delay. First these conditions vary considerably and for some the delays may be related to the underlying pathology of the disease, even after treatment but for others it's the medical complexity of the condition or the intervention that puts children at a higher probability of delay. And for some conditions there was a risk for episodic decompensation.

Second, the clinical severity of all of these newborn screening conditions fall on a spectrum, severity may be related to disease genotype, responsiveness to treatment or unknown factors. Individual outcomes can be related to early detection, access to medical care, timely treatment and treatment compliance.

Third, we realize that the natural history and the treatment alter natural history and developmental trajectories of many of these newborn screening conditions is very limited and studies frequently included very few children and did not necessarily include standardized developmental assessments.

And finally as Don mentioned there was very

limited guidance from early intervention on how to define a high probability of resulting in developmental delay. So we created this matrix to categorize each newborn screening disorder and we characterized risks of developmental delay, the medical complexity and the likelihood of episodic decompensation.

So here's the final matrix of our RUSP conditions and to place each condition, we conducted a literature review to identify all documented neurodevelopmental outcomes and medical risks. These studies reported on standardized developmental measures, so we summarized studies that reported on a wide range of outcomes including cognitive, physical, behavioral, neurological, special education, hearing and vision loss and disability.

Next, we documented the medical complexity of each condition and for each we described the effectiveness of available treatment, the treatment burden on children and families, the risk of episodic decompensation and neurological complications of the disorder and whether the disorder was a multisystemic disease.

Lastly, there are two pediatric metabolic geneticists categorize each condition and after their initial classifications all of the authors together discuss each disorder to finalize the presented classifications.

So I'm going to present three conditions as examples. Children with biotinides deficiency without treatment can develop vision loss, hearing problems, respiratory problems, hypertonia, lethargy, seizures, and coma and premature death can occur. However, early detection and treatment has dramatically improved survival and health in their developmental outcomes.

The treatment is relatively straightforward and effective and studies of children who were treated early were found to have no differences in developmental and behavioral outcomes compared to their unaffected peers. And we determined that biotinides deficiency had a low medical complexity and low risk of delay and treatment altered natural history.

And while it may be appropriate to refer specific children, for example, children who are identified or treated late, this disorder was not necessarily considered an established condition. Children with SCID present early in life with infection, diarrhea and failure to thrive and without treatment, SCID is often fatal in the first year of life. Newborn screening and early detection has dramatically improved survival for children with SCID.

However it's a complex medical diagnosis with a high burden. Families and babies must isolate to

prevent infection and treatment frequently includes a stem cell transplant and there's evidence that this transplant is related to slower gain and developmental skills and developmental delays for children with SCID and the consensus statement from the Pediatric Blood and Marrow Transplant Consortium suggested that developmental delays are likely a result from chronic infections, conditioning regimes, prolonged hospitalizations and isolation from other children and significant family stress.

So post-treatment children with SCID could benefit from specific early intervention services, such as physical and occupational therapy to regain functional skills after weeks to months in hospital. Additional services may include speech and feeding therapy because of mouth sores, nausea, GI pain and taste change that can result in feeding and swallowing disorders during and after transplant. And lastly, transplants carry significant risk of emotional and psychological consequences for children and their families and cognitive and behavioral interventions through early intervention may provide--may benefit children's social and emotional skills.

And so we determined that SCID was associated with high medical complexity and we concluded that it should automatically be qualifying all children for early intervention. Lastly, propionic acidemia is an inborn error of organic acid metabolism and clinical

symptoms often begin at birth within a few weeks and include poor feeding, vomiting, low appetite and hypotonia. Without treatment, children can experience episodic decompensation and coma--that can lead to coma and death.

So early detection and long-term management have reduced mortality but have not necessarily been linked to better neurological outcomes and the treatment is not curative and children can experience developmental ophthalmological and neurological complications prior to age 2. Children could benefit from a variety of early intervention services. Occupational and physical therapy may support children who have hypotonia and other movement disorders. Behavioral and psychological services may be beneficial given the emotional disturbances and conduct problems and hyperactivity, inattention and peer relationship problems and speech and occupational therapy may support feeding.

Lastly, because hearing problems and vision problems can occur in children with propionic acidemia, audiological and vision services may be beneficial. So we determine that propionic acidemia has high medical complexity and high risk of delay, even after treatment and we should--we believe that it should be an established condition and automatically qualify children for early intervention services. So after completing this project, our team

wanted to know whether early intervention could be considered as part of the net benefit equation as new conditions are added to newborn screening panels. And we think that early intervention could be considered as part of the net benefit but a mechanism to assess whether each would be eligible for early intervention is necessary.

So here is the template that we have developed. And we are awaiting the probability of developmental delay, the medical complexity after treatment, the number of states where the condition is currently automatically eligible for early intervention and whether there are published materials that recommend early intervention, or early intervention-related services indicate or developmental monitoring.

So 9 is the highest possible score, indicating that children would be very likely to be eligible for early intervention and 0 is the lowest possible score, indicating children would be unlikely to be eligible for early intervention.

So using this template with these same three exemplar conditions, we show that biotinidase deficiency has a relatively low score of 2 indicating that children be less likely to be automatically eligible for early intervention. There is low probability of delay, relatively low medical complexity and six states included on their

established conditions list. Clinical care guidelines do recommend monitoring for hearing loss and developmental delay. SCID scores of 5 indicating a moderate likelihood of being eligible for early intervention. SCID has a low probability of delay but a high medical complexity and is only listed on two states' established conditions lists but both clinical care guidelines and patient advocacy groups recommend formal monitoring for developmental delay and potential use of early intervention services.

And lastly, propionic acidemia scored and indicating a high likelihood of early intervention eligibility. It presented as a high probability of developmental delay, a high medical complexity and is currently included on fourteen states' established conditions lists. Clinical area guidelines and patient advocacy groups both recommend early intervention services. And now I send it over to you.

DR. BAILEY: Okay, we blasted through that pretty quickly and so I'm just going to wrap up with some inclusions, we are a little over time but I would like to make some concluding comments and then we can open it up for discussion.

So, what'd we just tell you? Well, first considerable variability exists across states and their definitions of established conditions and the newborn screening conditions we examined, we think that 29 of them should be considered as established

conditions given the criteria that we've looked at right now.

In comparison with what we've found is about 7.8 of these conditions on average are included in the states' conditions list. So our general recommendations are that newborn screening and early intervention programs could and should build two-way communication channels. Of course newborn screening interventional programs have something called Child Find, it's a formal way of finding children and newborn screening could be built into early intervention Child Find Programs. We think that early intervention needs to adopt definitions and standards so that all appropriate newborn screening conditions are considered established conditions. It's hard to imagine that will happen on a state-by-state basis. It could but it would take a long time and it'd be nice if there was some Federal guidance to help make that happen.

I know the Committee can't make recommendations for Federal guidance but we can since we're not on the Committee. We do think that it would be ideal for early intervention and newborn screening would collaborate, to collect and track data. Both systems have a strong need for long-term follow up data and why develop two different systems when they actually work together to help make that happen.

And so we, you know, personally think that

this Committee could consider likely eligibility for early intervention in weighing that benefit. And having said that, I don't think that early intervention alone is the criteria for benefit--determining as a condition for newborn screening. Because if there's no medical or dietary treatment that will help a child, then I don't think it's ready for newborn screening yet. Early intervention is not going to move the needle like some of these others would.

On the other hand, we think that early intervention can provide an added benefit when these treatments are provided and in fact for when some discussions are controversial and there's a close decision on what could happen it might be that adding this net benefit, this discussion about early intervention could help build the case for whether this should be under RUSP or not.

If we said that early intervention was the only criteria--was enough, was sufficient well there'd be hundreds of that then could be immediately added on to the RUSP because they are all--so many non-RUSP conditions could be eligible. So that's probably not a practice--that's not a practical situations so we think that combined with the work that you're doing it could be potentially helpful. I'll make some caveats at the conclusion.

So it--again, as I just said, at the present

time early intervention is unlikely to be the primary benefit. It is likely to be an added benefit to almost any medical or dietary treatment. Having said that, it's going to be almost impossible to conduct an evidence review of the benefits of early intervention for any particular condition. So if you went to Dr. Kemper and said "in your evidence review for GAMT or Duchenne or Krabbe or any disorder, go out and find all the evidence on whether early intervention benefits children for that particular disorder, our data won't be there.

And it's really not going to be possible to answer that question in the short run so we think it's really the access to services that we know are appropriate for children with disabilities and established conditions that--that's the criteria here And it changes the equation, doesn't it, from away from a standard evidence review to access to other kinds of services.

We do recognize that early intervention is not as comprehensive or as intensive as we would like it to be. It's a program that could need tremendous boosting and growing but nevertheless it exists and it's available for every child in every state. It enjoys wide support in almost every survey done. Families report high satisfaction with services and outcomes. So it's a good program and it could have benefit for children with newborn screening.

So again, this project was funded by the John Merck Fund. This is mentioned in my disclosures of other sources of support for work that I'm currently engaged in. This is our campus at RTI International. We have a very large presence in North Carolina but we have offices around the US and around the world and with that, we thank you for your attention and I look forward to some questions.

[Applause]

DR. CALONGE: Thanks so much and I'm hoping that you're willing to stand up there as we move to questions and discussion, that would be great. I just want to say it was a great presentation. I think the issue about additional benefit provided in terms of developmental therapy and screening-detected diseases is an important consideration for the Committee moving forward. I have questions as well but I'm going to start with committee members and then our organizational representatives and I'm happy to acknowledge folks who want a question and Jennifer, you get to start.

DR. KWON: Hi, Jennifer Kwon Committee member. I--that was an amazing talk. Thank you so much for looking into EI practices around the country. I--I think of other conditions that ought to qualify for EI such as premature birth or you know, neonatal encephalopathy. Is there evidence of benefit in more common conditions? Because I—I guess I've not

personally seen that but it's not necessary a literature I follow.

DR. BAILEY: Right. So is this still one for us? Yes.

So in general the answer is no, on a specific, on a condition basis and there are certainly conditions where there are--so it's very hard to do gold-standard randomized standards. You can't randomly assign children with one of those--some of those children with one of those conditions to get no early intervention and then others to get early intervention. It's just a very difficult, both ethical and practical kind of study to do so you have to build in, build other cases for that.

So again, there certainly are studies that look at, you know, does speech therapy help a child with a particular condition if you do this model versus that model of the more comparative treatment models but whether early intervention is beneficial than no early intervention, very, very difficult to answer in a kind of gold standard way that we would expect--the Committee would expect.

DR. KWON: And I think that that's important because we--we know that this early stimulation is important and it could be a great leveler when you have so many disparities but what you haven't talked about are the families that can't really take advantage of early intervention because they work,

because their children are cared for in settings that maybe EI staff are not comfortable going to. That are many families whose children do okay without early intervention services and I think that it would be helpful to sort of understand, that may be a helpful group to look at in terms of understanding the impact.

But one of the things that strikes me about intervention is it's a poor man's way, it’s--our society's sort of like way of helping children early on when we don't give parental leave after child birth and you know when we don't have other standardized policies in place to really help our children make progress.

DR. BAILEY: So I think I'll comment on the broader national setting on that, but you make some very good points and I think that—the assist--the discrepancies and disparities are true for almost anything besides early intervention, right? And so--but it's available and it's supported and a lot of early intervention try to go into what they call "natural environments".

And so it's--there's a big emphasis on providing the services in the places where children spend the most time, so it could be in a childcare center and working primarily with the childcare center staff and families as they can, and sometimes it's in the home. So there is some flexibility in

there for sure.

DR. CALONGE: Melissa?

DR. PARISI: Melissa Parisi, NIH. I want to thank you, Don and your team for this really important work and you know having a little bit of a background but probably not as extensive knowledge as you do, I had a couple comments and then a question for you. One of them is, you know, we understand I think a lot about the value of early intervention from some of the early work in the 1960's on infants with Down's Syndrome, which really established I think the case for how valuable early intervention services were for improving developmental outcomes for these infants and young children.

And I think that was really the basis for the legislation and for the programs that we currently have today. So although we don't have comprehensive data, I think for all populations such as the ones that we were mentioning, Jennifer, I do think that there has been some establishment of paradigms for the value of these services. And even if we did have parental leave and those kinds of other safety net-- supports in place, I think they're also is the likelihood that the value of early intervention services is beyond just giving parents time off. It's teaching them skills to help support their infants and children in ways that they might not have had opportunities to learn about.

And so I think that there are a lot of values to early intervention. The disparities certainly exist but if we wanted to really make a difference in society, I mean I think we would have availability, universal early child care and early Pre-K programs, I mean that would probably make the biggest difference you know universally. But that's a side point. I think that the work that you're doing is so important and it could in fact serve as One of the topics for one of the ad hoc activities of this group because I do think the connections between newborn screening programs and early intervention screening services are untapped and certainly if you've done so much of the background research to really establish this is an important topic that could be pursued by this Committee.

And then my final thing is a question about PKU and why it ended up in the Yellow Zone. And the one thing I didn't hear included in your analysis was the challenges of adherences to the treatment paradigms, and you know given that PKU is one of the first conditions identified in many of the state screening programs and that many states actually do have programs for early intervention for kids with PKU in clinics where they're following the development and recognizing that there are now more pharmacological treatments aside from just dietary interventions it still seems to me like this is a

condition that is at risk for developmental delay so I was surprised it wasn't recommended for automatic inclusion on EI list and that's it thank you.

DR. BAILEY: Would you like me to start with an answer to that?

DR. REYNOLDS: I will say that it was one of the conditions that we had to go back and discuss. I think we ultimately decided to leave it where it was because of the treatments that were available and the availability of them to-- I'm not a medical expert but I think that that you know the success of the dietary treatment was why we would left it where it was--but I think that is definitely you can make the case for almost all the conditions that you know you would want them all to be automatically eligible because I think that for specific children in specific cases they would still need services.

DR. BAILEY: And just to add to that I think that if the primary problem is adherence to a treatment regimen and that's not what early intervention typically defines as their goal because it's really helping the children with particular delays or problems or helping the family with coping with this now helping the family follow the medical regimen, making sure about the diet is there is a little that's why we had kind of this debate about whether that's really an eligibility criterion so that's why we didn't include it.

Going back to your very first point, if I may, the question I think is do we need to do a comprehensive evidence review of the benefits of early detection for every disorder or are there enough prototype examples that we have confidence at least that they're probably or is a high likely would because that's the only major there is that is there a high likelihood, right. I think if we have high confidence there's a high likelihood of benefit from early intervention for this condition to me you can make that assessment and that judgment even without a randomized trial for that particular disorder, but that's my perspective on it.

DR. CALONGE: Thank you. Shawn

DR. MCCANDLESS: Thank you, Don, Elizabeth, that was very fascinating. It seems to me though that, one of the things we've learned about biology is that there's no simplification. The more you try to break things down, to components to simplify the more you recognize that there's new levels of complexity there. But with that said, I've always had this very simple-minded idea as a geneticist that people are born some sort of genetic potential for their achievement. And I think this supports what you're saying which is that it doesn't matter who you are or what your underlying condition or whether you don't have an underlying condition, you have some-- you have a range of genetic potential that--that

maximizing and optimizing the environment in which you are raised will allow you to achieve your highest genetic potential.

So my question is, does that resonate with sort of what, where you've gotten to over the years in your thinking and secondly--I think it's really--if that concept is, if we believe that that's true then by definition your statement that early intervention should be generally recognized as beneficial to anyone who's--who has an underlying developmental issue or medical problem should be beneficial and then we don't need to do the case-by-case work so I totally agree with that. But I'm curious about that thought of sort of the--when do you agree that that's true and then the corollary might be for the purposes of newborn screening should we be focusing primarily on things that are going to either protect the range of potential or enhance the range—prevent it from deteriorating like the case of PKU or try to enhance it like some of the novel therapies that are being developed with gene therapies and things.

So a lot there and I apologize.

DR. BAILEY: Yes, that's a big question, a lot to unpack there. I think that in general, as you well know there are controversies about in general populations about genetic potential and limitations and so forth and so that's a whole, whole other

discussion and I believe that in general the environment can--can overcome any of the kind of physical challenges that people have and in fact with the constant changes in--not only in our environment but in our biology that there's a lot of potential there.

Here if you have a child with a particular genetic disorder, and I'll just take Fragile X syndrome as my example, so the many studies we've done shows the average development trajectory of a male with Fragile X syndrome is about half of normal development, right and so, an IQ of 50 and as you move--but there's wide variability around that.

So what's the genetic-- and some boys with Fragile X can read and live independently and work and others are nonverbal and not toilet trained even as adults and so you've got that wide range. So what does "genetic potential" mean when you've got such a wide variety and a particular single gene, single gene disorder.

So lots of other things and it's certainly not just environment that causes that, so there are biological caps, but it could be modifying genes, it could be any other you know, biological component there. The patient me, and looking at the data that we have. If I said would early intervention move the needle for children with Fragile X Syndrome from half to normal development, I don't think that's going to

be the case, at least early intervention as we know it today. So in that sense I think that there is a cap that a genetic disorder--a single gene disorder like that places that will make it very hard to move way beyond that. On the other hand, I think we can move the needle enough and we can improve quality of life in significant ways.

So I kind of hate to frame it in the context of that kind of cap because I don't think that in my mind is especially helpful. But I hear, I hear what you're saying. I don't know if that's a sufficient answer but it's a really complicated question.

DR. MCCANDLESS: Yeah, I know that, I think we agree about this that the level of complexity of the factors that impact what a person is capable of achieving sort of as a baseline are going to be so complex and variable that you can never study them efficiently. You know, you could--you would have to, there's no way to find a control for every individual.

DR. BAILEY: Only individual for every individual, any treatment. So you think about early intervention. That's a package, right? There's a lot of things that would be in there from different therapies to family support systems to curriculum A versus curriculum B. There's so many factors that would go into that and it would be impossible to study all of those things individually. It's really

that package that comes--comes together.

DR. CALONGE: Michael?

DR. WARREN: Thank you all for that wonderful presentation. I'm struck in thinking about the lists that you all provided in thinking about this kind of matrix approach that states already have lists of some sort, when they talk about eligibility and we already have programs in place. I think about our Title V maternal and child health block grants, I think about the state EHDI grants for newborn hearing and the grants that are about to be released with the newborn screening support that can already do this kind of connection for things that are already on the list.

So I'm curious. I always think about what's our role to advance this and technical system and figure that we're leaning on our grantees. As you all were doing this, did you identify exemplar states or approaches? You may not want to call out specific states but there are --models that are doing this really well that we could lean into from a TA standpoint or even in terms of requiring that of our grantees?

DR. BAILEY: Do you want to start with

DR. REYNOLDS: Yeah. I mean I think that looking at the two states that automatically qualify all children that were diagnosed with the newborn screening disorder. I think that digging in and

finding out, you know, how they got to that point would be really interesting. Like I think there's some component that we just need the state early intervention and newborn screening coordinators to talk and communicate. And so I wonder if that has specifically happened in that state you know has, two states that has already documented that all newborn screening are eligible.

So I think that that would be a great place to start and then we did ask coordinators, you know, what is the status of your collaboration. And I think that we found that there's a lot of states that said you know, we're developing passage communications. We're developing data share agreements and data transfer agreements and I think that that, you know, hopefully over the next couple of years, hopefully really demonstrates that by doing so there can be an outcome that shows now that states now are tracking whether kids are being referred after newborn screening diagnosis. But I think right now we just don't know what the--what the relationships are.

DR. BAILEY: We're also doing a study Elizabeth is leading on caregiver experiences with newborn screening and early intervention and trying to understand how the path that they got to and we're guessing it's a--with 800 families we're going to not find 800 paths but we're going to find a lot of different pathways to that.

So lessons learned from that. I think it will be really important and then maybe taking a state or two that's not doing it right now as a pilot and saying "okay, let's take State no. 27 and see how-- what would it take to move it? Is it legislation? Is it more training of staff? Is it pediatrician? What would make that happen? So there's a lot of work. There's still work to be done, potentially from the national level on down.

DR. CALONGE: Online we have Debra Freedenberg.

DR. FREEDENBERG: Hi. Good morning. Thanks for that great presentation. I really have two questions. A little bit more practical. One is we know that families can self-refer and do you have any feeling for how many newborn families and children with newborn screening conditions are self-referring to the ECI and is there any sort of evidence of outcomes difference versus a straightforward referral by diagnosis?

And then my second question or point is that in many areas there is a paucity of ECI providers and sometimes families are on long wait lists to receive services. I did note that backing into the thinking that we're going to consider using those that we should also consider the resources that are available out there for the families.

DR. BAILEY: Right. Two very good questions.

I'll get some very quick answers to each one. So the self-referral component is definitely there. Families can do that but the child still has to be determined eligible. And so if their child's condition is not on the established conditions list, they may have to make a pitch for that and make a case for it and will have to be told well we'll do surveillance for your child until your child shows the development delay or not. So there's some complications with that. Plus, I think families, my guess is after newborn screening are so concerned about their child's medical development or what they can be doing there that they, and many don't even know about early intervention as a possible set of services and so yes, that is one path that might be available but I wouldn't see as the primary--primary path. It could be part of the educational component for families with newborn screening conditions.

The other one that you're asking about of course is the challenges that early intervention faces. Well like a lot of fields, getting enough staff, enough trained staff to do what they need. If you look at a lab, Scott's told me how challenging it could be to hire you know people to work in a State Lab. These are State run community-based programs. They're not paying you know a ton of money to be working in early intervention so you do it for a variety of other different reasons and so—and there

are financial constraints as well and so the programs are not as intensive or extensive as we would like them to be. I certainly acknowledge that. It's not a good answer but--

DR. CALONGE: Natasha?

MS. BONHAMME: Thanks, Natasha Bonhomme, Genetic Alliance. I have two questions. One is when it comes to the scoring that you did. Mind you, I wasn't wearing my glasses so I may have interpreted something incorrectly. Can you talk a little bit about how the clinical side got two points and the parent or patient advocacy got one and kind of the difference in that, the level of the scoring there. Knowing especially in early intervention as you spoke in benefit to families, both from a clinical perspective but also as Melissa was saying, all the other supports and just how you came to that type of scoring?

DR. BAILEY: So Elizabeth, I'll answer that-- just a quick answer. Those are not about benefit. It's about something else. You want to--

DR. REYNOLDS: So I think that you know that we originally only had clinical care recommendations, so documented and we assume those were based off of published studies of kids that have said, okay, they do better with these services but I think that when we recognize that there's a lot of the diagnoses don't have any clinical care recommendations and

certainly a lot that don't have any developmental recommendations and so I think that we've found some patient advocacy group materials, you know reports. But not necessarily things that have been published but you know, has been put on their websites that they recommend to families after early diagnosis and we thought that was really critical to include but I think your point saying why are we, if we're considering the families and the parents as experts, maybe they do know more about the developmental outcomes that might not be included in published materials. That's a really good point but I think for now we have left it as different, different ratings but I think what you're saying is really important.

DR. BAILEY: So in terms of a Committee decision-making process, if there was no clinical guidelines for--no guidelines for what early intervention should be doing for this particular type of child and there is no patient advocacy group that had any--anything published anywhere, websites or anything then that would get a zero because there is no guidance out there, maybe potentially beneficial but there's nothing in existence. You know you can say that we're prioritizing clinical recommendations as opposed to advocacy recommendations but we did want to make sure we recognize and value what patient advocacy groups were saying or publishing. Sometimes those are not as evidence-based as maybe some of the

clinical care guidelines, although they may not be evidence based either.

Anyway, that's how we came up with the scoring system, trying to reflect the value of each.

MS. BONHOMME: That's helpful, that explanation and also knowing that, you know, there's some communities where the clinical groups would make a decision without patients or families in the room and some do, so just noting those differences and then my second question is if you could speak a little bit to, you know, what are the levers for change in early intervention? So is that more a legislative advocacy approach? Is it more something else, a Committee approach to add that context to? If there are changes, we would want to see how that actually happens.

DR. BAILEY: Well, that's a complicated, well, all the questions are complicated. I mean, the simplest, quickest change would be a change in legislation that said an established condition that includes any disorder that's included on the RUSP is an example of an established conditions list but the--the states, even then they couldn't really require states to include those conditions, it could be one of the strong suggestions. And that's kind of like what this Committee does, right? You can't require that a state screen for a particular disorder, you recommend it and so I think that would be kind of the

first way to harmonize things across the nation.

We can have an Advisory Committee, we can make that kind of recommendation, but it wouldn't be this Committee and you can make that recommendation but there's no comparable committee for early intervention programs. Once you go beyond that you go to the state level and so there are some national technical assistance programs. We can have workshops around those and have a building process on a state-by-state basis. Certainly, parent advocacy groups could get engaged and say "wait, why does our state only have, you know two conditions on the established conditions list"?

So, I think there are other scenarios. A lot of different things that need to be tried out and tested. Probably a combination of it.

DR. CALONGE: Jannine?

DR. CODY: Jannine Cody, Committee member. Thank you for a fascinating presentation but I'd like to point out to my knowledge EI isn't a one and done. Children can be enrolled, catch up and be dismissed from the program before they hit three, so from my way of thinking the bar should be very low for entry into the program for evaluation because they can catch up and it's not a three-year commitment. And plus, parents don't--as you said, parents don't always know about it. They don't know such a thing exists. Thank you.

DR. BAILEY: Well, so it's like a sunset law. You know, it's very hard to kick a child out of early intervention. You have to document that they don't have a developmental delay or they don't have an established condition anymore. So if you have an established condition, even if your delay is not evident by age 2 or 3, it still could be a condition that might likely lead to a developmental delay so they could stay in it. Once you reach age 3 to get into preschool programs, which are more public school oriented programs for children with disabilities, you have to have a documented developmental delay. And once you get to age 5 of course you can fit into the categories of learning disability or speech and language impairment or the other, all kinds of autism spectrum disorders.

Those are more the categories when you get into public school but in that 3-5 year age range it's really more in the development. You can have some diagnostic categories as well. So I don't think that's a huge problem but I do think that's you know, you can have a tail-off for sure and then children have to "prove that they need services in other ways" than you have to for getting into early intervention programs. But lifelong care of kids with disabilities is a huge, huge issue that we won't solve through newborn screening but it can start from the beginning. Set the foundation correctly.

DR. CALONGE: Jennifer?

DR. KWON: Thank you for letting me talk again. I just can't help but think about how distinct these two programs are. So we--we hear a lot about newborn screening programs and how this state administers their newborn screening programs, but when I think of early intervention, I know that it's Federal and the money goes to the State, but I really think of it as a county-based program, right. All of the personnel are county-based so I guess I really like the term Natasha used like what are the levers? So these are two very important programs for our children who are identified and how have this potential for developmental disability. So how can we use our resources wisely? So we want to set the bar low as Jeanine said but not so low that they're flooded with kids who don't have developmental needs.

So for example I was surprised to see XALD on that list because we don't think that under age 3 there are a lot of developmental needs. But yea, I just think that to me the finances are, I think I alluded before I was really curious about the finances. I just wonder about how these programs really can be joined. I think it would be great if they could be but I sort of wonder about that and so I'd like to hear more.

DR. BAILEY: I'll give a relatively quick answer. So in terms of, you're right. most of the

programs operating under county health departments or under school systems as well as about half the states, early intervention is under the Department of Education. About half of them is under health and human services so it's devolved under local groups to actually provide the services. State does set the standards so for what established condition is. It'd be unlikely that Davidson County would have a different list of established conditions than Mecklenburg County. I'll just give you two examples in North Carolina. So they have to use the same standard there for the most part.

In terms of financing, in some ways what we're talking about would have very little financial implications. The number of children identified through newborn screening that would go into early intervention programs is miniscule compared to the number of children that are actually in early intervention so it wouldn't be a dramatic like overloading the system any more than it's overloaded already.

I think if you had efforts to try to systematically combine them there would be some kind of coordination work that would need to be happening especially if you tried to do a combined data system which is a, you know, huge goal need but I think a tremendous opportunity for both fields. So I think there's some ways to maximize the synergy here.

DR. CALONGE: So, people have managed to ask five of my nine questions. I'm going to just jump in and ask a few more. And one is around funding. So you said per capita, is that before or after? Is that a responsive per capita funding and tied to that, is funding sufficient? In other words, does it need to be supplemented if it's at the state level, which in Colorado would require a decision item which is kind of the death to our bill in any state?

DR. BAILEY: Right, and from what I understand like the Medicaid expansion would be an example. And early in the federal supplement for newborn screening is not sufficient to support any newborn screening programs. So it's usually a combination of insurance, private insurance, Medicaid, state supplementation with state funds and with sometimes with parent co-pays. So but it has to--but it's very, wildly variable in cost across states. That's a whole other study that can be done is what's the--how's--it's kind of like paying for newborn screening, right.

Every state has a different kind of model for how they do that and it's the same with early intervention. The allocation to states in my recollection is based on state, the number of children in the birth age 3 age range rather than the number of children served, otherwise you'd be serving--you know, you kind of play that game in different ways.

DR. CALONGE: And that's what I would have guessed but I think, it's not been mentioned that financial barrier at a state level, state Medicaid level is a significant barrier for many states and something I think we need to continue to think about.

DR. BAILEY: I just made an editorial comment if I may that in one of the papers we wrote about what we were trying to think what some system level changes could be and if newborn screening had a similar model that there is a net--because there are hundreds of millions of dollars that go into early intervention programs and newborn screening, these are all project-specific kind of funding but there's no core per capita funding from the national level. It could potentially accelerate change but what it has to be paired with that is some expectations.

So states cannot get early intervention money unless you document that you have, that you've done individual family service plans, you've provided these kinds of services. You have case management services and so forth. So you can have that kind of support and expectation for newborn screening programs that could potentially move things along and help harmonize things. That's not your Committee's decision.

DR. CALONGE: The next questions are kind of related. So the medical complication category that upgraded conditions was of interest to me because I

fully bought into the concept that complexity increases the risk of developmental delay and I found myself wondering what is the evidence that developmental delay treatment is more effective or effective in the setting of medical complexity?

DR. BAILEY: You wanna?

DR. REYNOLDS: I think that's super interesting. I don't think that we have, I haven't looked at any specific research that has looked at, you know specific developmental services for developmental complexity and have proved, you know, to be beneficial.

DR. CALONGE: All right. Well that got me into the area of worrying about publication bias and people publish negative studies about interventions for developmental delay, but that's an evidence issue. There is a category of evidence called analogy and I think this fits right into the analogy setting, but, I don't see Alex, but if we think about where this might fit, evidence by analogy approach is something that could help inform the Committee. Because the thing that I'm kind of left with wondering how would you bring in the availability of services into the calculation of the magnitude of net benefit?

DR. BAILEY: So it's the magnitude part of your question that I think is the kicker, right. So I'll just give an example of a very different kind of

disorder that wouldn't be picked up through newborn screening. So we've been studying babies and actually NIH funded a study of babies affected by the general Zika Syndrome in Brazil. So those babies have, if you talk about medical complexity, these are babies with profound intellectual disabilities, profound medical problems that are going to be lifelong for sure. Families are left--you know, without early intervention the families are just left hanging there and so the supports that early intervention can provide families like that are really remarkable, not just to help the children but really help the family.

I know the family benefit a core part of this Committee's decision but I actually think that helping families can help children and so that's how I would make that kind of link.

DR. CALONGE: Thanks, and we're a little bit over time and so Bob, Robert, I'm going to ask you to hopefully be quick in your question or comment.

DR. OSTRANDER: If you can hear me at all. My Internet is scrambled. Quick question is, regarding how much weight we should give benefit of EI and similar services when we determine the ability for the RUSP and questions specifically about the timing of early intervention as opposed to whether it has benefit or not.

You mentioned with Fragile X case in the beginning and the key developmental time in the first

three months of life, and it occurs to me a lot of our identified conditions might eventually get to early intervention through clinical pickup but the diagnostic odyssey, the diagnostic pick up of developmental delays would come sooner if clinicians were to screen.

Do you think there's a way to study the benefit of the timing? For instance in families with Fragile X where you have an index case and then a subsequent sibling gets picked up early or Duchenne in this case, picked up earlier where you could get some data to help inform the evidence review.

DR. BAILEY: Right, certainly you can do some sibling studies, right. So in Fragile X we have a lot of studies where we know that about 30-35% of families who have one child with Fragile X have a second child before the disorder, before the first child is diagnosed. So you could do a sibling kind of study then for sure and look at whether the, obviously there's other factors that you'd have to control but within families you could see if the younger child who got early intervention services or the older child didn't, it would be one way to provide that kind of data. I'm not sure what the other components of your question are?

DR. CALONGE: And actually, I think, I hate to cut us off prematurely but in respect to the time per speaker, Robert will hold on that. Margie we will

have to move on at this point. I really appreciate the great presentation.

[Applause]

Research on Benefits and Harms from Uncertain Results

DR. CALONGE: We could talk about this for a long time. So we've invited Dr. Beth Tarini from the Children's National Hospital in DC to speak to the Committee about research on benefits and harms from uncertain results and I'd like to welcome Beth. She's an associate professor of Pediatrics at George Washington University and serves as the associate director of the Center for Translational Research at Children's National Hospital, where she conducts research and optimizes delivery of newborn screening services to families and children.

Dr. Tarini's research has been funded by the NIH, HRSA and RWJ Foundation and the Cystic Fibrosis Foundation. She's been actively engaged in newborn screening policy at the state and federal level and has previously served on the advisory Committee. She’s a practicing general pediatrician, a graduate of RWJ Clinical Scholars Program and the immediate past President of the Society for Pediatric Research, which is the largest U.S. pediatric research and its focus society. She's leveraging her recent MBA, congratulations, to improve the training and diversity of the research workforce and we're really

excited to have you today.

DR. TARINI: Thank you, Ned. Thank you for having me. So I'll get right to it. So today I've been asked to come here to talk with you about benefits and harms of newborn screening and the evidence that exists. So given we have 20 minutes we're going to go very high level as to what's generally there and what's missing and how my team and the states I'm working with are trying to close that gap. I have no conflicts of interest to disclose as I have served as a member of this Committee and as the AP liaison and importantly, any opinions expressed here do not reflect those of NIH or those of Children's National Hospital.

And so the goals for today are to illustrate the data gaps for the impact of false positives and uncertain prognoses with newborn screening. I'm going to pause because I know the title says uncertain prognoses only, that's going to come at the end. So there's going to be a little bit of delayed gratification and you might be a little bit depressed by the end too. So I'm just warning you on what's lacking. And then we're going to summarize the active research projects we have that are in to fill these data gaps.

So I don't have to go thankfully much into detail about newborn screening and the various ways in which it's delivered and the various services.

Most of our work has focused on the experiences after the blood spot. That’s not to say that there aren't others, it's just a matter of scope and funding and this is what we have focused on. And I want to be very clear with this slide. Newborn screening is a successful program and it should continue yet it is important to note that all screening has harms and it is unethical to ignore them. And failing to examine them counts as ignoring them. And so really when you look at a screening program as this Committee's well aware. It is about making decisions between the balance of benefits and harms.

This is based on Harris, et al. about the harms of screening. And everything is relative and everything is in balance. As Harris has defined harm and I know this has come up I believe in this Committee, the definition that they provide is any negative effect perceived by patients or significant other's resulting from screening compared with not screening.

And so it is in the eyes of those who undergo the process, generally form this definition. This is the definition we have used and the domains of harm that they set forth are listed here. They set them into physical, psycho, social, financial strain and opportunity costs.

Now of course if I had the entirety of the NIH budget at my disposal, we could study all of

them, but we do not. And so this is just to simply say there are broad categories that you can delve into when you want to discuss harms. I'm starting with harms. We will get to benefits later. And we have focused, our group is focused on the psychosocial, which has been, I would argue what has consumed discussion over the years.

We have focused our work on the false positive results on the, what we call "uncertain prognoses" which we'll get to in a minute. And so first false positive results and a little bit of orientation, many in the room are well aware of this but I just want to make sure we're all on the same page. So the collection of the sample happens. It is sent for processing.

You have within range and out of range. And then when you have an out-of-range screening result you then move on to confirmatory testing and evaluation, in which you can get one of three options. You can be deemed a false positive, meaning, you are cleared, you are told that your child does not have the disorder in question, of which where was a potential risk, given this is a screening test when the out of range occurred. You're inconclusive meaning we can't definitively say whether or not your child has the disorder in question based on the information at hand or your child does in fact have the disorder. And when the

false positive occurs, the child and the family are released, if you will, from the newborn screening system, sent forward to say congratulations there is no disorder. Your child is without any concerns regarding newborn screening disorders.

So this false positive, we'll start here, has consumed newborn screening to some degree since its inception. I put this here so that we know we're talking about something we've been talking about for 50 years. And this is an excerpt from a journal talking about what happened in '66 at the Bronx Municipal Hospital Center when they said they had parents coming with what they called PKU anxiety syndrome, presenting as acute and chronic anxiety, ranging in degree from mild period bouts to acute anxiety hysteria. They persist in the belief their babies are or will become mentally retarded.

Again, the era dictates the language. Despite negative tests and considerable reassurance and support from physicians, etc, etc, etc. That is sort of the crux of some of the conceptual model of false positives. We can go into others but this slide is here to say this is not a new topic. Historically much of the conceptual model based on the false-positive harm to a parent and the family is based around the idea that the child is somehow after the fact viewed as persistently vulnerable.

This is based on a phenomenon that Green and

Solnit first observed decades ago when children were admitted to the ICU, previously healthy, had a near fatal experience, recovered and the parents persisted in the idea that the child still remained vulnerable. The definition of that vulnerability being that they would over interpret threats to the child's health.

As an example, a cough could be seen as instead of an upper respiratory infection could be seen as a pneumonia. Everything became heightened. That is one of the concerns that has existed around newborn screening and we can go into the conceptual models and have hours of conversation about whether this is actually going on, if it's going on at all or whether there is some traumatic stress going on, if at all in newborn screening such that we have created a sort of traumatic stress event in an early stage of parent/child bonding when the child is apparently well and new, days to week old and this then becomes a lens through which parents may go back to as almost like a posttraumatic stress affect when the child's health seems to be threatened in the future.

So instead of over interpreting risk in the vulnerable child model, the traumatic stress model might say parents go back to this moment in time when there are threats in the future. So symptoms of vulnerable child, you might say "parents get stressed. It's part of the job. You signed up for it". Some that we have seen in literature. In other

cases, difficulty with separation from the child, infantilization, body over concerns, school underachievement.

This is very different, I should say, from Munchausen's by proxy. This is not what's going on. I just wanted to clarify that. And so here's the slide I think we all really should focus on. This is a slide that tells us how much we have, how much data we have on false positives on newborn screening and what does it look like. It's a busy slide and I'll take you through it one by one.

So this is 1980-2010 on the timeline so you have 30 year here of newborn screening and first you have colors that you see right up front and those colors show you the different types of disorder that have been studied because some might argue your experience depends upon what disorder you might have had a false positive with and we can go into that as well.

So you see we have a variety. We have hearing in orange, metabolic disorders in blue and there have been a few more since 2010 but they all share certain limitations. Hypothyroidism, cystic fibrosis and multiple newborn screening disorders. So we have a range of different disorders studied. The next thing to look at is the type of research we have, qualitative versus quantitative. You might not be able to see this as well but--but we have a mix, we

have some quantitative and some qualitative. You see that? You see that right here.

And the next thing that we have, where this was done. Most have the U.S. you have some here outside the U.S. You've had some done outside of Canada since this timing. And then you see the numbers and they're quite small. So this is part of the problem too are small numbers. And then the last piece, which is important and we'll get to data types here which is this PSI, a standardized instrument. So when we have quantitative data it's important that we can compare it.

So if you use the same outcome, you can compare it. If you don't, we're sort of comparing different scales and it becomes more difficult to say apples to apples until you see here it has this, this scale which is standardized and validated and is just recently begun to be used and we have it only in small populations.

So I would say to you that the literature on the psychological effects of false positives in newborn screening on parents is limited. It is limited in scope. It is inconsistent at times. There are certain signals that appear and our biggest challenge is that we have a preponderance of qualitative data and a minimum amount of—relative minimum of quantitative data of large numbers for which you can really understand what's going on from

a quantitative perspective.

And that gets to well, what is the data? And I sat on this Committee and "is there data? Is there data?" and the question really is "is there data and what does it tell us and what can we learn from it?" So yes, there's data on false positives and you'll see there's data on certain, it's just a matter of what type of data you have, who's it coming from and what is it telling you?

So quail--and this is very important, qualitative data and quantitative data are both very important. They tell you different things and they are both valuable in their own right. They can be abused in their conclusions and overextended. But it's like much of the world. And the use of data. So I think it's an important distinction. Qualitative data like interviews, focus groups is what we call "hypothesis generating". You generate hypotheses. You try to figure out the phenomena that are going on, sampling a wide range of individuals to ensure that you are getting all views of the elephant, if you will.

These separate data are rich in their experiences. These are details about experiences, they're limitations are that they are not generalizable. My experience is not the same as Dr. Brothers, nor as Ms. Brown. So we can say our experience is our experience. My experience may

represent and have similarities to others, so hence the hypothesis generating piece.

However it also cannot calculate prevalence. This has been a conversation I think where--I think it's very important to note you cannot say that because one person has it that the rest of the population has it, this experience. You cannot give any sense of what is the prevalence or burden of that--of that experience. That is a significant limitation of qualitative data.

So to say it never happened to me doesn't mean it's not a phenomenon that exists. To say it happened to you is not to say it is a significant burden to population. That is what we get to quantitative data which gets to the hypothesis testing piece. We are lacking in detail in understanding because we tend to ask specific closed-ended questions for which you have a set of responses that are very narrow but we can calculate prevalence and we can look to see what are the proportions of the population at hand that might be affected. And this potentially generalizable based of course On caveats of sample size in composition and this kind of Data comes from questionnaires and administrative data sets.

So I'm going to breeze through this because I want to get to the uncertain. So we have attempted to fill this gap of quantitative--what we would call

quantitative data gap in this project unresolved issues in newborn screening quantifying the harms of false positive result, And I thank my funders the Eunice Kennedy Shriver National Institute of Child Health and Human Development and acknowledge my colleagues at Children's National as well as my state colleagues at Virginia and Iowa newborn screening programs. And I'm just going to breeze over this I can go back to the day later Just to give you a sense of what we're trying what we have done what we are trying to do.

This is to answer the question who's experiencing stress related to false positives compared to those who have normal results so we have a multi-site perspective observational cohort study. parents of children enrolled through both of those newborn screening programs, the time of their categorization, they'll close out of their case at 2 years of age. An exposure group and a comparison group false positives and normals and again these two states, with this outcome as I mentioned in the parents stress index, validated 120 questions focusing on three major stress domains widely used scale

I may have these additional measures as well as vulnerable child parentings and child development. And here is the study just at large and breathing through this. We recruit consent and then begin

participation in the first six months of life and then the children go through six to 24 months of age. I say the children- really the parents are the participants, and they received an initial contact and survey, in which they fill out demographics and then at 6, 12, 18, and 24 months. They take repeated measures as we've noted here the PSI, the promise for anxiety the vulnerable baby scale etc, etc.

I didn't the initial demographics, we have a very detailed exploration of demographics child health screening experience and newborn screening household demographics. And then just sort of pat ourselves on the back we have 998 parents enrolled You saw the slide with the colors. The highest I could get was 150 maybe so we have 998 parents. Our attrition rate is somewhere around 10%. That is split about half between parents of children with false positives, parents of children with normal results and many as you can see here, common median age of the parents almost 32 at the start of about 4.8 months.

Important things to note 70% are dyads. Both parents are included in the study. Preponderance of females that is not surprising, a lean towards married and a lean towards only child which is important because that is a theoretical risk. And we do have some diversity we have about almost 10% Hispanic Latino. We have preponderance of a white

population.

I'm going to pause here to put a plug in because the NIH is constantly asking why can't you get the sample more diverse? I cannot reach out and tailor this study to children of parents who would identify as non-white because either the states don't ask the question on the card or it's not a value-- valid data point. So I have no way of doing it unless we link it to the birth records.

It's a significant issue if we want to get a diverse opinion in this field. Plug ended. So non-English speakers, etc., etc. So unfortunately, I don't have the data for you. We just finished the final piece of recruitment. The 6-months should be done in the next few months. I can come back with that with those data points. And I'm happy to tell you in the question and answer what I think it's going to be.

My sort of theories so after we started the false positive, we marched on to say where else are we having challenge with data newborn screening and it was around this. These uncertain, we call them uncertain prognosis These are children who had out of range results and gone to have inconclusive confirmatory testing evaluation and then they move on to either treatment or surveillance. I'm going to pause and say uncertain prognosis is our term. It has been used, the term diagnostic dilemmas have been

used. We understand that. We also understand some people would debate it's not a dilemma you've got a diagnosis. Whether or not we say the prognosis is uncertain is also a matter of lens.

If I tell you it's going to onset in adulthood it's that uncertainty. So we have to find some uncertain prognosis to mean there is some degree of uncertainty. When you tell a parent the degree of severity of the condition, the timing of onset and the type of symptoms that they the child makes experience if there's any degree of uncertainty, we will call that an uncertain prognosis.

Now, to some degree the question is who defines uncertainty. We will have in our study for almost ready to start recruitment, in our study parents are true positive and parents of uncertain prognosis. So in that way we can test whether our definition of uncertain Is really uncertain in the eyes of the parents. And I'm sure you're aware of these terms. This group of patients is I believe you discussed last time they have been referred to as "patients in waiting". This idea of they are not going to imminently or do not have current symptoms but they are waiting if you will for these symptoms.

This is not a new phenomenon. This was known in CF very soon after CF newborn screening. So this is not something that appeared on the screen. To see a foundation, cystic fibrosis caretakers have been

dealing with this for some time now, at least when I can remember being junior faculty.

I'm going to almost wrap up quickly what I can tell you about the data is that it's less than what we have for false positives. So for false positives we have a fair number of studies. Again the challenges it's limited to small qualitative base studies focused on specific disorders. In this case the peer review data few studies they tend toward small single center and majority qualitative but the scope of what we have is far, far smaller than that for false positives, and that was 30 years.

So I would say we're starting sooner so good for us. Issues have been raised in the literature. What are the benefits of knowing the avoided diagnostic odyssey. Parents say with reproductive benefits, access to early treatment harms of knowing they have to express anxiety of stress waiting for the disease, The effect on themselves, the effect on their family, the effect on the relationship and how they care for their child and also lost follow-up of whether or not they engage with the health system Which I think is also one of the true losses from a system perspective.

We have spent all this time and money to find these children who are at risk and if we lose even one. It is a huge, huge loss if we don't know where they are and they don't come back to care. And

so with that we were able to argue to NIH this was an important area for funding and I'm proud to say we have received for this project their highest rank score of 1 percentile from the NIH. They felt it was exceedingly significant. And I'm just going to give a brief view with expanded our team. Collaborators which include Children's National, Case Western and several, five states we have Iowa, Oregon, Missouri, Tennessee, and Virginia. All have signed up to help us with this study.

So I'd like to say I think our group has really done for health services a nice job of showing the states can be laboratories important laboratories for understanding the delivery of care in newborn screening and they have just done a bang-up job and I thank them for all of their work and dedication.

And this is to show we have a multi-disciplinary team, our team is not simply sociologists, ethicists or at the pediatricians. It includes genetic counselors, geneticists, public health, those with expertise in recruiting diverse populations, healthcare economists. So I think it's a wonderful, wonderful team that really brings it to first perspective and there are states, if you would like to join, please let me know. We may be talking to Illinois soon.

So just you understand the goal then of this project is to fill this gap by doing what we call

mixed method study. It may have come off that you could either do quantitative or qualitative but you can do both. And in this case, given that we have a posse of qualitative and quantitative research in this area, we're going to do a mixed method study where we do an interview and survey parents from the point of the categorization of the child into one of these groups and move forward for a year at least depending on how much funding we can get to understand how is their experience changing over time and how are they dealing with these situations for better, for worse and then for that we will come back to you for recommendations on what we find. And what that'll stop for questions.

[Applause]

DR. CALONGE: Kyle.

DR. BROTHERS: Thank you so much for that. I just wanted to give you an opportunity to- - well first of all thanks for that really great presentation. I wanted to give you an opportunity to speculate about the results for the false positive group. You know there's some analogous situations such as you know undergoing sequencing and getting some kind of uncertain information. Typically what we see in that context is truly adverse outcomes, is a small percentage around 1% or something like that.

And typically it's among individuals who struggle with mental health in their life, separate

from this event, but this event occurs in the context of a human- - a person's experience over the course of long period of time. So I just want to give you a chance to talk about that.

DR. TARINI: Sure I think that what you seein the literature is we find it in the population we really don't try it in aggregate. We find it in signals in population we don't find it in aggregate. I think that is a clue that there is if this phenomenon, or these stressors exist, or happening in some subgroup that you don't find any aggregate. And so that's the first piece so I think there are subgroups if there are any at risk.

I think your point about mental illness is a good one. I would broaden it to say the subgroups we hypothesize, that the subgroups are related to both what the parent brings to the table and what we deliver to them so what we call is signal receive effect.

So one parent may have had multiple miscarriages from IVF, a history of anxiety on Zoloft. Okay they may receive a signal different than a parent who has had five children. No pregnancy, disease, no chronic illness in the family. Without a doubt and they're coping may be different as well. On the other side is the message that we give the signal that we give to the parents.

If I tell you for instance your child could

have, is it risk of having congenital hypothyroidism, it's possible that they have it. There's many false positives that occur in congenital hypothyroidism but even if this is not a false positive your child, if they have this disorder may will require medicine, very easy to take, very few complications, overtime indistinguishable for from their peers. That’s one signal.

If I tell you your child has a disorder that could be fatal, if they don't - - if they don't fatal - - even harmful, taking the wrong formula, fasting, etc. etc. so we need to watch them closely over the next few days. So we wait to see if that in fact is the case. That's a different signal. When there's an imminent--the urgency and the severity just feel different theoretically to the parent. So what we've done is try to collect information on both of those so that we can examine what is that phenomenon that's going on.

Because I think now, I'm going to go on a soapbox here, I think to approach this topic as "it's a problem, it's not a problem" It's a little bit reductionist. I think the issue is--is this a challenge for parents in a program in which they've undergone mandatory screening, and then we have therefore had a hand, for better--for worse, and producing this outcome. Granted with the benefit of those children we've identified and treated.

Therefore we don't remove newborn screening. What we do is identify those who might be at the highest risk and then offer wrap around services or interventions of some kind. I would say, the analogy I make is with cancer 30 years ago you got the chemo you're lucky you lived. Now you can't go into a cancer center without touching 12 types of providers, cancer doctors, social workers, the psychologist, the chaplain, I mean there are all these other services.

So I would say that I think it's a subgroup. The question is who that subgroup is and the question is what would that subgroup benefit from, to mitigate any experiences, negative experiences that they're having as a consequence from going through false positive or an uncertain.

DR. CALONGE: Ash?

DR. LAL: Thank you very much. I wanted to say that the uncertainty with diagnostic results is certainly seen in the setting of newborn screening but probably more prevalent outside involvement and because of more extensive use of genome sequencing and not understanding completely how to interpret those results.

So the problem is, more than just newborn screening I think the solution probably has to be found and I know people are trying but there's two things. One is the and I believe that's my question, is the fact that--where this news is delivered, when

we do genetic testing outside of newborn screening. The patient and parents are already prepared ahead of time with the ordering of tests. It may come back and there's some pre-canceling that goes with it. That isn't the case as far as I know with newborn screening it just happens. It's one of those things that's going to happen with a birth of a child and you'll get the result.

The second is how there could be better understanding of the phenotype by the clinicians and can there be something that can prepare clinicians How to convey the news about uncertain results to families? Thank you.

DR. TARINI: Excellent question. So the first one is uncertainty is not new to newborn screening. It can occur in any actually facet of life and in fact if you read the sociology literature, there is much more uncertainty in medicine than we may recognize on a daily basis, and certainly there is such in genome sequencing. The point being but you are prepared to some degree. There's a bit of a "blind side" potentially going on in newborn screening. That is true.

I can tell you from, remember I told you today from the first survey where we asked about experiences. A significant proportion of the parents knew the newborn screening happened, more than we thought, I don't have the numbers off the top of my

head, they can tell you they saw it. Now sometimes they say they saw it and they didn't see it. They saw a heel prick and it was for glucose or for bilirubin or they bought the prenatal testing and that's a whole separate study we had, a separate sub-study we have, but more than we thought remember it being done. Which I see as progress when I sat as a liaison on this Committee people were like "what, what happened in the hospital?"

So potentially there seems to be improvement of knowing that it happened. I actually think, something that's not been discussed, is a new problem within that is they know it happened and many will tell us, but they left the hospital and they said it was normal. Which unless you live in Iowa, we know is unlikely or if you're in the hospital for four days.

So they--they know it happens but they're not aware that it's not yet over. And I can tell you as a practicing physician who's worked in the nursery, most of the time when the child leaves the nursery we say "make sure you get their yellow and weight-gain, yellow and weight-gain" and we don't say anything about this test that's called the newborn screening. And I think that's an area which we've not really looked at where awareness really needs to go because it carries the "it happened. I'm waiting for it." and so the parents are then aware of these other situations where there's this test outstanding

So that's, that's what I believe the next challenge is, that we haven't really discussed that we've seen in our surveys and in our interviews. To your second point, remind me, it was about the severity of the uncertainty?

DR. ASHUTOSH: Yeah, I think that there probably needs to be, there's already efforts to prepare the clinicians to--

DR. TARINI: Oh, yup, yup. And so this actually and maybe you should sit on the study section, is the basis for our next project, currently under review. Which is who should be telling the parents? What should they be telling them and how should we prepare them? My plug would be we spend an awful lot of time devoted to the testing and how it occurs. We spend a paucity of time related to how we actually communicate the results which I believe have significant impact, sometime rivaling that of the testing accuracy.

Of course a test must be accurate but we sort of leave the results of like "anyone can communicate them, it's fine". And we're doing this in a fragmented health system where we've chosen that generally the general pediatrician is the one to do this. That choice I would argue, is based on faulty assumptions currently. Some of which may have been true decades ago but are no longer the case. Primary care continuity is eroded. I can say that confidently

as a physician. The likelihood that you see the doctor, first of all the likelihood that you you're with the same practice, you knew the doctor ahead of time, low.

The likelihood you see the doctor post your child's birth, your doctor and your child's doctor, low. The likelihood you see a doctor you've seen before, low. So this idea that this trusted Norman Rockwellian physician descends upon you and carries you warmly through this process is a myth, number one.

Number two. We started this journey into newborn screening when there were 5 disorders, some of which were unknown, PKU, to the physician but many of them, congenital hypothyroidism, sickle-cell, they may have been rare but they were not unfamiliar to the primary care physician. Now they can barely pronounce them so they are both and unfamiliar and we continued with this idea that they can relay the information to the parent in a way that is accurate, consistent and answer their questions and prepare them.

And then we're going to add genomics on top of that, which we already know primary care physicians are not good at and acknowledge that they are uncomfortable with. And so I think we're going to need to take a step back as a community about how we think these results should be communicated because I

think you're spot on about the provider's roll in communication and the family's experience.

DR. CALONGE: Jeff?

DR. BROSCO: So, thank you, Beth. I think we'd all agree that this is critical research for what you think is going to make things a lot better. So thank you.

Following up on Kyle's question tying now to the first presentation, it would be hard to do this by condition, by condition, by condition?

DR. TARINI: Correct.

DR. BROSCO: So do you think as you're presenting your results from both studies, it should be able to sort of figure out, you know, there's some--one of the factors that might lead to greater or lesser harm?

DR. TARINI: Yeah, I think this is, in medicine we--we have categories and we believe those categories always following through, like medicines based on organ systems, but that's not how disease really happens and so we then have to adapt.

Similarly and understandably and intuitively we think these are based on conditions, right? Because that's how we see it, hypothyroidism, cystic fibrosis, sickle-cell. We learn them in categories in that way. It's not clear that the parents can remember or see them so I don't think that--first of all it's prohibitive unless the NIH is going to give

me 20 million dollars to get a sample size big enough for all conditions and it will take like 30 years for some of the most rare.

I think instead the issue is that—the factors that you say are at play is what we believe are the messaging to the parents of urgency, of severity.

And now we believe we had started to say we were going to use SIMD urgent time/urgent and time sensitive cut, but then we, everything was hunky-dory and then we went to the states and they said "Well, we don't actually use that necessarily." Or there's a disorder that could be on the time urgent, time sensitive or the time critical--it depends on what the level is.

So now when you try to apply even that concept at the level of the state, it falls apart. So you have to ask of the state how it has devised it's time urgent, time sensitive, time critical and that's sort of what we've done. That's the factor we've generally used. We could also explore other factors if people have ideas.

DR. CALONGE: Melissa?

DR. PARISI: Thank you, Beth. And thank you for the shout-out for NIH funding.

DR. TARINI: And NICHD.

DR. PARISI: We know that this research is really important and appreciate all your efforts in this space and we're certainly looking

forward to the outcomes in your study. I was reflecting as you were talking about potential differences. I don't know if this is going to be born out between a mandatory public health screening program and consented research projects and I'm thinking specifically since Melissa Wasserstein is on your advisory board and is leading your Screen Plus Project in New York and even Wendy Chung's Guardian Project in New York state as well, where they are gathering, probably not the same level of data that you are gathering but really trying to survey those families who voluntarily choose to participate in accessory newborn screening projects or in genomic sequencing in the case of the Guardian Project.

And you know, whether there are differences in the characteristics of those parents first of who consent and their experiences with getting an uncertain result. Just thought I would throw that out there and ask if you've had any opportunities to compare your study with theirs?

DR. TARINI: I do not believe that Melissa uses the PSI in terms of the quantitative outcome but I could check. I think I had a conversation with Dr. Goldenberg who I should mention is the co-PI with me of the Uncertain Project. He is also on Dr. Wasserstein's project.

We certainly could compare the qualitative experience certainly. I mean, I think this gets back

to the question about preparation, right. I mean and ultimately from a public health perspective these are not going to be, well the question is what is the paradigm in the programmatic implementation and if we do it in a continued mandatory setting then we of course may not have a full understanding.

Now that's to say we think when someone consents, that they know what they signed and I could argue that that's not necessarily, I mean, you're incrementally--your likelihood of understanding is better and being aware but it's not of course, full on when you move from a study to a consent in the hospital setting.

So you, I also would argue, fall off a little in your likelihood of understanding when you go into a soft consent of a hospital procedure or hospital testing. So it will be interesting seeing, we're more than happy. There's, it is not an accident, she sits on the panel. [Laughs] She has been wonderful.

DR. CALONGE: Michelle?

DR. CAGGANA: Hi Beth. Michele Caggana, member. Great talk.

I'm intrigued by the signal. So from a newborn screening perspective, we do a lot of work within the program in the lab to reduce the number of parents who are in the situations that you're studying. We developed materials for providers. We talk to parents when they call upset.

So from a, I guess the question is how do you control, and that's not probably the right word to use, but the signal, right? How are parents being told, you know, with the right urgency, with the right message, at the right time? From a program perspective how can we assist you?

DR. TARINI: Yeah, I feel for you. [Laughs] Because, I suspect, and I've talked to a lot of programs, that the faxes end up on the floor. Or the websites are not necessarily clicked on or it's the parents who are clicking on the websites, who are clicking on the websites often and I think the challenges, you are trying to put this control through another human being.

As parents know that's sort of not—when you're trying to channel through another person it doesn't necessarily go the way you want. And then you're channeling through, you're trying to control or impact a process that involves at the state level, thousands of individuals of which the likelihood of a repeated event becomes not rare, but uncommon.

So if I train Kyle and he's ready to go, he may not have another false positive for three years and then I have Shawn getting one. And then I'm like -- Now Dr. Farrell has tried, and has worked with some success to do an on-demand sort of assistance. So that's one way to do it. We're here for you so at least you can get to the on-demand and then get rid

of that, you've lost your edge and your understanding and your implementation skills.

Another way, which I know the programmers don't necessarily like to hear is that you do it. Because you are, and you do it for certain things. And I mean, you choose where you believe that it's most impactful that you deliver the message. And if it's a signal issue, for instance from a palsy perspective, if we find that it's those individuals who have these types of false positives and that's the effect, then and that's a risk factor, then maybe the states say "should we be the ones delivering the message" because the risk here is too high and it's not working to give it through the primary care providers.

DR. CALONGE: Sorry, I recognize that we blew through the break that you didn't have and I want to extend a little into our lunch period as well to allow for some questions from the organizational reps.

I did want to just add a couple of comments myself and one, you know, being someone who spends his professional, academic career in evidence-based recommendations, I'm excited to bring some structure to what seems to be the specter of potential harms that those of us who buy into that concept that you've sealed very early on, that ignoring harms is unethical.

Trying to fill it in with evidence and research is very important and can put some shape and some sense of magnitude to that specter, that some of us who raise in almost every discussion so I do appreciate that. I do want to point you to GRADE-CERQual if you haven't.

I'm excited about the addition of qualitative information to the evidence base and hope that we think about how to structure that in our evidence reviews going forward because it is data. It should be recognized as evidence and figuring out how to best inform our decisions is important. GRADE-CERQual does that and I would point you to the National Academy's report and our study about the use of mixed method data including qualitative data in decision making as an application, so I appreciate that.

So with my couple of comments I'm going to turn, it looks like Robert lowered his hand so I'm going to turn to Marc Williams online.

DR. WILLIAMS: Thank you, Ned. Marc Williams, American College of Genetics and Genomics.

Hi, Beth. And congratulations on some really excellent research. I concur with the comments that have been made that this is extraordinarily important.

I want to build on what Ned had just said about the specter of harms, because I think that this is a really important concept that we have dealt with

frequently which is the idea that we elevate harms which we think of as hypothetical to some equivalency with benefits. And in some sense, we've seen that reflected even in this discussion in that the amount of time that we've spent discussing harms and study of harms has basically excluded any discussion of benefits and how we actually balance those out.

So I do think it's critically important to do the research that you're doing to try to quantitate harms so that we can actually have a reasonable discussion of apples to apples which is what are the quantitative benefits? What are the quantitative harms so we can achieve a benefit as opposed to pitting hypothetical harms which are inevitably inflated it seems, in the genetics field at least, which I think Kyle had eluded to earlier with the real benefits from these programs?

DR. TARINI: Yeah, I would argue—agree 100 percent. I would also argue in the false positive sense we kind of know the benefits. We discuss the benefits when the children are--when we discuss what's the benefits of getting screened so I would push a little to say it's not a one-sided discussion of harm, of the false-positive harms to some degree because the benefits are so often scrutinized in the evidence review. Granted the point is well taken. The bones of the harms, if you will, are a little bit thin and osteoporotic if you will. To your point

about the benefits, that's why we lean so heavily on the second study on benefits and harms because we felt in the uncertain, that was important to know.

That uncertainty is not always a negative for many people. It doesn't have to be. So we have to have a much more balanced piece when we talk about the uncertain experience.

DR. CALONGE: Yeah, and I think the only additional thing I would add, Marc is that I understand the concept of elevating it to greater than the benefits but it remains in evidence review as this, this uncertainty measure and remember that deciding where you fit into a matrix, whether it's ours or the USPSTF or the old E-Gap metric, it depends on evaluating that certainty of the evidence so I think that's just an issue to keep in mind, you know, whether or not the decision is certain to be correct and at what level.

Natasha?

MS. BONHOMME: Great, thank you. Natasha Bonhomme. Genetic Alliance. Great presentation Beth, as always and a number of the points I have were touched on, but one thing I wanted to note is that I hope that this presentation of the work that you're doing doesn't just let our both federal funders as well as others who fund newborn screening initiatives think "Great. Beth has got it".

[Laughter]

MS. BONHOMME: But to really show that this could be a portfolio of work and delved into a lot of different areas across different agencies and again across other funders who are very invested in newborn screening. So there's a little plug to be able to expand this. You are superwoman but I don't know if you can do all of the research, all at once at least.

And then I also wanted to touch on the point about when--about newborn screening when people leave the hospital and then they say oh I had no idea and how interesting it would be to compare that to other situations, right?

I think no one thinks that anyone—first off, I think that most parents are like "Wait, you're actually letting me leave with this baby?" even though they look perfectly healthy. There's that component, let alone that there could be something else.

Whether that's a newborn screening condition or you know two days later they have to come back for jaundice. So I think there could be some places to compare there. Not just around genetics and genomic screening but just what happens compared to the first thing that is happening with your new baby from a medical or health perspective and we could learn a good bit on that.

And lastly, I'm really glad that the concept around the way that I was framing was not just what

are the harms or what is causing it but the how. So really back to the communication. We saw that in our studies in terms of people really saying it's really just how I got the information. Once I understood it, I understood you know, this is not great but I could actually deal with that. So that came up.

My one question is, have you thought about in terms of the study, I know it goes 'til years of age, what that might look like if we could follow up with those parents or families at four years of age, how might that be to be able to see, you know, maybe-- again, hypothesis. Maybe someone says this was a harm or however you're going to contextualize that. In those first few years but then later, maybe that has subsided. Has that come up at all?

DR. TARINI: Yes, everyone always wanted an IH renewal and so and once you have all these parents, you know, you hate to lose them because you've spent so much time building the cohort. I do think that that we spend a lot of times focusing on what happens in the infant field, if you will, first year or so of life and then it will be interesting to see if this experience for any of these parents comes back. This is a sort of comeback issue.

The example I use as a pediatrician is, for example that parents will come to me with a three-year-old girl who has a urinary tract infection, very common. So a common occurrence. And there's usually

no greater specter of why they got this, and some of the general pediatricians may remember, parents will say "Is that related to the ultrasound that said they had big kidneys when they were a baby?" Which is also, incredibly common-ish, right. And so they see these two abnormalities as linked, right, in ways that I thought hmm, I wouldn't have thought of that but I could see how you, how they would. And so they go back to something that was abnormal that I was not even in my--under my radar and that makes them anxious and overly concerned about this very common and treatable issue.

And what it portends and so that's the sort of question I think when they're 4ish--plus/minus, do they revisit this for some reason and have we not sort of inoculated them, to say it's done, it's over. And to your point about—to answer your question--and to your point about the--not happy with how it happened.

The genetic counselors will say, Kathy Wickland, a former member of this Committee, that once there's a bad experience with the communication for instance, they can go way back to all of these things. This is when it gets difficult because it might not have been a generally--all the things that happened in the process of communicating might not have been awful but once you have an awful element in it, everything bad becomes awful through that awful

lens.

And so that makes it difficult because some of this, some of the communication may just be just fine but if it's tainted at one point and at the end, then everything becomes up for--being torn at, so it becomes a challenge to sort of figure out what really is the issue.

DR. CALONGE: Deborah, you have our last question or comment.

DR. FREEDENBERG: Thanks, Debbie Freedenberg, AAP. Beth, thank you for this important research but when you were talking about the variants, not variants but uncertain significance results, it sounds like you were suggesting a paradigm shift in that primary care provider would no longer be responsible for providing information to the family.

And you know, I have some concerns, as Michele said, states spend a lot of time mitigating, putting people in those positions and a lot of time in providing education and providing the backup for the primary care physician and often those conversations happen before that primary care doc actually talks to the family, so kind of the "just in time" model and if we were to change that paradigm, you know, I'm concerned about the establishment of a longer term relationship for their primary care.

As well as the state would be involved in a limited timeframe and many states don't have the

resources to do that right now and how that would work going forward. Would that really not help establish long-term care and also the reality is, if that child were to need more care it's a physician that has to do that referral, based on the way our medical system works now. And if it's okay, you could address some of that?

DR. TARINI: Excellent question. Yes, you are hearing that correctly. There is a questioning on having a--are we optimizing the communication process in its current form?

I think this is the next area of many opinions, little data. So if you look--because we just submitted this grant, this proposal. If you look into the literature on primary physicians' communication to parents of out-of-range newborn screening results, you will see very little, now even less than the uncertain literature of direct questioning of the primary care physician's experience.

Most of what we know from them comes from other people telling us what they do or their experiences with them. Often the states, it occurred to me at the APHL newborn screening symposium, everyone was telling me about--there was no pediatricians in the room and everyone was telling me, appropriately so about all of their conversations and interactions with the primary care physicians.

And I was like well we really don't know from their end what's going on, we don't know the processes. It's all these sort of edges of the elephant. So I would argue, we cannot assess the conversation. We do not have the data to assess what's going on, we have that box of the primary care physician's office.

We have everyone's perspective on it, but the actual individual carrying out the actual communication. Which is a problem in a national mandated public health program that relies on a primary care physician to--to implement one of the most critical pieces of it. and so I think we need to know from a primary care perspective what's going on.

I think your point about research is well-taken. I think if we're doing it--it would cost less but we're doing it worse. I would argue that maybe we should spend a little more money to do it better. But I don't know that. I don't have the data.

And to your point about--I agree, to clarify. I don't think the primary care physician should be sent to the corner to sit and face the wall. I think they should be part of the conversation. They necessarily should not be the sole and/or major communicator of that result.

And I'll close with the example I use. My primary care physician sends me for a mammogram. They do not report the results to me. The results come from the radiologist. I discuss the results with my

primary care physician. They review the results with me. They discuss if it's abnormal and needs a biopsy. They're part of the care team. They are not delivering that service.

They are coordinating it in part of the care team and their lack of not being the sole or key communication point does not decrease their value involvement as a member of the team.

DR. CALONGE: Well, Beth. I know I'm speaking for everyone in the audience how appreciative we are of a very great presentation. I want to assure Dr. Bailey and Elizabeth that we feel the same way about their presentation. Thanks so much for an incredibly useful and informative morning and Leticia, can you tell us a little bit about lunch logistics?

MS. MANNING: Thank you, Ned. So we are going to reconvene here at 1:00 p.m. We'll have a shorter lunch. Just outside of the screen doors is a cafeteria. There are various food items there to the back, through a little hall there. One of the escorts can show you, there's a little store with different snack items and lunch items and drinks in there also. The bathrooms, there's bathrooms there and there. There's bathrooms on this side also and so I'll see you back at 1:00 p.m.

Federal Agency Collaboration to Improve Newborn Screening Data Integration

DR. CALONGE: If folks can find a seat, we'll get started again. I know that Shawn is, Dr. McCandless has not returned quite yet, but I think in the interest of time we need to get started. And I see Christine, if you could just unmute Christine Dorley and make sure I know that you're back with us, that would be great.

DR. DORLEY: I'm here.

DR. CALONGE: Thank you, I appreciate that. Welcome back folks, to the afternoon session. Our next two presentations are going to describe how Federal Agencies are collaborating to improve newborn screening data integration. We have presenters from CDC and HRSA.

Sickle Cell Data Collection (SCDC) Program

We'll first hear from Mary Hulihan from the Centers of Disease Control and Preventions Epidemiology and Surveillance Branch of the Division of Blood Disorders. She will be providing us information on the sickle cell data collection program.

She is a Health Scientist in the Epidemiology and Surveillance branch with the Division of Blood Disorders at CDC. She's participated in activities related to sickle cell disease and thalassemia surveillance since 2008. She currently is a project office for the several cooperative agreements

connected to sickle-cell, including characterizing the complications associated with therapeutic blood transfusions for hemoglobinopathies and the sickle cell data collection program. And so I'd like to invite Mary to the podium.

(Audio interference.)

DR. CALONGE: Sorry, Mary I'd like to invite you to the screen, how about that?

DR. HULIHAN: Wonderful. Thanks so much and thanks for having me here today to share information about our sickle cell data collection program. Next slide, please.

So just to give you a bit of a background About the priorities of SCDC are sickle cell data collection program. It's really multifaceted even though the name may have you think otherwise. You see at the top of your screen certainly data collection is that the heart and is the framework for everything we do but if that Was all we were to do, it really wouldn't lead to any outcomes or favorable aftermath.

So really data needs to be collected and put into use. That data is used to a number of different means. But community engagement and communications are two of the main ways. And hopefully at the end of the day really what we're striving to do is use this data, work with our partners work with the sickle cell disease community, to improve policies at the federal state local healthcare setting level, to

improve the lives of people living with sickle cell disease.

And as you see there on the screen there's a few different examples of each of these different priorities Next slide please. That one, great, wonderful.

And so what does our SCDC program look like? It is a compilation of data from many sources. On the left side of the screen you can see those listed. So these data sources are each accessed and utilized by the states and territories that are participating in the SCDC program. Those 11 states and territories that are currently participating are showing in the map on the right and across those 11 states I think that we are covering a little over the third of the US sickle cell disease population.

And so those states collect newborn screening data, hospital discharge data and Medicaid claims, emergency department data vital records, protuberantly death data and data from some of the larger sickle cell clinics in each of their states.

The data that's collected is individual data level data. It does have identifiers and it's because the data is then deduplicated and linked across all of those different data sets. Now the final data set that is produced is housed and maintained by each of our state partners. The only information that is shared out of the program both to CDC and to external

researchers to other states at this point in time is Aggregate level of de-identified data. Next slide please.

And so why is this important is certainly the main topic. Today we have newborn screening for sickle cell disease in the United States and in many states, we've had it for quite a long time. We do have it in all 50 states. Why is newborn screening itself not enough for individuals with sickle cell disease?

And the real reason especially here in the United States is when we look at what happens to babies born with sickle cell disease and see what happens long term. They are not receiving the care that they need. I think this graph here is a really great example of what's going on. This is data from two of the states participating in our program California and Georgia. It is broken into pediatric on the left side of the figure and adult care on the right side. And so those two states we've looked at all the individuals living with sickle cell in their state and look to see the most basic question. Are those individuals receiving care from a hematologist? This won't even necessarily be a sickle cell specialist. And what they found over the period of three years, about a quarter of the children and over 10%--A quarter of the children in California and over 10% of the children in Georgia never saw hematologist

over a 3-year period. Those are the people who know how to take care of their disease, those are the people who are trained to take care of their disease, and those are the people who could provide specialist care. That many children were never getting connected to that pediatric hematology care.

And when we look at the adults it gets much, much worse again over a 3-year period over half of the adults in California and over a third of the adults in Georgia never saw hematologist over a 3-year period. And so we need to use information like that that's collected nurse surveillance program, SCDC combined with information from all these different data sources to do a better job in Following up these individuals long-term and better understanding their health--healthcare outcomes. Next slide please.

And so what can we do with that information When we do follow it up long term? So I'm going to provide three examples. These are taking place--actively taking place and states participating in SCDC. The first is from Georgia.

Very interesting in their surveillance data. They're really, what is long-term follow-up data to do a better job of understanding pain management and care for pain related to sickle cell disease in the state of Georgia. What does that pain management look like? What are the policies surrounding that pain

management? And what can this surveillance--what information can it provide to perhaps change policies around sickle cell pain and pain management in the state? Next slide please. Another example of success is taking place in North Carolina. They're using this surveillance data, this long-term follow-up data to identify which emergency departments in the state provide the most care to individuals with sickle cell disease that have been going to those emergency departments, working with the Medicaid program in the state to administer surveys to individuals with sickle cell disease who receive care and those emergency departments.

And we're providing emergency departments with tools and education to improve the care that they provide to individuals with sickle cell disease, and then the Medicaid program is going back in and doing post-care surveys with those same individuals. So using this surveillance data to really target outreach education to improve practices surrounding care for sickle cell. Next slide please.

And in our third and final example. This is taking place in Michigan. This is a relatively new project. It is a combination of efforts from the team at the University of Michigan, who is the grantee for SCDC and their partners within the state health department. They're using the SCDC data to identify individuals who are eligible for a newly expanded

children's special health care services program in Michigan.

So this program was in Michigan created when funds were put towards the program. They identified individuals in the state they felt would be eligible for the program. It was around 400 people. By using the survey and its data they realized that it was actually over 2500 individuals who were eligible for this program and eligible for the expanded benefits of this program.

And so now they're using this data to reach out to those individuals, to their healthcare providers to make sure that they're aware of the program and to enroll those who wish to do so. Next slide please.

Okay I'm going to give you more examples in ways that this project is benefiting individuals with sickle cell disease in any particular given state. I have given some links here if you would like to learn more. We have web pages with data from the state publications, Fact Sheets. There was a recent MMWR article published, which is a surveillance summary of the program it's a very in-depth look at the history of the program, the methods the ways the data is resulting in active change in the states participating.

And we have an ongoing quarterly newsletter called “Bloodline” and that provides updates about

project-related activities in the states, including our work with the community and with policymakers. So you can go to the link that's provided there and you can click. This newsletter can be delivered to your inbox on a quarterly basis. Next slide, please.

This is my contact information. I absolutely welcome any questions you have after the meeting today at any time. We're here. We're happy to help. I will now turn it over to continue the conversation. Thanks so much.

Implementing the Blueprint: Implications on Newborn Screening

DR. CALONGE: Thanks Mary for a great presentation. I hope you can stay around for the question and discussion period. We're going to turn now to Jeff Brosco. He's going to talk to us about implementing the blueprint and it's implication for newborn screening.

Jeff, we know is a historian pediatrician. He serves as a director for the division of services for children with special needs here at HRSA In the Maternal and Child Health Bureau. He also continues to teach and practice General Pediatrics and Developmental Behavior Pediatrics at the University of Miami, Miller School of Medicine.

For over two decades Dr. Brosco has had a series of leadership positions for the Florida

Department of Health's Children and medical services and previously served on this Committee. So I'll turn things over to you Jeff.

DR. BROSCO: Thanks Ned. How many of you heard or read the sentence that newborn screening is one of the most successful public health programs over the last 50 years? Everyone should be raising their hands. How many of you have wrote that sentence as well?

[Laughter.]

What I meant to do now is answer a couple of questions or lead towards answers of things that although we say that we don't have a lot of evidence that the programs, actually we've evaluated them and do so in a continuous way, especially with long-term follow-up and that individual children may get identified.

But do we get the treatment they need? What I'm going to try to do is talk a little bit about the blueprint but connect what we heard earlier today from Don and Elizabeth and what's to come next from Mary on sickle cell disease and then lead into my other CDC colleagues, Amy is going to join us and Carla.

I'm going to go faster through the blueprint part. You guys heard Dennis Kuo talk about the blueprint. One of the questions you asked were what's new about it? And what do we do about it? So I'm

going to try to answer those questions for you today.

I'm going to start with connecting to what Mary just said. This is an editorial that came out in pediatrics about a month ago and it's extraordinary. Right, that almost half the kids we identified from newborn screening don't get disease modifying treatment. Right, this is--We can't let this go on. This is where we are right now with our system of care.

So part of our responsibility especially at HRSA, is to make sure the system works especially if we identify a child in newborn screening that we then make sure that they have access to the care that they need. And what are the things that we do now the program set we do at HRSA is we have these treatment demonstration programs.

We have a bunch of clinics that are funded, Dr. Lau is one of our PIs, and we try to make sure that the children are receiving their care. We also fund community-based organizations and try to help families get from newborn screening to a treatment center that has center of excellence ratings. So that's kind of what we're doing. A very small part of it but I want to show how this connects to the bigger part.

So remember that the children who were part of the newborn screening often fit into this larger category of children with special health care needs.

Many of them have developmental behavioral disorders. There's a whole list of medical disorders. There's actually 13,000 more conditions that fit into this broader category. Pediatrics is really full of very rare extraordinarily rare conditions that complicate it.

So how we put it all together is that the children who have these conditions tend to have more, more in common with each other. Then they do with children who don't have a special health care need. So the CYSHN population is what many of us deal with and that's where this Committee is sort of located in the federal government, and it's defined as a child to as basically more healthcare needs, more education needs, more therapeutic use than a child typically needs.

The blueprint for change started actually 3 or 4 years ago, you've heard this already and really involved families, subject matter experts inside and outside of government, public health folks, who basically said "Where are we going, what do we need to do?" And out of that came there – I think eight different papers. Any of you tried reading these back-to-back? I did. It's completely and totally overwhelming.

There's like 12 principles, 40 strategies. It's extraordinary what we put together. It really is a beautiful idea of what the system could be. But

it's a bit overwhelming. So one of the things we tried to do was try to make a little -- sort of we put in these categories of quality of life and access to services, financing health equity.

And it's still a little bit complicated to go through all those things. So we, these slides don't move really fast, do they? And go. Oops and now it's gone all the way. One more. Okay. So what to do about the blueprint we've been doing access to care and finance for decades.

And getting further along we certainly have made some progress. What's really new about it are two things. Quality of life and equity. What families told us Over and over again is we're really glad you're measuring immunizations and hospitalizations and missed child care visits.

What really matters to us is -- is my child going to school. Are they playing? Are they happy? Are they thriving? And in fact are the caregivers doing well, right because caregivers are very useful for understanding. If they're doing well then probably the children are doing well or vice versa. If the kids are doing well, they're probably doing well.

And the second thing they told us is they wanted to make sure that we're reaching every single child. That equity is critical for the work that we do. So how do we put this together? We took that

whole big blueprint, those 40 strategies and everything else and said it's pretty simple. We want to make sure every child gets the services they need so they can play, go to school become a healthy adult and so that grownups and siblings will be thriving too.

So how do we do this? We want to measure what matters. This is good old-fashioned public health and this is how it's going to start linking in to the earlier presentations and where we are with newborn screening. One of the things we said was yes we want to measure what matters, quality of life. So we wanted this maybe kindergarten readiness, healthy weight, reading at grade 3, successful transition to adulthood. The range of things that most of us are important to our kids. And it would be great if we were using these measures across our grants, our managed care organizations, Our Title V and so on. We also think that we need at least one condition specific measure. I'll share a couple examples of that in a minute. In part because we want to know how that particular group of children are doing, but also especially for children with intellectual instability, autism.

These may or may not be -- the universal measures may not be the best ones. The big league too though is to look at the population level. And for a long time we've been asking of our grantees is: how

many trainings did you do? How many children did you reach? How many families did you talk to? But that's just a numerator. The denominator is often huge.

So what we're trying to do now is we want to know what percentage of children are reaching this level, whatever that's success level is. And in fact the equity part comes in because we want you to take that same equation and look at it--just aggregate the data based on historically underserved groups.

Whether it's rural status, race, ethnicity, limited English proficiency, whatever that may be. And then think about accountability not in terms of We're holding you responsible for the outcome, but we're holding you responsible for monitoring, planning, and then reconfiguring your approach. So one example is in deaf and hard of hearing infants. So probably many of you know that this is a key part of newborn screening. And we fund at HRSA an EHDI coordinator in every single state to help make sure the system runs well.

And we have been focused mostly on the 1-3-6, Were they screened by one month of age, get a diagnosis by 3 months, and we're connected to Part C early connection by age 6 months. But what we really want to get to though is language acquisition. Age 3 is probably a good time to measure that as you heard from Dr. B and his colleagues, that's when Part C goes out too. And so it's a good time to know.

Because every child who's deaf and hard of hearing should be in a Part C program.

And if we work closely enough, this is where the data integration comes in we should know what percentage of children who are deaf and hard of hearing in each state has language acquisition and the average clinical range. So think about what this does then. It tells our EHDI coordinators, it's not just your job you can't possibly drive every kid to the clinic and make sure each child gets everything they need. You can't do that alone.

But what you can do is convene stakeholders in the state. You can put up a pipeline like this you can show the numbers and say where are the leaks in the pipeline in our state. Is it at the 1-3-6? Is it a matter of audiology screening? Or is it at the early education site, Part C program? Where can we work together? What's our strategic plan for improving outcomes, and can we show them over time the percentage of children with the average level of language acquisition continue to go up?

And again as I mentioned just aggregate the data based on key things like race, ethnicity, rural status, whatever it may be in your state. So we think by doing this we can measure quality of life and get to equity and have a continuous quality improvement system. So that's the deaf and hard of hearing.

I'm going to remind you I'm going to run

through these slides. This will look familiar. It's almost like PTSD for some of us that have been doing this a long time, right. So these are the slides that we show every year about how this Committee has been saying we have to do long-term follow-up, and follow through, and we've got all these publications and we've got this incredible work. I think Cindy Hinton's here right. Look at this, doesn't this remind you of something?

We've been saying for 15 years we need to have a system like this right? So where we are now is we think that it's time to actually do this. And so we are taking first baby steps towards this and I think about it in a very simplistic way. And that is if there's three buckets of data, and the first bucket of data is kind of what happens in the lab. And when you get a result does that result is it a yes? Is it a no? Understanding there's false positive and uncertainty. In a few minutes Amy and Carla are going to talk to you about Ed3N, and how that bucket can really be understood and data analysis done at the CDC can help states decide yes or no the risk analysis. I'll let them talk about that.

The second bucket is about notification confirmation and that is letting the family know and physician know and the clinical team know, confirming that they're going to do a diagnostic workup.

And that third book is a long-term

longitudinal clinical care that we've talked about for a long time. That's where public health surveillance fits in. So just to remind you that the data matters between one and the other. And that is for Ed3N lab analysis things to kind of work, you actually need to know well did that value of 12 turn out to be that condition or not?

So you need to have some feedback from the clinical bucket two to bucket one and okay three might even be helpful too, right? Because if you have that then you know about late onset conditions and how children do over the long term. Once they allow bucket number two we spend a fair amount of time on this Committee talking about new steps, and figuring out how to improve timeliness, and as you know through Propel and Excel, we are, hopefully very soon.

I'm looking at Alisha to see how soon, but we're thinking about very soon, which states are going to be starting to fund the work on implementing the conditions, short-term follow-up and long-term follow-up. So our goal is to make sure the states have at least some of the capacity to be able to do this.

And then bucket number three while you heard just now from Mary Hulihan about one particular condition which is sickle cell disease. But there's also a fair amount of long-term follow-up happening

in the EHDI deaf and hard of hearing world. And there's something happening with other conditions.

But they're sort of haphazard. And we in HRSA also fund about five or six different long-term follow-up projects and they've done some remarkable work putting together and saying okay it's just a graphic for how we think of long-term follow-up data--But we want to have we have state public health evaluation things we need.

And in this clinical follow-up did that particular child get what he or she needs and then there's research needs. You--this kind of Venn diagram shows you that sort of core set. So what we'd like to start thinking about is how do we connect buckets one and two and three and have an infrastructure that allows us to do this so that there's information going back and forth. We think this is a long-term project. But we want to get started We want to get the first steps going.

I didn't realize this was one of those cool slides it does all those things. Keep going. So what are we aiming for? In some ways we're already doing this well. And hemophilia is a really good example. We know the treatment makes a difference. And CDC currently now has a program called Community Counts. And so not only do they measure things like joint bleeds, because if you have fewer than four joint bleeds a year that correlates with levels of

ability/disability but they're also looking at things like high school graduation.

And you can see that by continuously monitoring it. We at HRSA fund programs to make sure that they are doing quality of care, that they are doing the training that they need to do, and they're getting pretty close to reaching all the kids in the United States. So it's getting closer to percentages and not just numbers. So it is possible to do this. So in conclusion what we're hoping is to be able to work together with the federal partners, create an integrated data system that over time starts to link these different pieces And it starts with a kind of public ideal. If we're going to screen a baby for a condition, then we have some responsibility for knowing whether the program is working and the children are getting the particular treatments that they need.

We need to make sure that every child is getting what they need so they can play, grow into a healthy adult go to school, have friends, all those things. So thank you.

[Applause]

CDC's Ed3N Project

DR. CALONGE: Thanks, Jeff. And lastly, we're going to hear from Carla Cuthbert and Amy Gaviglio on CDC's Ed3N project, which stands for enhancing data

disease detection in newborns.

Carla is the Chief of Newborn Screening in Molecular Biology Branch in the Division of Laboratory Sciences National Center for Environmental Health at the Centers for Disease Control and Prevention. She has been in this position since December of 2009. She serves as a CDC representative on the ACHDNC and is a co-chair of the inner agency coordinating committee on newborn and child screening Which provides input to the secretary at the HHS on national newborn screening discussions.

And her colleague Amy Gaviglio currently works with the CDC’s Newborn screening Molecular Biology Branch, the Association of Public Health Laboratories, inspecting health and several other genetics and rare disease organizations. She's a certified genetic counselor and founder of connections consulting which provides public health genetics genomics and rare disease services across the country. She's been working in the newborn screening and rare disease space for the past 15 years. She co-chairs APHL's new disorders in newborn Screen works group and there's a member of additional national groups. Finally, she serves as the Chair of the NBS Expert Panel for the Clinical and Laboratory standards institute and is currently the chair of Minnesota's Rare Diseases Advisory Council. So, we welcome you both, and Carla.

DR. CUTHBERT: Thank you for having us. We're really excited about being able to present on our Ed3N project. This has been a passion project indeed for us. We have been working at it for a very long time as you will find out. So, I'm just going to give a bit of the overview. Amy is going to be able to go a little bit more in depth about where we are, to just sort of skirt over the surface of what the project is and what good it will do.

So again, the whole idea behind this project has been something that--that started many, many, many years ago. And you know as again, branch chief, we have an excellent team of scientists to work with the States, But I'm always trying to think what's going to happen in the next 5 years.

How can we as a branch position ourselves to really meet the need. And this part of this slide actually refers to the presentation I did in 2013, 10 years ago when we were celebrating 50 years of newborn screening and really the big question is what do the current challenges tell us about what we should expect for the future and how can we know what to do.

So again we're plagued with the goodness there are more conditions, more complexity. We have more testing and so on. And so that became part of the foundation for one of the issues that we wanted to be able to address as we move forward. And what we

understood was that there are a number of programs, as we're generating more and more data, the data handling is going to be a very significant issue that we would actually need to deal with.

So over the course of the last couple of years, from in 2017 I remember very clearly pulling aside people that I could find in corridors and asking them how are you doing, how are you managing data, is this a thing? And from that moving on to other discussion. What's a programs in workgroups and Committee meetings, we eventually had no meeting in 2019 where we really wanted to have a discussion on data science is it applies to newborn screening with the idea that you know, there's an opportunity for us to be able to think about how we can incorporate some of the practice of data science into our workflow, to help make our test better, to operationalize and how to make some of the tasks of what we're doing and just to be able to handle some of the data a little bit more effectively.

So, during that time Ed3N was essentially defined, and we were able to start the development work and do some of the pilot testing and so on. We put 2028 as a full Eco Live, but again I'd like to put some caveats there. We are a federal government.

We do depend on funding and we depend on every-- everything else moving forward. So that's the tentative goal, in 2028. So in terms of identified

gaps and so on that we identified during this process we do acknowledge that there's been challenges with respect to harmonization between states and testing practices with respect to data output and capacity and then it inadequate number of data analysts to be able to support this activity an operability specialist and so on.

And there is a disparate amount of ability and resources for our programs to be able to analyze some of the screening data and to improve performance. Not to mention there are silos, one off instances, and so on between the programs and other-- other relevant health programs.

So that being said, when we had the 2019 national data analytics meeting, the session lead did ask the question -- a series of questions, there were a number of questions that we were asked, but they asked for some of our thoughts on the need for some kind of national newborn screening data platform.

And I won't go into it in detail of course but you know some of the general points the majority of the respondents that shared what's --that they felt that it was important, data analytics, and that sort of thing. That they would probably use it about at least weekly but it should be housed at CDC and that deidentified level, individual data especially in the realm of clinical diagnosis and so on, should be included.

So taking all of these things together the discussions that we've had, the data that we've reviewed and so on, we embarked on creating What is now termed Ed3N. It was called the data hub for a very long time until my boss told me you can't use that word because CDC is making a data hub so you can't call it that.

So conveniently we were able to come up with this particular name and of course it stands for enhancing data-driven disease detection in newborns. The tool the platform really aims to improve risk assessment with newborn screening that would allow for more timely diagnosis and intervention and newborns that are truly at risk for increasing numbers of diseases.

Providing a tool to newborn screening programs, we would hope that it would decrease disparities across newborn screening programs in terms of data analytic capabilities, which should also translate into better screening experiences by parents, by families across the country.

So those two aims would be cheap through Ed3N making this fully supported tool available to newborn screening programs. We would expect that this should increase our capacity and infrastructure as a nation, to collect aggregate and analyze newborn screening data without placing an additional burden on newborn screening programs that are already stretched then in

trying to perform their own day-to-day activities.

So understanding the potential for Ed3N as a tool and we were able to sort of ride that wave that CDC has been recently on. We started the conceptualization of this project just as CDC was getting into data modernization. It was so convenient. One of the nice things that has happened as a result of this, we tried to put our project in front of as many people as was listened and were very glad to let you know that we were one of eight programs identified in the non-infectious disease center to be selected for accelerated modernization of an IT system.

So it's different, it's new. I'm excited and we get to benefit from some CDC resources that they're actually creating for the rest of the agency.

Amy's going to continue with a little bit more about what it is, and will help to define just where we are.

MS. GAVIGLIO: Thank you Carla and members of the Committee, so as Carla mentioned, my job today is to take us a bit from the abstract in Ed3N into the actual where we are.

So Ed3N actually exists. We have built much of this. This is a screenshot from the landing page of the Ed3N platform which as Carla mentioned is a web-based, cloud-based platform. You can see that there will be three essential modules within Ed3N so

we start with our evaluate module. This is the module that I'm going to focus on most today because this is the piece where we really envision programs putting their data in and really using it, potentially in their day-to-day to get a holistic look at the patient centered newborn screening process.

The middle area is known as explorer and this is an area where we would incorporate aggregate de-identified data from all other programs. So this is an area where we can really start to look at things like novel biomarkers, QI metrics, more on the diagnosis piece so really where we can actually start to look at our data pool together as a country, which of course is very, very important since we are talking about rare disease.

And then the third area is what we're calling the educate area. So we want to make sure that as we're incorporating more data analytic tools and as we're talking more about these different kinds of algorithms that everyone feels very comfortable with what's going into it. That they don't feel like this is a black box that we have the utmost transparency into what we're doing behind the scenes in Ed3N.

But again for the remainder my talk will be focusing mostly on this evaluate portion. So as we delve into that, you can see that the evaluate portion in and of itself will also have kind of three modules that will capture the three main buckets of

data that we get in newborn screening.

Although I'm going to be talking about them as though they are separate. I want to point out that they will all be integrated at the patient level. This is going to be the beauty of Ed3N is that we can actually look at the things from a patient perspective. We're not going to be just looking a biochemical data separate from the regular data, separate from clinical data.

But will collect all pieces, or those three pieces of information, understanding that you the utility of Ed3N, the utility of any data collection system depends on how easy it is to get the data in. We are looking very heavily at not doing any manual entry. We will be looking into using and leveraging things like HL7, FIRE, getting this directly from newborn screening laboratory information management systems, or LIMS or case management systems that will be transferred securely and encrypted into Ed3N, where you can have near real-time patient data processing analytics and digital visualization, with the ultimate goal, as Carla mentioned, to modernize and improve our ability to do risk assessment in newborn screening but also to just have a better understanding of how we are doing with newborn screening overall.

So for the remainder of these, I'm going to kind of delve into each of the modules separately and

I'm going to start with molecular module because interestingly it is the most well-built out for us at this point and we have worked quite a bit with the newborn screening community on this, particularly the CDC-APH on molecular subcommittee to examine what the current workflows are, to do the requirement gathering and to actually do some beta testing and pilot testing.

So you can see here that some of the challenges that have been identified and the idea of bringing more molecular, especially sequencing data into newborn screening is the idea of having to interpret these variants and especially having to interpret them in the context of having no phenotype.

The idea that we -- you know, the need to curate this data, the need to have more collaboration across programs so you can see what other programs have picked up and maybe how they have interpreted that as well and then again I'm going to kind of keep highlighting the idea of this ability to link the molecular data back to the biochemical data and clinical data so we have that full patient picture. So when we are done with the molecular module which we hope is fairly soon, ultimately we will be able to provide an end-to-end solution for programs who want to incorporate sequencing into their newborn screening programs. So we will be trying to give them tools to make this easier and a bit less scary to do.

So we've been working with our office of advanced molecular detection at CDC. They have an offering called LIMS Lite so that will provide some of that wet bench processing as well as the bioinformatics piece for them so we are in the process of validating that right now. Programs who already have their own bioinformatics pipeline, they can plug it into LIMS Lite if they want or they could just start at the point of Ed3N which is where you would really put in your variant identification or your variant call files and we will actually walk you through the variant interpretation process.

It is a -- we are bringing in all of the evidence that you would normally need to do that interpretation into one place. So it's all in one place. It gives you all of the data on that variant and really kind of walks you through it in a really easy way. You can also see if another state has detected this variant and how they have interpreted that as well.

We will of course, you know, we don't want to continue to silo data by creating yet another platform that doesn't speak to another platform so we are very keen on making sure that we are contributing to the greater knowledge base, so providing this information, the ClinVar. We're also looking at using tools that provide some of this curation and especially the literature search functionality

directly for the programs as well.

We move to the biochemical module and so much of this I think is not going to be surprising to any of you in terms of challenges. We've heard many of this in discussions in terms of variability and cutoff determination, challenges in harmonizing data. Just the rarity of the diseases make it very difficult to decide where our cutoff is, decide what our algorithms should look like and obviously always our goal is to minimize false negatives while keeping false positives low.

So we are continuing to kind of work on -- on this right now. I want to acknowledge that we are looking to use data analytic techniques like machine learning to try to improve this. We know that there are other systems out there that are looking at this, have looked at this, have implemented different ways to improve risk assessment for biochemical analytes. Rest assured we're looking at ways to leverage those existing tools and kind of bring everything into, into one place as well so. Biochemical continues to be worked on.

The last one that I'm going to talk about today is the clinical module and though I am talking about it last, I think this is perhaps the most important module that we need to think about because it's really important for us to understand the outcomes of our testing in order for us to actually

improve our testing.

And so for the clinical challenges of course we've heard many of these again. States are collecting critical data elements. It's very hard to get the clinical data. We still rely very heavily on faxes. There's really been a lack of a coordinated system for the capturing of clinical data over time and you know, again that ability to link that clinical data back to biochemical and molecular data. Even within programs the clinical piece is actually siloed from the lab piece.

So this is a schematic of kind of our vision of the clinical module, which gets a lot into kind of what Jeff was talking about as well. I do want to say for the purpose of Ed3N as our kind of use case no. 1 is just to get that diagnostic data.

Again, we want to make sure that we know what of these cases were deemed true positives, false positives or maybe to Beth's point, uncertain prognoses but so we want to look at a way to seamlessly, electronically get clinical data directly from the medical system to state programs and from state programs to Ed3N.

I put in the bottom here, just an acknowledgement that there's a lot of work going on in this space with a lot of federal partners but there are a lot of mechanisms like e-Case recording that I think we really need to look into as ways to

getting this data more and more.

And this, if we're able to build this for diagnostic data I think it's a pretty easy leap to think about how this could be expanded to think about collecting data a longer term as well.

Certainly, I think we can't talk about data use aggregation collection without talking about data privacy, especially in the case of a mandated program so this is something that has and will remain front and center of all of our work with Ed3N.

So first and foremost any program that is going to be using Ed3N and contributing to Ed3N will have to sign data use agreements. These have been approved already by CDC's Office of the General Council. We are in the process of ratifying these with several newborn screening.

We do have several newborn screening who have already signed data use agreements thus far. We did just receive word that we passed or got through the paperwork reduction act process, which, despite its name is a ton of paperwork.

[Laughter]

So that was very exciting but essentially that means that we can now work with all programs in the U.S. to really make this happen.

The last bullet point might be kind of a newer topic is we think about how we actually link some of these records in the concept of collecting

deidentified data. There are some really cool, nerdy technologies out there now called privacy enhancing technologies or privacy preserving record linkage. Big movement in the rare disease space on this as we think how to collect data and maintain privacy. So we're looking at some of these newer technologies so that we can maintain privacy but still really get the data and outcomes and understanding that we want.

So I think this is our last slide and just again to reiterate what Carla said that this is absolutely a passion project. I always think of this as Carla's baby and I'm the babysitter. But we really feel that what we are doing is exactly what is needed. We have talked about this for so long and we are very excited to be starting to actually build it.

So with that, happy to take questions.

DR. CALONGE: Thanks Carla and Amy and now we'll turn to discussion. As we get started, I think one of the areas of success of this particular community is the representation from other national groups in the membership and I will tell you my experience in other areas, working with federal government across agencies, we're doing a little bit better in newborn screening than perhaps in some other areas. And that's very rewarding and exciting to see.

I want to congratulate and thank the people from the different agencies who work across

organizational lines in the interest of public health in this very important area of newborn screening so I thank you for your commitment to that and I wish it was true of all interagency activities at the Federal level.

That comment being made I'd like to see if there are any questions. Remember, we heard three presentations, one on data gathering around sickle cell disease, then HRSA's approach of trying to find a system of--to support long-term follow up in the interests of actually meeting the proposed benefits of newborn screening as a system. I'm reminded in looking at Scott that I think thinking about Jeff's presentation reminded me that we almost always focus on the labs and that that maybe not the right area of focus because without the rest of the system, the follow up then all we do is generate positive tests without actually translating that into health benefits.

And then finally Carla and Amy talking about the CDC program. And I'll start with a question, seeing none yet, which has to do with will you be thinking about supporting the uptake in implementation of Ed3N with cooperative agreements to states that's often one with a lot of other data issues?

DR. CUTHBERT: So cooperative agreements in as much as we would be funding the state specifically to

put money in, again we'd be happy to do that and HRSA is doing that [laughs], so one of the nice things about being able to leverage the different federal partners, we have different areas that are fairly discreet and I think I can say that, and Jeff you can jump in here too, is that we'll be building the infrastructure leveraging some of the agency resources but certainly being able to partner with HRSA with them being able to fund some of the States in this regard. It's going to be very, very helpful.

DR. BROSCO: Yeah, so we definitely rely on Carla and Amy and the CDC lab folks to do the hard work of figuring out the data analysis stuff and we through our Propel grants, we will be supporting states to work on follow up data, both short term and long term and working directly with Ian. So the answer is yes.

DR. CALONGE: Thanks. Natasha?

MS. BONHOMME: Natasha Bonhomme, Genetic Alliance. Great presentations everyone. My first set of questions are in regards to Ed3N. I have so many sheets of paper here. Let me make sure I find it. I really appreciate that one of the aims is to decrease disparities across state programs and the family experience. I was wondering if you could add a little bit more context to how we would know we have done that on the family experience side. I think that is something we are always hopeful for but now, you know,

back to what Jeff said in terms of measure what matters, how will we do that so we get that so we see that full story? And do you see that as a part of Ed3N, part of CDC? All of us doing it. Just your thoughts on that.

MS. GAVIGLIO: Yeah, it's a great question and I think some of it is looking at the--you know, the potential impact on both false positives and false negatives and not talking even the psychosocial piece but just having to go back in to, to get a repeat specimen. Having to go back in and go to a clinical evaluation so in some ways if we can have more kind of parity around just the numbers of false positives and negatives that states are putting out by using better data analytics in the context of second tiers.

In theory, we think it will make less of an impact on families but there is so much more that goes into the family experience and I think that's highlighted a few things really well that may be a bit outside the scope of Ed3N in terms of--I could not agree with her more on the need for better communication and those things as well. But from this perspective we were kind of thinking of it in terms of you know, not putting people into the system who don't need to be put into the system or making sure people who do need are being detected. That's kind of the scope that we were thinking with that particular statement and I think Jeff wanted to -- or you have a

follow up?

DR. CUTHBERT: Yup. I'll just jump in very quickly and just say that for Ed3N as well, which this is just a data analysis and IT, we still have the rest of the branch that deals with methods and so on so this information is going to feed back into our algorithms and methods so that you know, it will influence whether we're identifying what we really want to identify and can help with the quality improvements for some of the methods as well.

MS. BONHOMME: Yeah, I think that's really helpful, particularly since yes, there's the psychosocial component with families but even just that which it's funny to say this because Amy, you and I talk about this all the time, what are parents actually being told in terms of even--we know some families aren't even told the right condition is out of range let alone--so hopefully this--being really helpful in that.

MS. GAVIGLIO: Sorry. I do want to comment that one of the things we really want to focus on in Ed3N and again Dr. Tarini brought this up is how important getting better race ethnicity data is as well and so I do think that's one of their focus as well as how can we, you know, help programs linked to vital records to get some of more of that data as well. Not only on race, ethnicity but socioeconomic status, education, geography and are testing

algorithms truly the best for all babies.

So I think that's another way that we hope, you know, looking at data more holistically can maybe help us start to answer those types of questions for families as well.

DR. BROSCO: So I'm so glad you raised this question. It brings up a bunch of things. First of all just to kind of know where we are. So you've heard from Ed3N. They've done a lot of work. So bucket number one, we're really moving far along. Bucket number two in some ways is new steps and bucket number three we're just starting. It’s little pieces of things in different places.

When we fund states through Propel for quality improvement, we're not telling them you must do this particular thing. We're saying to states what are the things in this category that you think are most important. And it may be what's coming out of this discussion this morning especially is, maybe family experience is something that should be included along with timeliness.

So if we include those kinds of measures, that can be a good way to do it. and even more importantly broadly in bucket number 3, what pool, if we thought about quality measures and across all of those conditions, you'd be really hard pressed, right? So joint bleeds might work for hemophilia and language acquisition may work for deaf and hard of

hearing, but what cuts across everything, all those 13,000 conditions. And it might be the single common denominator is caregiver wellbeing. And that if – if parents are doing well, if caregivers are doing well, if families are doing well then probably our system is working pretty well.

So at the sort of furthest reach, you know, we had this idea that we'd like in a year to eighteen months or something like that have a road map for how we get there, right. This is a ten-year project, five to ten years. We'd like to have a road map for how to get there. And at the end of the day it should be "is that child thriving? Is that family thriving?" So every little piece back would have to lead to that.

MS. BONHOMME: Great. I appreciate you saying that. It's the perfect segue to the question I had for you which is you know, yeah--right on. Do you see that last part of what you said as one of the —as bucket 3 or is that another bucket that we're going to be creating?

I guess another way of framing that is you know, the title of your presentation is implementing the blueprint, implications on newborn screening and this was really focused on data and I didn't necessarily see but maybe I'm just not seeing deeply into this, you know, anything that would address the current concerns that we have around newborn screening that are outside of state lab and data such

as lawsuits or even just the more general education around news.

Again, we talked about education for families who are diagnosed but families that don't have a diagnosis and who go through newborn screening also have educational needs. So all I'm trying to see if this the whole lens, a slice of it. just trying to puzzle that together from your viewpoint at this point in time.

DR. BROSCO: I admit, I'm a little confused by the question. I just stated the blueprint is for all children with special needs. All 14 million. So we really do have a much broader vision and I was trying to talk about, was it related to newborn screening and to kind of go back. We think that one of the best ways to get there is to measure the things that matter. Such as family wellbeing, child wellbeing. And that if we hold ourselves accountable to it then all of the pieces start to fit together.

So for example to use the deaf and hard of hearing, that sort of pipeline, it may be--if the family experience is the single most important thing for improving that outcome and so that might be what the EHDI program in some states focuses on. But it may also be that the real problem in other states is you just don't have the equipment to do newborn screening in the first place. So we are not trying to say that there's a specific thing that any one

grantee or States should do because we don't know the needs as well as they do.

What we're saying is, let's all aim here. Let's count to this, keep track of it. Let's really make sure that we're measuring it and hold ourselves accountable to a continuous quality improvement approach, which we hope would actually address some of the concerns you have. Because I don't know if that answers your question but --

MS. BONHOMME: It does, and I think EHDI is a great example because there are so many different types of grantees in EHDI and so many different agencies involved in that, which is a little bit similar and a little bit different than newborn screening. So I think if that's a model to be looking at that's definitely something to follow up on, so. thanks.

DR. CALONGE: Shawn?

DR. MCCANDLESS: Thank you. I wanted to ask Dr. Hulihan and then Dr. Cuthbert and maybe others, what lessons did you learn -- first this is Shawn McCandless, I'm a Committee member, what lessons did you learn from the sickle cell data collection planning? Like how did you determine what questions to ask? What data that you were going to collect? How did you engage clinicians, families, and other stakeholders in that process? And I'd like to basically ask the team from the Ed3N project what's

your plan for that same aspect for the newborn, other newborn screening conditions?

DR. HULIHAN: That's a great question. I would say at the beginning of this program, which was really about 14 years ago was when the first funding came through. It has ebbed and flowed since then so it maybe hasn't gone at quite the speed that we anticipated to begin with, but we are where we are. And it was really about defining individuals with sickle cell disease across the various data sources that we're using and so that was where a lot of the focus on the data collection was and then what information was available in those data sources, were those the data sources to collect that information.

So, for example, we have Medicaid claims data, and that gives us a lot of information about healthcare encounters, about what the diagnosis is during an encounter, what the procedure is doing an encounter. What it does not give us is laboratory values or values you know about weight, about height and so we had to really carefully consider with the data available to us was it the appropriate place to collect information.

So that's kind of where the process started. We also had a--I mean numerous meetings, discussions with people from every end of the spectrum when it comes to sickle cell disease. From people living with the condition, community-based organizations, health

care providers, policy makers, payers, blood banks.

We really tried to reach out to local organizations, national organizations about what information was important for them in order to be able to improve their care and improve their policies and where we are now is we've got a pretty good handle on those original conversations we had and the information we received but we think that there is so much more that can be included in the program and I think at this point we are trying to figure out the best infrastructure and the best really framework for including more and more and more information because there is quite a bit more that would really inform the work that we're doing.

DR. CUTHBERT: Shawn, Amy will answer that in terms of data collection. Is it more about clinical or laboratory data?

DR. MCCANDLESS: I was thinking more about the clinical long-term follow up data.

MS. GAVIGLIO: Yeah, I'll take a hit at it but I think first and foremost again, just to acknowledge that our initial scope is diagnostic data so we haven't quite put our heads around you know, ongoing, long-term data. That being said I think we are very aware and I think we need to continue to be very aware that what we're trying to do is not necessarily not all, that there are things out there that have been done and a lot of information that we can

leverage.

So we've put together a -- what I think is a fantastic group of individuals who are helping us think through this including Dr. Parisi and Dr. Caggana, Dr. Brosco. So we are looking at, and we've kind of pieced it out into three phases so what are the data elements? What do we need? And where are they, which is a really great point. Can they be matched to standards like LINKS, SNOMED, USDA, ICD, alphabet soup.

So that will be our first, kind of know what we're collecting and then we will move to how are we collecting it and we will be looking at different models out there and mentioned e-Case recording. That's more with infectious communicable diseases but why couldn't it be applied to this. So we'll be talking more to that methodology of how because for this to work we cannot be faxing back and forth. We cannot be asking busy providers, busy public health professionals to manually enter this. From there then we will talk more about that record linkage piece. So that is kind of a three-phased approach that we've identified for how we will move forward with this, if that answers your question.

DR. MCCANDLESS: I think, I think it does. I do have a question though for the record of linkage. Is that something where you're imagining the data aggregation at CDC will supplant the need for

data linkage within the state itself because I'm afraid a lot of -- it seems that a lot of states don't really have good data linkage, either to individual medical records but even between vital statistics and newborn screening.

MS. GAVIGLIO: Yeah, I don't know if it will supplant it so much as -- it probably will depend on the State in terms of what they have in terms of their own linkages but that is a potential benefit that we've talked about. With Ed3N, that for those states who have very disparate systems if we are putting everything in one place, could this now become a just really great resource for them to have data in one place as well that we would providing them rather than you know, them having to try to figure out how to link what are typically antiquated systems.

DR. CALONGE: Melissa?

DR. PARISI: Melissa Parisi, NIH. I have three comments. Some of which will be quick. First of all, congratulations on making your way through the Paperwork Reduction Act, one of the most misnamed pieces of legislation ever passed by the Federal Government. So that's fantastic and I guess my second comment is, you know, as Federal partners I think sometimes people are always amazed that agencies talk to each other and we actually do communicate and we coordinate and we've been doing this for, I'm

thinking at least 10 to 15 years.

We have monthly calls among our Federal newborn screening partners so we really do try to do things that will enhance and support one another even though we have our individual missions and mandate, we really do try to coordinate as effectively as possible and think these programs are a great example of that. So kudos to you all for putting this together. And my third comment is one sort of related to the NIH role and we typically are in the space of trying to develop the evidence base and some of the data to inform some of the development of assays and incorporation of screening programs into the rest and through that we've been able to utilize the newborn screening translational research network and some of our pilot contracts to help support screening programs in the early stages that can help inform adoption and even the evidence review for conditions to be added to the rest.

And then finally in our role as trying to provide evidence base, I was really pleased to see the slide about the Ed3N molecular end-to-end solution and thank you for adding ClinVar into the mix there. My only suggested edit would be to make Is a bidirectional arrow. And I say that because what we've been able to do through the ClinGen and ClinVar resources, which, I don't know if this Committee has heard much about these resources in the past or maybe

this would be a topic for a future Committee meeting, but essentially we are funding a number of curation panels, probably I think around 200 now and these panels of experts, international experts, basically discuss variants that are associated with different disease conditions and really try to create the evidence-base for clinical utility for genes associated with disorders, many of which are rare, genetic conditions, as well as variant interpretation and pathogenicity.

And these really critical resources to be able to interpret the molecular data, that are going to be generated through newborn screening programs as we have more and more conditions that really have as secondary tertiary level sequencing to confirm. And just to kind of close the loop on the value of this resource is that several of these, you know, several hundred panels of gene and variant curation panels involving over 2,000 experts throughout the world, there are quite a few that are focused on newborn screening conditions.

There's one for PKU, one for galactosemia, one related to Urea Cycle disorders, aminoacidopathies, VLCAD, hearing loss, congenital heart disease. I'm sure I'm missing a few. SCID. Many inborn areas of metabolism. Lysosomal storage disorders are included within these panels and there's a very structured mechanism for making those

disease assertions that involve experts reviewing the literature and clinical knowledge of experts who know this condition and applying the ACMG framework for determining whether a genomic variant is pathogenic or not.

So I think that this be a great resource that will tie in very well to the Ed3N framework and I hope enhance the ability of this resource to succeed and save some effort on the part of what you're trying to do, because it's a very labor-intensive process. So thank you.

MS. GAVIGLIO: Now I will own the misuse of the arrow in the slide, you are absolutely right. It should be bidirectional and it actually already is. We've already connected to ClinVar to Genomenon with API, so yeah, we will certainly provide information there, but we will be heavily relying on that data as we walk through the variant interpretations. Thank you for pointing that out and we'll update the slide.

DR. CALONGE: Jennifer?

DR. KWON: Thanks, Jennifer Kwon, Committee member. Dr. Hulihan, well first of all I should apologize. I am so not a high-level thinker and for me the purpose of a registry or data collection in newborn screening is really to improve clinical outcomes in the children who are identified.

So that's why I was really interested in having you follow up on the comments you were

starting to make. It sounds like you had plans where you like to see your sickle cell data collection system go. One of the things that I was curious about was that three-year data collection in California and Georgia where you showed how abysmal follow up with hematologists were.

Is there any sort of mission among the states that are participating or other states to --to have that be like a benchmark, you know, to create a benchmark for hematology follow up and to try to meet at or try to have the next iteration of data collection show those sorts of results or maybe I'm misinterpreting what your system can do?

[Static]

DR. HULIHAN: No, no, those are great questions. I think what you're describing is certainly something that the system can do and I think the, the word that curses sickle cell that the treatment demonstration program is doing is really aimed at exactly what you were just mentioning, getting more people into care with hematologists with the sickle cell experts and so I see that as being a great opportunity for CDC's sickle cell data collection and HRSA's sickle cell disease treatment demonstration program to continue what has started, what has become a very healthy and collaborative relationship and figure out how to make it even stronger moving forward.

So I think what you just described is something that can certainly come about as a result of that collaboration. But taking it a step back maybe, or maybe forward, to what you asked. One way that the data is currently resulting in-in positive outcomes. Well we're not measuring how many individuals are receiving care. We have the information, it's just not something we're looking at.

What we are aware of is the data is being used to show where there are geographic locations, that care is not received because the care doesn't exist. There are no hematologists in that region. There are no sickle cell clinics in that region and the states participating are actually taking that information to their state legislation.

New clinics are being opened so we're seeing changes in that format although it's not something that we're measuring but it is something that we intend to do as we move forward.

DR. BROSCO: And if I could add to that, Jennifer, that is exactly what the intention is. So if you think of that bucket number 3, you know – you do it for research, you do it for public health surveillance but you also want to do it for clinical care.

As Mary was saying, we have these treatment centers all across the U.S. and the goal, in some

ways it's starting to happen, is linking with the CDC so we can say where are all the people with sickle cell disease? Newborn screening in some ways is easier because you have a denominator. In theory, you know all the children that have been born, you can follow all of them and can say "what percent are we missing? Why are we missing them and how do we make sure we stop doing that?

Our programs for sickle cell disease are across a lifespan and we don't want to wait a hundred years to get to every one of them, so by partnering with CDC you know, one of our treatment centers can say well who else in our state?

Now we not on the individual level yet but as you heard we can start looking at where in the state there may be some issues. So that's exactly what we're going to try to do, to make sure that every single person with sickle cell disease has access to high quality care through a hematologist.

DR. HULIHAN: To add a little bit more, when we're talking about sickle cell disease we're talking about access to care, it's much bigger picture than just a clinic being, you know, a physical location. There are so many additional topics and considerations that we have to keep in mind that have to be addressed and I think that's another area that our programs can work together to make sure that it really is not just are you in physical proximity to

somewhere that offers care for your condition.

There is a lot more to it than that and those are really good topics that we can start to work on.

DR. CALONGE: Online we have Marc.

DR. WILLIAMS: Hello, Marc Williams of the American College of Medical Genetics and Genomics. Thank you Ned.

I do have a question but I'm going to start with an observation about the topic that we have been focused on for the last few minutes, you know the collection of the clinical data which is so important and yet has represented a relative void. The observation is that we, as Melissa alluded to, we have three separate organizations that are funding efforts. We've got CDC and the Excel program that we heard about. We have HRSA that has funded new steps and now is going to be funding Propel and Excel and now NIH presents funding to newborn screening translational research network.

And I do think that we're kind of converging on the realization that we need to move into the clinical realm. I know in the funding announcements in the Propel and Excel programs that there was an emphasis on being able to create infrastructure to collect some of the clinical follow up data and that there's an expectation to have a plan in place to be able to collect some of that.

Clearly Excel is looking at moving at that.

Newborn screening translational research network has actually done that and created the Longitudinal Pediatric Data Resource or LPDR that is starting to do that for some conditions. I think that while it's really important for leadership of these programs to meet, it's also important for groups below the leadership level to get together, particularly for someone who's trained in informatics to have our informaticists and computers scientists and data scientists talking together to make sure that we're using standards and interoperability communication standards that are available to lower barriers to sharing and a collection of the data from laboratory information systems and ultimately from state health departments and electronic health record systems.

Lastly I'll just mention that there is one big source of data that is not going to lend itself easily to this type of collaboration and that is the data that we heard about today, which is early intervention and school-based programming. For a lot of conditions, the developmental and educational follow up is going to be critically important to understand the benefit and that's an entirely different system that has nothing to do with HHS.

So we have a lot of work ahead of us. Now for the relatively trivial question which is to the Ed3N project. You mentioned privacy and I was curious if your database is FISMA compliant and if so, at what

level of FISMA compliance are you currently at?

DR. BROSCO: So Mark, this is Jeff Brosco. Just to answer the hard question about Ed3N. we are already working with the Department of Education in trying to figure out how Part C in newborn screening can be linked so what you heard over her today from Don about that is exactly the place we want to go.

MS. GAVIGLIO: Yes, I believe right now our system is more moderate compliant.

DR. CALONGE: Ash.

DR. ASHUTOSH: Just a brief comment. One is that I did kind of feel in a panel like this, in a session like this, perhaps listening directly from a patient advocacy organization member that had previously had a condition approved and listed and what has been the experience of the patient community and being able to access longitudinal care in medical homes and so on, I think that that's one thing that could be considered.

Second issue is also in term care. I think they maybe had started to allude to some of the huge areas that there exist. When we are talking about newborn screening, a lot of these are very rare diseases so just in the morning, the model of early intervention linking that to newborn screening was being proposed.

I wonder if at some point one could consider that the barriers to crossing insurance coverage to

see an expert or medical home that maybe in a different location in the state or across state boundaries, those barriers could be lowered a little bit. Because many of those are pretty artificial and just seem to be administrative barriers and that would, might enable a lot more people to actually get expert care. Thank you.

DR. CALONGE: Michele?

DR. CAGGANA: Hi this is Michele Caggana, Committee member. Thanks for the presentations. It was good to see some of the Ed3N overview. I have kind of three--kind of--the first is Dr. Hulihan it's good to see you again.

So back at the APHL Symposium in 2022 we had a talk from part of the KENO Fund Julie Cantor, a physician and pediatric hematologist and adult hematologist from Alabama and she sort of reiterated your numbers there about how children and adults who have sickle cell disease don't, they don't have a hematologist that they can go to and how they get their care and she just worked on this quite, quite a lot over her early career.

And I think some of this work goes all the way back to those RUSH projects, I don't know how many years ago, when this all began and there's some data out of New York that showed, like you sort of had mentioned, if you follow kids in and out of Medicaid over a 10-year period they come in and out

with new numbers and clearly they're not getting the standard of care across all of the members of the program.

So I'm wondering if there's a way or any plan to expand this framework for other states across the country to sort of truly get a collection of sort of the outcomes and how people who are living with sickle cell disease are doing overall?

DR. HULIHAN: Very timely question. We have a new funding opportunity out and the applications are due May 11th and so, yes. We anticipate that we will be funding a total of at least 13 states, that's what's available with current Congressional funding for this project so our intent long-term is that this is a national program.

It is resource dependent, but it is certainly the intent that it will be a national program and I think for those who may not be aware, the sickle cell population, particularly the pediatric population, but that really -- across the lifespan is largely insured by Medicaid and because of the differences of Medicaid programs from state-to-state it really is important to see how those differences come to play in sickle cell disease and a condition that is-- individuals with those conditions certainly do rely on the healthcare system quite a bit so that insurance coverage is very important in their healthcare. So yeah it should be a national program

at some point.

DR. CAGGANA: Okay, thank you. And then for Ed3N, I will reiterate what Melissa said, she actually took my first sentence away here but the whole bidirectionality of ClinVar--I think newborn screening programs rely a lot on ClinVar as is right now and when we see that nice little checkmark of CLINGEN that we're like "yes" when we find a variant in good shape, but I think also as newborn screening can educate and help out the diagnostic, commercial academic researcher labs, trying to identify and characterize.

And I think the pieces that are being built into Ed3N are going to help us answer that question because everyone always says newborn screening, we don't have a phenotype but eventually we do, right. And so if we put that information in and we found something in New York and it was found once in Texas and once in California we can start to put that data together and we're never going to get rid of the variants of uncertain significance but hopefully we'll be able to, to characterize them better. There's really power for the numbers in this program, so happy we're moving along.

And then the last thing I just wanted to kind of reiterate is that there's a lot of funding opportunities that are out there for state programs and newborn screening. Just want to remind people

that not all states have the ability to apply for and accept funding, so I think we really have to work on sort of the best practices piece and able to disseminate our findings through various channels that we do now, but I think we have to remember that as well that just because there's money out there, at the end of the day we have to make sure we close the gap for everyone. Thank you.

DR. CALONGE: Scott. I appreciate your patience. I'm going to, since we're out of time I'm going to give you the last comment, sorry Karin.

DR. SHONE: I planned that so I could have the last word. No, I -- I've never been accused of being patient before. So a couple quick things.

Jeff, you had said something that in every child deaf or hard of hearing should be in Part C and as a parent of a child who's hard of hearing who met the definition for EI in one state but didn't in another state I would say that's a goal not a reality. That's exactly what Don and Elizabeth were saying this morning.

Completely, just a comment. I want to move on to -- I have sat at that table and now this table and outright stated that despite what Melissa said about the agencies talking together that I never really saw evidence of that, and I want to say that the presentations today, you guys came with receipts to show that yeah, it's working so I appreciate that.

So now ten or fifteen years into these discussions, what can we -- putting on my ASTHO hat -- sorry, Scott Shone, representative from ASTHO. What can we do to help to make sure that the ball continues to roll, the stone--the snow, whatever the analogy is that we can continue to push this so we don't. You know, I want to put my efforts where my mouth has been for a while and say what can we do to help with that and I would say on the State side, you mentioned that there was no real requirements for Propel but there kind of was which was that we had to partner, now my state had which we kind of had to partner with Excel which I think is a great carrot.

It kind of just throws out, like Michele just said, you can apply for it but for those that can then say now we have money to do this, now we have to do this to our state leaders, that's a big help. And I'll leave it there given the time. So what can we do? And thanks.

[Laughter]

DR. CUTHBERT: I don't have anything. Except to say that when we were thinking about some of our interactions, our intentional interactions, your name did come up often, so.

[Laughter]

DR. BROSCO: Yes, so just to clarify. So all grants come with requirements. There's no doubt about that. What I was trying to say is that what we're not

saying that you must do this particular quality improvement program. We want states to, or any grantee to figure out what works best in that 1 circumstance but we can't just throw out 1 requirements.

Now I'm saying in terms of help, we all have to do this. This is a total community lift, right, and for almost all of the different buckets there's going to be roles for everybody and that in fact what we're hoping is that we sort of draw out this map, you know this map to this getting to this integrated data system that we've all been dreaming about for years.

Yeah, there's going to be places where ASTHO fits in and places where ACMG fits in. There's going to be places for everybody. So don't worry. You're on board.

DR. SHONE: But it would be helpful to be very pinpoint and have a specific ask, like should health officials help drive data use agreements that get bogged down in legal, the lab directors--

MS. GAVIGLIO: Yes.

DR. SHONE: Right, to my point, Amy. So that level of specificity I think would help and then on the clinical side, our colleagues at AAP and ACMG and all the others to say this is what's needed, because we're here and without it we're just going to go back to ten years from now saying the same thing of we're meeting again.

MS. GAVIGLIO: Yeah, I was going to try to

think of more practical ideas, definitely thinking through and helping us move through the data use agreements would be beautiful. Not to say that we want them just to be shepherded through but if you do have questions and concerns, reach out. Set up time to meet with us. The Texas Program did that. It was very, very helpful for us.

So one, I would say just be amenable to reaching out to us and please give us your concerns and feedback because we want this to be something that programs feel comfortable using and if no one tells us what their concerns are, we aren't going to be able to address them.

I think the other thing is to be willing to think differently and evolve a bit. I think sometimes when we've talked about this project, and understandably so it's a bit terrifying to programs to think they're putting their data somewhere and how are they going to use it and so I think it would help us to move forward if we could all buy into the importance of this and not buy in blindly but be willing to kind of go on the journey of we need to start aggregating our data or we will be here. I will be 80 years old up at this mic yelling at people.

DR. CALONGE: Well I want to thank all of our presenters for a great session this afternoon and in the interest of respect to our public commenters, we're going to shorten the break. I'd really like to

ask folks to try to be back in your seats in about five minutes so we can get started with public comments and make sure we allow space for all of those who have come and signed up to present and some applause from our presenters as we find our way to the washrooms.

[Applause]

Public Comments

DR. CALONGE: If I can get my Committee members to come back, that would be great. We received 17 requests by individuals to provide oral public comments to the Committee today. There have also been three written public comments that were distributed to the Committee.

Kathleen Smith

DR. CALONGE: I'd like to start by inviting Kathleen Smith up to the podium. She's here with her daughter, Lily.

MS. SMITH: Hi. My name is Kathleen. This is my daughter Lily. She was born a happy, healthy little girl inside of Maryland, just a couple hours south of here.

As months went by, Lily was progressing normally, reaching for toys, almost rolling over and holding her head up by herself. At about 5 months, Lily started crying and becoming very stiff. I then

started noticing that Lily could no longer hold her head up and was arching her back in pain. She was inconsolable. We took her to Children's National ER and showed them documented video of what she'd been doing in weeks prior. They took it very seriously and immediately gave her a CT scan at which point they said she had white matter on her brain, something I had never heard of and won't ever forget.

They said they needed to keep her 24 hours to do a sedated MRI. When the doctors came in, they were very glum and they wanted a lot of history from Ben and I. They eventually told us that she had Krabbe disease, to contact hospice, to take as many pictures as possible because she would not live to see her second birthday.

At what point we went on the website of the NIH and found out there was lots of research going on in Krabbe by Dr. Escolar in Pittsburgh, Pennsylvania. That's where we went. It happened on a Friday. We were there Monday morning. She conducted all sorts of tests. We just wanted her to keep her as comfortable as we could for as long as we had her. Little did we know that Dr. Escolar was willing to do a stem-cell transplant on our dear Lily.

So we met with the BMT doctor, we were told all the scary things that can happen. We balanced our options and we said we're sure going to regret it if we don't do it. So we went through a transplant. I'm

not going to say it was easy, but look what I got. If I haven't done it, she wouldn't be here with me today.

Yes, she can't speak by mouth, she can't eat by mouth but oh my goodness, her personality shows. She has an eye gaze device that she uses to communicate with her eyes so if her physical therapy comes to the house, she says "No way. Go home. See you later." Her little personality is definitely there.

Now months ago you got to meet Michael Wilson. I do believe he did a video conference for you guys. Would you believe he's almost the exact same age as Lily? He received a transplant prior to any symptoms thanks to his angel brother Marshal.

Because of him, Michael was able to live. Is it fair that we have to lose a child to save a child? I don't think it is. And I thank God every day that we were able to catch Lily and give her a lifesaving stem cell transplant.

I hope that each of you could look down in your hearts and know that a child-like Lily is still a child. She still is somebody's daughter, somebody's granddaughter, somebody's sister. They're worth saving. Thank you.

DR. CALONGE: Thanks, Kathleen.

[Applause]

Anna Grantham

DR. CALONGE: We're now going to turn to public comments via the webinar and I'd like to welcome Anna Grantham.

MS. GRANTHAM: Hello, my name is Anna Grantham and I am the Director of Newborn Screening for the Hunter's Hope Foundation. Hunter's Hope first nominated Krabbe disease for inclusion on recommended uniform screening panel in 2007 which resulted in this Committee's vote of 8-7 against recommending Krabbe for the RUSP in 2009.

Since then, we have worked tirelessly to systematically fill the evidence gaps provided by this Committee. The differences between Krabbe newborn screening now and in 2009 are extensive and include nearly perfecting the screening method to virtually eliminate false positives, creating clear and decisive follow up and treatment protocols and vastly improving patient outcomes.

In addition to the numerous medical and scientific articles published in 2009 proved that these advances also seen in the ten states currently screening for Krabbe. Babies with early infantile Krabbe disease are successfully receiving treatment within the first 40 days of life and patient's with later infantile onsets have successfully been followed and receive treatment at the appropriate

time.

Also, many states have updated their screening protocols, as these advancements have been made. New York for example has clearly shown an 81 percent reduction in referrals each year and clear improvements in patient outcomes. Furthermore, Krabbe can be screened together with Pompe and MPS I and for states using PerkinElmer screening method this can be done for almost no additional cost, by merely flipping a switch on a machine.

After over a decade of work and millions of dollars spent, the Krabbe newborn screening experts unanimously agreed that we had finally filled the evidence gaps provided in 2009, and that it was time to renominate Krabbe disease to the RUSP. This time we made a calculated change in our nomination, followed the pass of SMA by only nominating the infantile and late infantile Krabbe disease as the core condition.

Throughout this Committee's February 9th meeting, which resulted in a tie vote, a multitude of unprecedented procedural and factorial errors took place. We submitted out letters to both the Secretary of Health and our response to Dr. Calonge as written public comments as they describe in detail our concerns, which are far more involved than I can share in my allotted time today.

You can find them on the Hunter's Hope

website. I want to be clear, our purpose in submitting two nominations to this Committee and really the crux of our entire mission is very simple, to save children's lives. For nearly 20 years we have been relentlessly fighting for nationwide newborn screening for Krabbe disease, so that children with this dreadful disease have a chance to live.

The evidence is undeniable. Krabbe is a horrific disease. By their 4th month of life, children with the most common and severe form of the disease rapidly begin to lose almost all voluntary function. These babies are inconsolable due to their unrelenting pain and extreme feeding issues. Once they are diagnosed with Krabbe it's too late. The disease will continue to progress and the child will die, typically by the age of two, their entire lives will be filled with immense suffering and the inability to crawl or walk, to speak, smile, cough or even swallow. The evidence also shows that babies identified through newborn screening have very different outcomes from what I just described. They are independent, they communicate, they go to school, they smile, laugh and play. Most importantly, they are living.

Yes, there is variability when it comes to outcomes for children identified through newborn screening but the outcomes for children not screened for Krabbe at birth are 100 percent the same, certain

death. Just last month we learned of two symptomatic toddlers, newly diagnosed with Krabbe who tragically were born in states not yet screening for the disease.

And every delay caused by this Committee's every changing mandate for additional published data will result in the death of even more U.S. children. These families will inevitably learn that the federal Advisory Committee to their government's Secretary of Health voted against the inclusion of Krabbe on the RUSP, resulting in very few states screening for the disease and the deadly consequences for more than 138 U.S. children and counting since this Committee's decision on Krabbe in 2009.

These families will not only receive the devastating diagnosis of Krabbe disease but they will also learn that if their child had just been born in a different state, they would have had a chance for lifesaving treatment, a chance that this Committee voted against, twice. These children and families deserve a crystal clear path forward for Krabbe's inclusion on the RUSP that is consistent with the other conditions that have been added. These families deserve your Committee to never losing sight of the fact that your decisions are a matter of life and death for our nation's children. It should not be this hard to save a child's life and this Committee is the nation's biggest barrier to giving children

with Krabbe disease the chance to live.

Please, help us save their lives. Children with Krabbe disease deserve to live.

DR. CALONGE: Thank you, Anna.

Vanessa Werner

DR. CALONGE: Next we have Vanessa Werner.

MS. WERNER: Hello I'm just going to try to get myself situated here. I hope you can hear me.

Hello my name is Vanessa Werner. First of all I want to thank all of you for your time and giving me the opportunity to share our story today. I'm parent to a beautiful 17-month-old boy named Damon also known as DJ.

At 16 days old, DJ was diagnosed with infantile onset Krabbe disease and this was only caught in such an early age because he was flagged via newborn screening. I'm fortunate enough to live in Pennsylvania, one of the few states that have had Krabbe into the newborn screening panel. Krabbe was added into the panel in Pennsylvania in May 2021 and DJ was born on December 2021. Should he have been born any earlier in another state our story would look very different and be filled with hopelessness. A little bit of back-story.

My husband and I struggled for 3 years with infertility before moving forward with IVF. We did genetic testing on our embryos but typical of genetic

screening doesn't test for rare diseases like Krabbe.

I'll never forget sitting in the neurologist office as we were getting DJ's diagnosis and being informed of our options. They told us because it was caught early he would most likely be eligible to receive a cord blood or bone marrow transplant to slow the progression of the disease. They also presented us with the option of doing nothing, which is a valid option for some families but it can be a guaranteed death sentence for children by the age of two, as we just heard.

The doctors recommended we visit with a Krabbe expert across the state of Pennsylvania, and an evaluation had already been scheduled for the very next morning at 8:00 a.m. I was hesitant and it was also overwhelming. And even thinking about just driving across state through the night with a two-week-old newborn, our dog, and while still healing from an emergency c-section, completely exhausted me. But then my husband turned to me and said "we went through so much to bring him here, let's do everything we can to keep him here. So this sealed the deal for me and we packed up our belongings and headed out to Pittsburgh that night.

We spent the next the ten months living in the hospital while DJ went through not one, but two transplants. It was an incredibly hard year with a lot of setbacks and complications, but we don't

regret our decision to give him every chance at life, not for one minute.

Newborn screening completely changed the trajectory of DJ's life. DJ was flagged for low GALC enzyme and high psychosine levels. Normal GALC is essential for proper myelin sheath formation around the nerve including those in our brains and in our spinal cord. Psychosine is a highly toxic substance that accumulates in the absence of GALC.

So to give you an idea of just how much the transplant has helped DJ in terms of measurable values, prior to transplant, DJ's GALC enzyme at birth was 0.23, well below normal levels and at 100 days post-transplant his GALC had risen to 2.7 normal level. And at birth DJ's psychosine levels were incredibly high at 55 and at 100 days posttransplant that level had dropped to 7.

Today, DJ is thriving with us at home. Does he have developmental delays? Yes. Does he require daily medications and is he tube-fed? Yeah. But does he smile and laugh every day? Absolutely. Does his face light up when you sing to him and snuggle him and kiss him? Every time.

My heart goes out to all the families who have not been granted the special opportunity that we were fortunate to receive simply due to our location of residence. It's my sincere hope that Krabbe is added to newborn screening in every state across the

U.S. so that all children affected with this horrible and incredibly unfair disease have a fighting chance at longer, happier and healthier life. Thank you.

DR. CALONGE: Thanks, Vanessa.

Stacy Pike-Lagenfeld

DR. CALONGE: I'd now like to turn to Stacy Pike-Langenfeld.

MS. PIKE-LANGENFELD: There you go. Just needed to start my video. All right.

Hi. Thank you so much for the opportunity to speak today. I'm Stacy Pike-Langenfeld, President of Krabbe Connect. Please know that I am grateful to the ACHDNC Committee members and their mission to reduce morbidity and mortality in newborns and children who have or at risk for heritable disorders.

However, as with any committee, whether it lies under a federal or state, city, county, corporate or non-profit designation, communities at times need to reevaluate and reconsider or take time to implement some new changes to ensure at the very least the standards set forth for establishing and operating are being accomplished.

Today, I would like to take a moment to make you aware of some troubling items impacting an unfairly balanced assessment of Krabbe disease. ACHDNC members are appointed to this Committee to utilize their education and professional experience

to fairly and without bias, evaluate and assess conditions for the RUSP.

Some members of this Committee have a high incidence of voting no when evaluating conditions for the RUSP. My question to you is who is responsible for monitoring the personal interests of the ACHDNC Committee members and ensuring members chosen can be fair in their evaluation is and assessments?

On several occasions throughout the Committee's discussion on Krabbe disease, the phrase, "in my opinion" was used. Just as jurors are required to listen attentively to both sides of an argument, in light of the credibility and reliability of the evidence and make a fair and impartial decision based on the facts and the law.

The ACHDNC Committee should follow the same protocol, making impartial decisions based on current credible and reliable evidence is your job. Hence, it's time for the Committee to reevaluate the process and procedure in place today. Newborn babies lives depend on them. ACHDNC Committee's vote on Krabbe disease resulted in a tie. According to your bylaws, if a vote results in a tie, the Committee can continue the discussion to try to reach a consensus.

Alternatively, the Committee may decide to postpone the vote to allow for more time for discussion and deliberations. These options were not presented to the Committee. In fact, the vote was so

rushed that the ACHDNC Committee did not solicit input and feedback from a variety of stakeholders, including patients, families, advocacy groups, healthcare providers and the general public.

Can you imagine if you were being accused of a crime and you were unable to call any witnesses to the stand? Or your attorney was not allowed to cross-examine? The ACHDNC is subject to Federal Open Meeting Laws and Regulations, which require that its meetings be open to the public and that interested parties have the opportunity to participate in the Committee's deliberations.

The ACHDNC did not follow this proper deliberation. You broke the bylaws of this Committee. Proper deliberation where stakeholders can cross-examine the Committee ensures transparency and accountability in a Committee's decision making process and allows key assessments from stakeholders, many of whom are experts to be considered.

Thus, it's time for this Committee to reevaluate the process and procedures in place today. Newborn babies' lives depend on it.

Lastly, it was evidenced that there was a lack of knowledge on what you, the Committee members can recommend. During the review of Krabbe disease, members of the Committee were unsure if they could advise second-tier testing if Krabbe disease was added to the RUSP.

When a new member is appointed, do you have a formal training process where members are trained in their roles, responsibility and level of authority on the Committee? This would seem like a crucial training to help ensure all members feel comfortable in their role, can navigate discussions and allow the public to see that the Committee members can confidently and accurately operate.

It's time for this Committee to reevaluate the process and procedures in place today. Newborn babies' lives depend on it. My message today is clear. I am here to ask that you take some time to reevaluate your process and procedures. It's time for the Committee to have an appeal process and an expedited review process for conditions that have previously applied for RUSP approval.

Mistakes and errors happen. We're human. It's okay to ask for grace and conduct another review. I would see that as honorable and I think that most people in this room would as well. Newborns have the right to receive necessary medical care and treatment and are supposed to be protected from harm and neglect under child protection laws.

The review of Krabbe disease went awry and we owe it to the future generations of newborns who will be impacted by any life-threatening disease, a fair, unbiased review of a condition for the Recommended Uniform Screening Panel. Today, I dedicate my

comments to all those who have lost their lives to Krabbe disease, including my daughter Michaela who died at 2 years of age, 20 years ago today. Thank you for your time.

DR. CALONGE: Thank you, Stacy.

Joanne Kurtzberg

DR. CALONGE: Next we have Joanne Kurtzberg.

DR. KURTZBERG: Hello everyone. My name is Joanne Kurtzberg and I'm a pediatric transplant physician who pioneered unrelated cord transplant for treatment of Krabbe disease. I testified here a few months ago on the day I expected the ACHDNC to recommend the addition of Krabbe to the RUSP. Unfortunately, that did not occur so I am back today to address some of the perceived gaps that may have prevented some of the Committee members from voting in favor of adding Krabbe disease to the RUSP.

Through systematic monitoring of transplant outcomes, we learned years ago that transplant did not help symptomatic babies with Krabbe disease. In contrast, babies transplanted before 30-40 days of life dramatically benefited from transplant in multiple ways. Not only was their life extended, but they never developed the extreme irritability that's presenting in symptoms in untreated infants.

Furthermore, they gained developmental milestones, have normal vision and hearing, do not

have seizures, have normal cognitive development, are able to communicate, go to school and enjoy age-appropriate activities, meaning they are both living and experiencing life.

These initial outcomes were published in 2005 in the New England Journal of Medicine and outcomes at 5, 10 and 15 years have been documented in four additional peer review publications. Over the past 16 years, approximately 20 presymptomatic babies born into affected families have been treated. A very small number because most families don't know they're at risk.

In contrast, I've had to tell hundreds of parents whose babies were diagnosed after months of distressing symptoms that it was too late for treatment and their baby would die of Krabbe disease.

When, 17 years ago, New York State began newborn screening for Krabbe disease I was ecstatic. Finally, babies would be diagnosed early enough to have access to treatment so that fewer families would watch their babies deteriorate whilst experiencing diagnostic odysseys, only to find out that their baby was going to die of a disease that would have been treatable if they could have been diagnosed through newborn screening.

Since that time, outcomes of 13 babies with infantile Krabbe disease, identified through newborn screening and undergoing transplantation have been

reported in four additional publications, showing that 11 out of the 13 are surviving through 2-16 years after transplant.

A concern was raised as to whether the outcomes of babies with infantile Krabbe disease transplanted after diagnosis through family history versus those diagnosed through newborn screening are different. Correlating the data from all publications as well as following many of these patients firsthand, I can confirm that the clinical outcomes are not different. What is different is that parents of babies diagnosed through newborn screening have no prior knowledge of the disease and with targeted support they quickly learn about the disease and make critical decisions about the options for their baby.

Since the meeting in February there have been opportunities for additional communication with the ACHDNC which we greatly appreciate. Requests for additional information included additional evidence of outcomes of transplant for infantile Krabbe disease, information about the toxicity of transplant in the first two months of life and evidence that identification of children at risk for later onset Krabbe disease is beneficial.

We responded in a 20-page letter that can be accessed from Hunter's Hope website, documenting that there are several publications reporting outcomes after transplantation for infantile Krabbe disease in

both children identified because of the family history and children identified through newborn screening.

Numbers in both groups are small because this is a very rare disease but frankly the vast majority of cases are reported in the medical literature. Thus, there is no gap in this evidence. Furthermore transplantation of young infants is the treatment of choice for multiple rare and life threatening conditions, including SCID, congenital bone marrow failure syndromes and other leukodystrophies.

The main additional risk of transplantation in these young infants are effects on dental development, teeth development, which can be addressed with reconstructive therapies after full skeletal growth has been achieved. This is hardly a barrier to a therapy that saves lives.

We were also asked about parental perceptions of newborn screening and informed that the compelling testimonies we've all heard at the last meeting of the ACHDNC were parents of children treated with transplant for Krabbe disease are not considered evidence. Rather, evidence is a peer-reviewed publication in the medical literature.

Surprisingly there is a report published in the International Journal of Neonatal Screening in 2020 entitled "Family Attitudes Regarding Newborn Screening for Krabbe disease". Over 170 responders,

including 138 with a family member with Krabbe disease diagnosed with symptoms, 20 diagnosed through newborn screening, and 12 diagnosed because of the family history, 165 or 97 percent supported implementation of newborn screening for Krabbe disease.

Lastly, I agree that we're still learning about this small population of children identified through newborn screening who are at risk for later onset Krabbe disease. I agree that this is a challenging population but I do see a path forward, focusing on the infantile cases identified through newborn screening.

Moreover, the nominated screening approach identifies the infantile cases 100 percent of the time and eliminates the possibility that a family who's newborn is not affected would have to worry about Krabbe disease.

To summarize, I submit that the perceived gaps in the nomination package have been addressed and do not believe there's a need to resubmit the nomination to add Krabbe disease to the RUSP. As an alternative, I strongly recommend that Krabbe be re-discussed at the office meeting at the ACHDNC with a repeat vote on the nomination at that meeting.

Thank you all for your attention.

DR. CALONGE: Thank you, Joanne.

Matt Blum

DR. CALONGE: Next we have Matt and Jennifer Blum.

MR. BLUM: Hi everyone. Just Matt here. Unfortunately my wife can't make it. But thanks so much for the opportunity to share my daughter's story with you today.

Chloe was born full-term actually right on her due-date and everything seemed perfect at the time. Normal length, weight, head circumference. She passed her hearing tests and all the other initial exams. No issues identified. In fact, there wasn't a single indication whatsoever for any of us to suspect what we would later find out many months down the road, that Chloe was born with a congenital CMV infarction that was silently attacking her ears and attacking her brain right as we held her in our arms. By about 4 months or so we started to see some developmental delays, but it wasn't really until her six-month checkup that we truly became concerned.

All of a sudden her head circumference had plummeted off the growth charts. She was having secondary microcephaly and you know, that kicked off a barrage of testing. By 7 months our neurologist sat down with us and basically showed us that the imaging revealed that she had a significant brain malformation and if it wasn't life-threatening, which

she couldn't rule out, there was no way to say whether she'd be able to walk, talk, have higher level cognitive abilities. It turned our world upside down.

Shortly after we had her hearing retested because CMV was one of the possible culprits and learned that she had mild hearing loss in one ear and had become completely deaf in her other year at that point and ultimately we wouldn't be able to definitively confirm the root cause of her disabilities until after her first birthday.

It took us an additional 4 months of testing to rule out all of the other possibilities, plus working with the Connecticut Department of Public Health to send a sample of her newborn screening card to a lab in Alabama for positive confirmation.

Today, at 17 months, this is my little girl. I'm grateful to say that Chloe is thriving. We could not be more proud of her. She's such a happy girl. She's truly an inspiration for our family. Although she suffers from global developmental delays and hypotonia or weak muscle strength which has caused a number of challenges for her, in addition to her hearing loss.

She is smiling 24/7. She is getting stronger each week and even taking steps now. She is learning how to hear and learn via her new cochlear implant. But the point I want to emphasize to this Committee

though is that our family is the fortunate exception to the rule. There are so many families out there with babies in Chloe's position who aren't lucky enough to get their children diagnosed in time for the early intervention if they're even able to identify diagnosis at all.

Typically it can only be definitively diagnosed within the 21-day window after birth. In addition, the base majority of CCMV families out there do not have the time and resources to work with seven different therapists each week, like Chloe has done.

According to the CDC, congenital CMV is the leading viral cause of birth defects and developmental disabilities in the U.S. However, only 9% of pregnant women have ever even heard of it and our family certainly falls in that camp. Each year a staggering 30,000 children, one out of 200 babies are born with CCMV and while, yes many of them will be just fine an unacceptable number of them will not be.

Of those 30,000 babies each year there are 400 deaths and 6,000 children like Chloe with permanent disabilities. There's so much more that could be done just to raise awareness of CCMV but also to help progress efforts to implement universal newborn screening, so that each and every one of those 30,000 families will have equal access to testing as well as the opportunity for treatment and

other early intervention services which are so, so crucial for early intervention trajectory and outcomes for CCMV children.

Thanks for your consideration and hope for your support for these efforts.

DR. CALONGE: Thank you, Matt.

Pamela Jinsky

DR. CALONGE: Next we're going to turn to Pamela Jinsky.

MS. JINSKY: Can you see me? And hear me?

DR. CALONGE: Yes.

MS. JINSKY: Okay. Similar to Matt's story, again my name's Pamela Jinsky and I have a daughter who was born with congenital CMV and her story is quite, just -- I don't know all the words for it. It was a roller coaster because we didn't know that congenital CMV actually caused all the disabilities that she has now.

So I'm going to give you the rundown real quick, but so I had her May 29, 2015 and before that I had numerous appointments. I went to the perinatologist, all of these labs done and I just knew she had an echogenic bowel and that her ventricles were not symmetrical, which the perinatologist never said anything about CMV. The point I'm trying to make here is that CMV is never mentioned from numerous doctors, numerous medical staff. It just goes on and on for about the first ten months of her life. But she was born--when she was

three weeks and 5 days early and she didn't have to go to the NICU. All we knew is that she needed an ultrasound because of the ventricles in her brain.

Once ultrasound was performed it was then noted that she needed an MRI. So the MRI showed that she had a brain bleed, two shunts in her brain as well as she might have hydrocephaly ND again CMV was never mentioned. On top of that, she failed a newborn hearing screening three times while she was in the hospital.

With that, we left clueless as to why she had these things going on with her brain and at this point we didn't know if she was going to have hearing loss. So we followed up like everybody else does and to the follow up appointment was the hearing, ENT and with that this wasn't quite accurate so we got a second opinion when we went down to the children's hospital here in Madison, Wisconsin. And there, same thing. CMV never mentioned. We just knew that she had microcephaly, polymicrogyria and she didn't need a shunt. So we were very excited that she didn't need that but her hearing was still not right so we had to go back and to more tests at the Children's Hospital and there they said she was bilaterally deaf, bad. Cochlear implants would be the next step if we wanted to go that way so we transferred all the care to Milwaukee Children's Hospital and with that, we did also make an appointment with a neurologist to see what—what was causing this.

We had no clue what was causing all these conditions. It wasn't genetic and we just kept fighting, looking for answers, and I was just kept searching looking for why this was happening to my daughter. So then CMV finally was mentioned, that these look like exactly the markers of what CMV would be.

Well now by that time, I didn't know how to figure it out, how to figure out how she got CMV because as Matt said it's the first 21 days of life, you can find out definitively. So with that we had asked doctors in Wisconsin and trying to get opinions about what I was trying to find, what this was. So finally I was able to get a hold of a doctor locally and they suggested to try and see if you can find the RUSP panel, the newborn blood spot.

So with that, it was already past her first birthday so they're supposed to dispose of it after the first year of life. Well it happened they still had it a month and a half after they should have disposed of it. And the only place that they were able to actually pinpoint if it was positive or not for CMV was at the University of Minnesota, from Dr. Mark Schleiss is the one that actually definitively positive showed that she had CMV.

So we were very fortunate that had happened. But overall in the end the big epic fail as I call it is they knew as she was in my womb that the

perinatologist put on my records, my health notes that there were markers of CMV and she never mentioned to us, me or my husband at the time. Never mentioned CMV. And that hurt me so much that they would leave this information about from us. That they wouldn't tell us. It could be this and never told us.

So after that 16 months, 18 months later I actually sat down and talked with the perinatologist and I said "Why. Why didn't you tell us about this? Why didn't you tell us about CMV?" I'd never heard of it, nothing.” And she goes to me "What? They didn't test for CMV after she was born?" And I was just like--I didn't know what to think. I was just so angry at the system and how they failed my daughter Pella. With that too is with CMV the number one diagnosis is or symptom is hearing loss. So to add that to the RUSP panel, there are so many kids out there that have hearing loss, like my daughter where if I didn't follow up we wouldn't have known that this is something that actually came from a virus.

We are just blessed that I am a determined advocate for my daughter to find out what was going on with her. But overall it's just been a rollercoaster from that time on and I've been a strong advocate for my daughter Pella and she is just about 8 years old now. She is nonverbal, she cannot talk. She can smile, but she can't walk. She can't--she has to be transferred everywhere. She can't crawl

and she is, has cochlear implants.

She can hear and understand you—mainly she uses her mode of communication is sign language or communication device. But in the end, Pella, my daughter wants to be like everybody else and do what everybody else is doing no matter if she can't do it exactly like them, she wants to try as much as she can.

So to ask in the future when the CMV voting is for the nominee can you guys please consider stating other families like mine to go through what we did in trying to find this diagnosis that was there from the start before she was born.

This is very critical for early intervention, especially when it comes to hearing loss. All right, thank you.

MS. MANNING: So I first want to thank everyone that has shared the public comment thus far and for those of you that will be providing comments next, please limit your comments to four minutes. We have several folks that have registered to provide public comments and we want to ensure that we get to all of them. Thank you.

DR. CALONGE: And thanks, Pamela for your testimony.

Danae Bartke

DR. CALONGE: Next I have Danae Bartke.

MS. BARTKE: First, I want to say think you to the Committee for allowing me to have this chance to speak. My name is Danae Bartke and I am the Executive Director of HCU Network America. HCU Network America is a 501(c)(3) patient advocacy organization that focuses on supporting research to improve diagnoses and treatment, providing educational resources for patients and caregivers, creating connections across the HCU community and ensuring that all patients are diagnosed as early and efficiently as possible.

HCU Network America connects more than 600 families across thirty countries with medical steering committees comprised of HCU Medical experts, patients and caregivers that have had -- experiences.

First, I would like to acknowledge and applaud the Centers for Disease Control and Prevention for their efforts in revising newborn screening protocols for classic homocystinuria. The agency has recently published two pieces of literature regarding its first-tier multiplex assay for homocysteine and second tier, multiplex, newborn screening liquid chromatography with tandem spectrometry method. HCU Network America encourages the Committee to share these approaches with state laboratories investigate adjusting their cutoffs in implementing a more efficient and accurate newborn screening process for classic homocystinuria amongst other disorders.

Second, HCU Network America is hosting a newborn screening update and roundtable discussion on Monday, May 22, from 1:30 to 3:00 p.m. Eastern for State newborn screening programs. This interactive discussion will feature Acosta de Pérez, the Laboratory Chief at the biomedical mass spectrometry laboratory newborn screening and molecular biology branch at the Centers of Disease Control and Prevention, who will present on the Agency's first and second multiplex approaches.

Additionally, representatives from Colorado, Massachusetts and New York whose newborn screening laboratories will share screening and vision updates, best practices from their perspective states. We encourage all newborn screening program colleagues to attend. Please reach out to us if your state program has not seen an invite yet and we hope to see you there.

Again, we would like to thank the Committee for the opportunity to speak and we again applaud the CDC's progress despite all the circumstance. Thank you.

DR. CALONGE: Thanks Danae.

Dean Suhr

DR. CALONGE: Next, we have Dean Suhr.

MR. SUHR: Good afternoon. Greetings chair and Committee members. I am sorry to not be there in

person. We are enjoying some well-needed rain today. I am Dean Suhr, President and Co-Founder of MLD Foundation, over 20 years ago. MLD is a rare, terminal, neurometabolic disorder. The majority of cases are late infantile with the symptoms starting as early as 12 months with full engagement by 24 months.

Over the last decade, Professor Gelb of the University of Washington has been developing an MLD assay. He validated that screen with over 100 thousand spots tested in his lab and we're now part of the New York Screening Plus newborn screening project. No babies identified there yet, but we do have several EU pilots. We're just shy of 100 thousand babies screened to date including 3 babies already identified in Germany. There's a waiting period before they're referred to therapy, but at least one of them has been referred to the EU approved gene therapy already. The confirmed assay is repeatable, accurate and cost-efficient. We started our MLD newborn screening key opinion leader or KOL work in 2017.

Since then, MLD has an approved and commercialized therapy in the EU since December 2021. It's called Libmeldy over there. That's not the U.S. name or at least not yet. Back in the U.S., OTL200 has an FDA RMAT designation that has been subject of numerous pre-VAL meetings and it's eligible for rare

pediatric review voucher so we're planning on a quick review to the FDA.

So our timelines are firming up. With a VLA filing according to the sponsors mid-year, we recognize the Committee desires and improve to therapy to accept the nomination and so we're rapidly doing that. The nomination prep is underway.

Our first KOL meeting as I think I mentioned was in 2017. Our expert advisory group focused specifically on the RUSP has been meeting since February 2020 and currently we have an international consortium that is supporting this project.

The current target is to submit a nomination as early--in early 2023 in line with an anticipated VLA-FDA response, a positive response from the FDA. However, there are some concerns.

Uncertainty being the top one of those. Most recently, as we've heard about and probably will hear for the next few comments, the DMD and Krabbe reviews and the votes, we're concerned that the process and the clarity and stability of that aren't quite there and so that makes it a bit of a moving target for us and that really makes it really difficult for us to put a nomination together to address what we don't know might be slightly changing criteria. We do recognize that rare disease--in the rare disease space, flexibility in evaluation is good. There also has a downside if the—the requirements to target that

is changing too. The second concern is the use of data from pilots and babies or babies identified outside of the United States i.e., the EU. For Libmeldy, the therapies were developed in the EU, in Italy and it was approved there first and hence that's why it's--everything is more progressed over there.

Professor Gelb will be talking a little bit later about Anna Velon and identifying babies and I encourage you to listen to those comments as well. We're in full support of that. And then with the capacity of the Committee and your eternal review group. We feel that the impending tsunami of additional nominations.

We've got several repeat nominations potentially on the docket. We just remain concerned about priorities and throughput.

And then finally, more of a philosophical comment, but just something to inspire you. You know, the FDA has "do no harm" up on their, you know, on their billboards and then the ACHDNC through the rest of their approval kind of has that similar philosophy. You don't use those same words but it always seems, and we heard this a little bit earlier in today's session we're talking about the harm of newborn screening.

Through that small, small number of people. But that harm often doesn't seem to as broadly or as

bluntly include that death is a harm.

Doing nothing, not approving a nomination leads to death and I just, I just encourage you to think about that as you go back to your evidence-based work. We need to have ethical undertones as well.

Thank you.

DR. CALONGE: Thanks, Dean.

Niki Armstrong

DR. CALONGE: We're now going to turn to people who are present and I'll invite them up to the podium and the microphone starting with Niki Armstrong.

MS. ARMSTRONG: On behalf of Parent Project Muscular Dystrophy and the Duchenne Patient community, thank you for the opportunity to speak today.

My name is Niki Armstrong and I am the Newborn Screening Program Manager for PPMD. I'm pleased to provide an update on our Duchenne newborn screening efforts. Following the nomination and prioritization presentation and disappointing vote in February, we are grateful for the opportunity to streamline and update the Duchenne RUSP nomination package with the plan to resubmit this month.

I'd like to take this opportunity to provide some clarifications regarding some of the questions

that were raised during the DMD discussion last meeting. I think you all are aware from previous comments that I've made that Duchenne has multiple therapies that are approved and available and it's really on the cusp of a--huge changes in the treatment paradigm. Corticosteroids are standard of care for all patients with Duchenne and they are well-documented to have multiple benefits including extending the amount of time that boys can ambulate as well as slowing the decline of both lung and cardiac function.

Exon skipping therapies, which are approved for about 30 percent of people with Duchenne, have also been shown to delay the loss of ambulation and to slow decline in lung and cardiac function. With emerging evidence to suggest that initiating those earlier has increased benefits. And then we have gene therapy. One gene therapy is under FDA review right now with the PDUFA date of later this month. Another gene therapy just completed enrollment of its pivotal phase 3 trial and three other gene therapies are still in earlier phases of clinical trials.

One of this earlier phase clinical trials enrolled our youngest patient to date, a 7-month old and recent data was presented at a meeting that at nearly two, his development remains typical, which is not usual for Duchenne. There are currently clinical trials recruiting in Duchenne and a steroid

alternative that also has a PDUFA date of later this year. So there are huge things happening in the treatment world of Duchenne.

It's important to understand that Duchenne is different from many other conditions that are currently on the RUSP. Some of these differences are actually to our benefit. So Duchenne is X-linked and because of that X-linked nature it's actually easier to understand variants of uncertain significance. We can do familial segregation studies and actually pretty easily figure out most of them.

However, probably the biggest difference and an area where we had issues is incredibly slow progression in Duchenne. While muscle damage is present at birth, and we know this because we are using a biomarker of muscle damage for newborn screening, boys with Duchenne continue to make developmental progress until about 4 or 5 years of age. Their progress might be slow and they can certainly benefit from targeted therapies as discussed this morning but they make progress. Each at their own rate. Until they reach their plateau. At that time of plateau, that child has accumulated a significant enough muscle damage that the muscle tissue is being replaced by fat and fibrosis. That replacement is irreversible and will continue until that muscle becomes nonfunctional.

People with Duchenne typically survive until

their late 20's and we know exactly how Duchenne progresses and we know how the treatments work when we start them at the typical ages.

The approved treatments are effective but they are long-term. They require long-term dosing and provide long-term benefits. As most of us know, clinical research is difficult and expensive. I would love to find a cohort of boys, you know, and follow them for 5, 10, or 15 years but unfortunately the boys who are now 10 or 15 that were diagnosed around birth, the standards of care are completely different and exon skipping therapies weren't available so that data isn't as easy to come by. And then there's the question of how much benefit is enough? Is a higher Bailey gross motor score after a year of twice weekly corticosteroids enough? Is data that initiating an Exon skipping therapy a year earlier probably extends the time of ambulation enough? Newborn screening saves lives and I know that we all feel a great responsibility towards that but Duchenne is not going to be SMA, nor is it PKU. Current treatments for Duchenne are not cures. however, we know that the current treatments slow or delay muscle damage and because they slow or delay muscle damage, we know that there's going to be benefit for newborn screening. How much benefit? It's going to take years to know exactly.

We've gotten survival to the late 20's with

our current standards of care. Maybe we'll get another 5 years of walking. Maybe we'll get another 10 years of incredibly important upper limb function. Maybe we'll get another ten years of life and any one of those is enough to make newborn screening for Duchenne worth it.

Thank you.

DR. CALONGE: Thanks, Niki.

Paul Melmeyer

DR. CALONGE: Next we have Paul Melmeyer.

MR. MELMEYER: All right. Good afternoon everybody and thank you for the opportunity to provide comments and updates. There are ongoing efforts to add Duchenne Muscular Dystrophy to the Recommended Uniform Screening Panel.

I am Paul Melmeyer, Vice President of Public Policy and Advocacy of the Muscular Dystrophy Association. MDA is proud to serve the Duchenne as well as Spinal Muscular Atrophy, Pompeii disease and other rare muscular disease patient communities.

MDA was a proud cosponsor of the nomination of Duchenne muscular dystrophy last summer and under the leadership of Parent Project Muscular Dystrophy, we provided the evidence that the Committee required for consideration.

We were disappointed that the Committee voted not to move the Duchenne nomination to full evidence

review in February but we are undeterred in trying to move the nomination forward.

In addition to the points that Niki Armstrong with PPMD just made pertaining to the availability of effective treatments for individuals with Duchenne as well as the potential approval of a gene therapy for Duchenne later this month and how these important treatments are -- how important these treatments are for delaying the onset of many symptoms with Duchenne, Mason and.

We also wanted to provide updates and comments on several additional points raised by this Committee when discussing the nomination in February.

First, the Committee expressed concern about the availability of confirmatory testing for state newborn screening programs to confirm the diagnosis of Duchenne via next generation sequencing. Frankly, we do not share this concern, as access to genetic confirmatory testing is not demonstrably different than the genetic testing defined in the SMA2 gene for SMA or to the genetic cause of Pompe disease. These genetic tests are substantially less expensive than they used to be and are fully accessible to state programs and providers.

In addition to free genetic testing programs, genetic tests cost just a few hundred dollars at the very most, to find the genetic causes of Duchenne and related muscular dystrophies. With over 40 CLIA

certified labs performing Duchenne genetic testing and with this number expected to grow, this number is greater than labs conducting confirmatory testing for other RUSP approved conditions.

We are also paying close attention to the evolving state policy environment pertaining to the use of dry blood spots. Well, several states are considering further limiting the use of dried blood spots in secondary research, law enforcement or other venues, the use of dry blood spots for confirmatory testing within the initial newborn screening process is not something of concern as of yet.

Second, the Committee questioned the necessity of screening for Duchenne muscular dystrophy at birth instead of exploring the appropriateness of testing for Duchenne at a later date. Perhaps the one-year wellness visit. We would strongly disagree with this approach. The presence of elevated CK levels in newborns with Duchenne is evidence that muscle damage caused by Duchenne is happening prior to birth and continues throughout the course of the disease.

To intentionally delay diagnosis only allows this muscle damage to continue unchecked for at least a year. furthermore, according to CDC, anywhere from 10-30 percent of children don't even have their well-child visits with health system inequities exacerbating this further for minority populations.

Finally, without going further today during my testimony, we will be addressing questions pertaining to the false positive rate within the pilot studies, expectations of newborn screening for Duchenne at the population level and more.

In conclusion we look forward to addressing these and other concerns with our renomination of the package in the coming weeks and are happy to answer any further questions. Thank you so much for the opportunity to testify today.

DR. CALONGE: Thanks Paul.

Elisa Seeger

DR. CALONGE: Next we have Elisa Seeger.

MS. SEEGER: Dear Chairman Calonge and members of the Advisory Committee for Heritable Disorders in Newborns and Children.

Thank you so much for the opportunity to speak today. My name is Elisa Seeger and I'm the Founder of the ALD Alliance. I wanted to share some thoughts, concerns and hopes for this Committee and the future of newborn screening.

I would like to draw attention to the advocacy work that our coalition has been doing to end "death by zip code". As many of you here know, the state where a baby is born determines which conditions they are screened for, leading to inequalities across the country. To end death by zip

code, the country must prioritize complete RUSP implementation in all 50 states. During the November 2022 Advisory Committee Meeting, we heard from several state lab representatives about how funding is one of the major barriers to efficiently implementing newborn screening conditions.

The CDC under their newborn screening quality assurance program and HRSA, both offered funding opportunities last year through grants intended to help states to build capacity to support the implementation of the RUSP conditions. The demand was high as a record number of ten states applied for the CDC grants, however even though all ten state applications were approved, funding was only able to be provided for half of them and even though states ultimately were underfunded.

While these funding opportunities are important, they are not enough. State labs have made it clear that they need consistent, flexible and sufficient funding every year in order to keep up with the conditions that become eligible for newborn screening.

We will continue to push for more federal funding for states and their newborn screening programs and hope that state lab engagement in the newborn screening process continues as our voice and hard work is vital for ensuring that geography does not dictate life and death for newborns.

During the last Committee meeting in February, we, like many others, were disappointed with the decisions to not move Krabbe or Duchenne muscular dystrophy forward in the condition nomination process. We understand that these decisions came after careful consideration by the Committee but the outcomes were a devastating setback for the two disease communities as well as newborn screening as a whole.

We also believed that the way the Committee came to these conclusions shed light on some of the fundamental issues that the Committee and its process for reviewing conditions for the Recommended Uniform Screening Panel face.

First, we want to point out that the Advisory Committee, discretionary charter and underlying statute both specify the need for 15 or an odd number of members. The obvious reasoning behind this is so that when votes occur, there will not be a tie and so the intent of the Committee will be clear.

During the February meeting, the vote on Krabbe nomination resulted in a 7 to 7 tie, because only 14 voting members were present. The Committee concluded that according to Roberts' rule of order, the motion did not pass. Nowhere in the charter or underlying statute does it advise or require the Committee to follow Roberts' rule or order and we believe that the vote should have been postponed

until 15 votes were able to be casted, as was expected when the Committee was established.

Additionally, we urge the Committee to formally include a minimum of two expert members of the nominated disease community to participate in the evidence review discussion. As we saw with the Krabbe presentation and with past presentations, questions can arise that are beyond the expertise of the presenters so it is important to have disease-specific experts on hand to step in and provide education and clarity.

We also feel it is important to permit organizational representatives to participate in the evidence review discussion as well. Perhaps most important of all is the need for the Committee to provide consistent standards for all nominated conditions, using an amount and type of evidence based on condition specific factors, such as rarity, severity and unmet need.

I would also like to express concern over Dr. Kwon's remarks during the Krabbe Review. Here are two quotes. "I think that for me the most difficult part of this particular newborn screening program is how people react to the fact that they're told this information and to me it's one of those programs that really reminds you that this is an unconsented activity and this is something that we're imposing on families." Another quote "but the program itself,

newborn screening itself is an unconsented task, basically that people having babies are paying".

It is my hope that any voting member of this Committee would believe in newborn screening and focus solely on the condition being reviewed, not be blinded by their own beliefs which are no doubt rooted in their own personal experience, having to be the ones to break the news.

Not diagnosing these babies at birth does not magically make these conditions disappear. It leads to a diagnostic odyssey for the families and most likely the inability to intervene and to save a life. I think it would be beneficial to review voting membership requirements in addition to reconsidering membership due to bias.

I implore you to have more voting members that represent the rare disease patient population. We are hopeful that lessons can be learned from the outcomes of the last meeting and the condition nomination process could be improved for future disease nomination conditions. Thank you for your time.

DR. CALONGE: Thanks, Elisa.

Kim Stephens

DR. CALONGE: Next we have Kim Stephens.

DR. STEPHENS: Hi. My name is Dr. Kim Stephens and I'm here today as the President of Project LIVE

and the co-Chair of EveryLife Foundation Community Congress newborn screening and diagnostics working group and as a parent advocate.

We offer the following comments to inform the Committee's ongoing efforts to enhance engagement with stakeholder communities. In the weeks since the Committee last engaged, our community members have raised concerns with how the Committee approached their decisions during the two votes at the February meeting and you've heard a lot about that today. And while the decisions themselves were disappointing and presented significant setbacks for each community, much of the frustration of the community stems from the processes involved in making each of these decisions.

As newborn screening advocates who are helping to drive the evidence development and implementation, we offer the following observation from recent Committee proceedings. With specific comments in regard to the Committee's charter and overall transparency and consistency, relating to the authorizing charter of the Advisory Committee.

Our community has noted that recent Committee’s discussions have often included issues beyond the specific scope of the Committee's charter.

On numerous occasions we have seen thoughtful and extensive conversations that explore the cost of clinical interventions and parental decision making in

the contest to follow up care and interventions. As parents and clinicians and community members, we agree. These are incredibly important topics, however it is the existence of an intervention treatment and the impact of that intervention treatment that are integral and germane to a nomination. Discussions to explore the costs of those clinical interventions and parental decision making are outside the scope of the charter of this Committee.

Related to transparency and consistency as has been previously noted, our communities are seeking increased transparent from many. We appreciate all the enhancements being made and as further enhancements are being made, we'd like to highlight two areas. With respect to Committee member selection, we continue to be unaware of the process around new Committee members' selection.

Specifically, what are the considerations including with on boarding of new members. Is there training or an orientation process so that new members receive deep acclimation to newborn screening system prior to making a decision that significantly impacts it? How is the overall membership balance of the Committee considered in terms of professional experience and expertise? Given the life-altering global significance of the decisions that are being made by this Committee, transparency and member selection, training and governance is critical.

With respect to conditions, nominations and evidence review it seems that each time a new condition is brought up for review the evidentiary standards begin to shift without prior conversations. For example, during the Krabbe disease nomination discussion, there were multiple discussions about having to update the decision matrix and the vote to change the matrix scores highlights apparent shifting of standards that leaves future nominators, as we heard earlier, guessing as to what's required to add a condition to the RUSP. We urge you to reach out to Committee, to member communities, to patient advocacy groups, researchers, public health labs and address these concerns. As members of these communities, we have seen the benefits of newborn screening. We understand that your decisions dramatically change the lives of thousands of Americans and we want to work with you and we're committed to bring about change but we need you to help us or meet us half way.

Thank you very much.

DR. CALONGE: Thank you, Kim.

Lesa Brackbill

DR. CALONGE: Next we have Lesa Brackbill.

MS. BRACKBILL: Good afternoon. My name is Lesa Brackbill and my daughter Victoria died from Krabbe disease in 2016. I can assure you that I speak

today from more than just a parental perspective. I know the science. I know the data and that has informed what I will say today.

One of the greatest lessons I have learned in recent years is the concept of listening to understand. I have learned to approach different perspectives with humility, a willingness to be wrong and an acknowledgement that others know more than me about some things. I assumed that membership on this Committee meant that a commitment to open-mindedness, to science and to acknowledging that others know more about certain conditions than members of the Committee do which is why nomination packages containing hundreds of pages of evidence are required.

As I watched the proceedings on February 9th I listened with the hope that justice would finally be served and with faith that the system would work properly and that's not what happened. Instead, I watched in disbelief as the afternoon unfolded and people with a known bias against screening for Krabbe disease, one of whom published a paper about it, were placed in charge of the benefit/risk analysis. I watched as misinformation was shared about diagnosis and treatment. I observed as the Committee asked questions amongst themselves that they couldn't answer instead of asking actual experts to clarify and inform.

Your response letter listed three evidence gaps, two of which were fully included in the package and the third one is not even an existent issue. What I learned on February 9th is that even the best systems are susceptible to failure.

We in the advocacy community are encouraged to trust you, to allow the evidence-based process to work instead of legislatively mandating that conditions be added which we are very good at doing. You ask so much of each rare disease group, both in time and in money, which can be millions of dollars before we even nominate and we comply because it seems like the right thing to do. So what are we supposed to do when that process is overridden by bias, neglects evidence and ignores statutes? What do we say when the goalposts are moved mid-consideration? What are we supposed to do when the parental perspective is completely ignored?

One of the most frustrating things I heard that day was that treatment was too risky because of a 10 percent chance of mortality, which isn't even an accurate number per published data. It's actually 5%. For Krabbe, MLD and other rare diseases the alternative is a 100 percent chance of death.

Most importantly, it's not your job to decide for parents whether or not it's worth that risk. It's the parents' choice whether or not they take that risk. You decided on February 9th that parents can't

handle this decision of Krabbe disease and robbed them of the opportunity to try, and that is an experience that I have lived that I would wish on no one.

You met Lily's mom earlier. Her parents have no regrets about transplant, Ezra's parents have no regrets, Emmalynn, Ty, Regan, Gina, Michael, Owen, Grayson, Arthur, Cloud AJ, Niko, DJ, David, Joshua, Jackson, Faith, Degan, Zoey, William, Jeremy, Elmer, Laura, Jervay, Jasper, Scarlett, Lexy, Ashley, Bell and so many others.

Their parents do not regret transplant. They're grateful that they had the choice, though many of them had to lose a child to save one. This is not an exhaustive list of names and it's certainly a shorter list than it should be. My daughter's name should be on that list along with hundreds of others who have suffered needlessly.

It should have been our decision, our story to write but a lack of newborn screening for Krabbe disease wrote our story for us. I am grateful that most of you have not lived the nightmare of child loss. I urge you to listen to those who have and to the scientists and clinicians who have spent decades working on Krabbe.

For the sake of the Krabbe disease community and for all the rare diseases that will follow in hoping to see their condition added to the RUSP, I

ask that you genuinely consider what I have said today. But mostly I hope that you will humbly be willing to admit that perhaps you were wrong. Because lives are literally depending on it. Thank you.

DR. CALONGE: Thanks, Lesa.

Annie Kennedy

DR. CALONGE: Next I have Annie Kennedy?

MS. KENNEDY: Good afternoon. I'm Annie Kennedy the Chief of Policy Advocacy and Patient Engagement for the EveryLife Foundation for Rare Diseases. And offering some comments to complement those of Kim Stephens who presented a few minutes ago and many of my colleagues here today.

For over the past two plus decades, I have had the privilege of growing to understand what a unique and extraordinary our newborn screening system is. Comprised of a diverse array of experts, each with a unique role to play, the spirit of collaboration among our partners is unmatched.

Outside of the setting of these Advisory Committee proceedings, our patient advocacy groups serve as central components of our newborn screening ecosystem. In fact, patients and patient advocacy groups are perhaps even the central components of our newborn screening ecosystem.

Few, if any nominations have come before this Committee without the leadership of a patient

advocacy group. Organizations whose missions often were initially centered around providing support to patient communities and seeking new therapies and development, yet realize that early identification was critical to this role.

As you know, developing the evidence requires decades, dedicated staff, millions of dollars, and most importantly it requires that advocates and clinical and scientific leaders learn the newborn screening system. In order to learn the system we have benefited from the generous mentorship of newborn screening experts.

Oftentimes these mentors have been members or former members of this Committee and always our mentors have been passionate leaders who've taken the time to help us develop plans for our individual conditions and the community at large.

For decades our communities have collaborated with our federal agency partners, state labs, government leaders, industry and provider groups. Through and from these collaborations, our patient advocacy organizations and the clinical and scientific experts with whom we work have developed assays and validated screening measures, designed and conducted pilot programs, established ICD codes, published and disseminated care standards, published fact sheets, supported registries, epidemiology studies and longitudinal data repositories, conducted

patient preference studies, established follow up programs and outreach systems, established national clinical care networks, collected health economic data, and so much more.

We have not only worked to move individual nominations forward and shared learnings and mentored others, but we've also formed coalitions to ensure that our federal and state agencies, your federal and state agencies have the authorities and the funding resources required to conduct this lifesaving work.

We work together in disease agnostic coalitions to share resources and mentor one another, just as you and the former Advisory Committee have shared resources with and mentored us. So as the Committee considers future enhancements to our processes, we continue to wonder why isn't our extraordinary ecosystem, this vibrant newborn screening ecosystem that exists outside of this room, fully represented when we walk into it? While we have highlighted many opportunities to more fully reflect our ecosystem and our partnerships within this Committee previously, today I'm just going to underscore one. Why, after we collaborate together for decades do we prevent those who could provide critical expertise to eliminate any uncertainty prior to a vote from being made available to the Committee?

So we again ask that the Committee formally include an expert member of the nominated conditions

community in every discussion of an evidence review to be able to address questions that when they arise throughout the discussion that proceeds a vote of a nominated condition. We thank you for your continuous assessment of these processes and the many ways that you contribute to our newborn screening ecosystem inside and outside of your Committee roles.

Mike Gelb

DR. CALONGE: Thank you. Next I have Michael Gelb.

DR. GELB: Hello. My name's Mike Gelb, professor of Chemistry at University of Washington and my lab, I guess I'm the troublemaker. I develop newborn screening assays for example MPS I, MPS II and Pompe that are now on the RUSP, so I guess I think I know what I'm doing with the newborn screening assays.

I want to announce that I am leading in a request to the Committee aimed at reevaluation of the N of 1 rule. The requirement to find at least one confirmed newborn with a disease in a perspective pilot study and for the patient to go on to receive treatment.

In a written report to the Committee along with greater than 100 signatures of supporters will follow in a few weeks. So in 2016, the Committee transcript which led to the N of 1 rule provided two

reasons. A single policy applied to all conditions so as to not appear arbitrary and to establish the newborn found with the disease went on to receive treatment.

So let me provide the following proof that a study with deidentified dried blood spots can identify newborns certain to have the disease. So in our study of 30 thousand deidentified dried blood spots, we tested for the bile acid disorder CTX and the lysosomal storages use NLD.

In both cases we had proof of no false positives and the best possible evidence of no false negatives. Let me say that again. We had proof for no false positives and the best possible evidence of no false negatives. We identified one newborn certain to have CTX and one for MLD.

Yes, we want to find newborns with a disease rather than a biomarker anomaly but in these studies the biomarker is proof of the enzyme deficiency and the genotype is well known from case reports to be severe disease causing.

In my interactions with at least 50 metabolic disease physicians we all agree that the presence of the disease in these cases are certain. You don't need N of 1 to establish that early treatment is needed. This Committee proved that. Illinois and Missouri are live for MPS II newborn screening. The patients identified and receiving treatment are too

young for experts to conclude that early treatment is important. MPS II was added to the RUSP based only on evidence from sibling studies. Not from perspective pilot studies. You made that very clear.

What about proof that N of 1 is needed to show that treatment will be provided. In the case of CTX, experts agree that treatments should start as early in life as possible. The treatment is FDA approved diet, supplementation with bile acids and the standard of care is to initiate treatment if the biomarker is elevated and the genotype clearly supports CTX.

Not a single CTX expert will have a problem initiating treatment with a clear biomarker and genotype signature of the disease. For MPS VII, another study we did a hundred thousand deidentified pilot, found zero false positives. Let me say it again. Zero false positives. It's published. One positive patient turned up, the one we found in Seattle Children's Hospital with the same genotype and birthday, who was then diagnosed with MPS VII, put on ERT treatment and surely we don't need an additional N of 1 for this disease. Since 2016, the N of 1 ruling early checked in North Carolina and screened plus in New York, which I applaud. Carry out pilot studies with current consent. After several years enrollment, it's something like 20,000 and it will take many years, maybe a decade to find N of 1

for some of these diseases.

These are the only perspective pilot studies in the United States and they show that the N of 1 is virtually impossible to achieve in our current system. Everyone knows about the GAMT story. It is ironic that N of 1 was satisfied with Utah and New York going live with current led legislation, exactly what this Committee is trying to avoid in the spirit of uniform newborns across the United States.

A better policy is to consider each nominated condition based on available evidence and to invoke N of 1 only when essential. I'm not saying you don't need it but sometimes you don't. I'm certainly not suggesting that we avoid the Wilson and Younger criteria or that we ask states to add new conditions without additional resources. Nobody is asking that. That would be crazy. Along with over a hundred of my colleagues I urge you to consider a better way for the future of nominated conditions by allowing the flexibility to relax the N of 1 rule by letting the Advisory Committee and HRSA carry out an initial review of a nominated conditions for those that have sufficient evidence to move to full evidence review. Really, what is the purpose served to find one more patient with CTX or MPS VII? Thanks for this important work that you do and for listening.

DR. CALONGE: Thanks, Mike. And now I have Susan Tanksley.

DR. TANKSLEY: Good afternoon and thank you for allowing me to deliver public comments today.

My name is Susan Tanksley. I'm the organizational representative for the Association of Public Health Laboratories.

My comments today pertain to counting conditions or more specifically the lack of uniformity in how state newborn screening programs count conditions. By now, everyone here has likely seen or read the article from *Investigate TV*, "Death by Zip Code" that addressed this topic.

Since that piece came out there's been at least one additional follow up article and some of my newborn screening colleagues have been contacted to provide background information or interviews for additional articles that will address what reporters are calling a great health divide.

This topic is of great interest to me, not only as the Deputy Director of a large public health laboratory but also as a chairperson for APHL's Newborn Screening Condition Counting Task Force. We are a group of 17 members representing newborn screening laboratories and follow up programs, clinicians, parents and international partners who have been working over the past two years on a framework, a set of guiding principles or rules to achieve uniformity in how states count the conditions on their newborn screening panels.

We are also proposing a few next steps that we feel should be recommended by the ACHDNC prior to asking programs to adopt this new framework. Before I dive into these, let's first establish why it's important for states to have a standardized way to count conditions that they're screening for and counting seems very simple but it's made incredibly complex because of the nuance involved in how you define screening.

For our purposes in the taskforce, we determine that a screening program is truly screening for a condition if the following criteria are met: the program intends to find all cases of a particular condition and the program would investigate any false negative or late diagnosis of that condition to determine if a change to their algorithm cut off from methodology could have detected the case.

Given these criteria, we believe it is misleading to count secondary conditions on a state's newborn screening panel, since true identification of those conditions requires a medical workup and differential diagnosis and therefore a program can't be said to be screening for them but these are difficult concepts to translate, especially to a parent or a family who just wants to see their child's newborn screening condition on a state panel.

From their viewpoint, the distinction between primary and secondary conditions seems arbitrary when

you look at a newborn screening panel and the implication that every disorder on that list would be screened for. Moreover, the belief that more is better is hard to change when it applies to so many situations and themes in our world. And did many states include secondary conditions on their state panel in response to their states desire to appear on par with their better than, their neighboring states. I'm aware of several other states whose programs have been asked how many conditions they screen for as many as State X. this makes true comparisons in areas for needed improvement within a program difficult to identify because it obscures real differences between programs.

The number of conditions from one state's panel may even differ depending on the source. For example, NewSTEPs reflects that my newborn screening program, the Texas program screens for 33 conditions which represents the core conditions, while at HRSA in our own newborn screening program website reflect that we screen for 57 conditions. Which is core and secondary.

For another state, NewsSTEPs reflects 34 disorders showing their core while HRSA reflects 57 conditions and the state's newborn screening website reflects 56 conditions. So three different counts, all from one state, as illustrated above, the secondary list adds to confusion by state programs, providers and the public as to whether these disorders are truly being

screened for versus possibly being detected for a screening through a core disorder. It also largely drives the confusion as to condition counts and is defined by the criteria already stated, we as newborn screening programs cannot say that we are truly screening for any of the secondary conditions.

Moreover the secondary list is not all encompassing as there are other diseases such as Zellweger's spectrum disorder and many others that aren't listed on the secondary conditions but can be detected through screening for a core condition. And thus, it does not provide accurate nor updated information.

For these reasons, the condition counting taskforce recommends that the ACHDNC remove the secondary conditions from the Recommended Uniform Screening Panel as an initial next step. Messaging around changing this practice of having a secondary list should indicate that other diseases may still be detected through the practice of screening through the core RUSP and these possibilities should be communicated to providers as part of a differential diagnosis, such as the ACT sheets.

Our taskforce also recommends that ACHDNC updates certain core condition names and groupings based on current knowledge of these conditions. In terms of nomenclature and how the conditions are specified or defined on the core panel. For example,

phenylketonuria on the RUSP should be changed to phenylalanine hydroxylase deficiency. There needs to be specification for what the targets are such as congenital adrenal hyperplasia and its classical CAH that newborn screening programs should target. And consider lumping some conditions together, such as hemoglobinopathies caused by different betaglobin variants.

There's new knowledge of some of the diseases and nomenclature has evolved to reflect this, keeping the core RUSP list updated to reflect current terminology aids in provider, patient and public understanding. Only in this way can states truly be compared.

For example, thanks to this Committee, the addition of SMA screening with a very specific target, absence of Exon 7 has aided a clear communication and assay development and can serve as a model for this work. We feel it is important for the ACHDNC to make clear recommendations regarding these changes prior to presenting our framework for standardization for condition counting, as this will facilitate states' ability to adopt the framework.

In APHL's 2022 survey of state newborn screening programs, a significant number of states indicated that changing the number and the list of conditions on newborn screening panel would be much more likely if the changes weren't keeping with the

national recommendation from this Committee.

Thank you for your attention and your action on this important matter.

DR. CALONGE: Thanks, Susan. I want to also thank everyone who came before the Committee today to make public comments. The Federal Advisory Committee Act, or FACA was a recognition by the Federal Government that decisions that impacted the public needed to have public, the availability of public comments, public input and engagement of the public in order for those decisions to best exemplify what the public felt was important and needed to come to the table with.

And so your participation in this process is key to the Committee doing continual improvement, to having the impact that the Committee wishes to have and to continue to move forward in this specific area here of newborn screening.

All the comments that we've had today will hopefully inform the Committee as we start to look especially at Committee processes and trying to improve those moving forward in time. So I really appreciate it especially recognizing how presenting in front of other people in public speaking is not something that everyone enjoys doing or wants to do. I thought everyone was so eloquent in their presentations and so passionate and so moving. So I appreciate that.

Acknowledgments and Awards

I want to move on and finish the day though by doing some recognitions to Committee members who are departing after this meeting. Both Dr. Brothers and Dr. DeLuca joined the Committee in March of 2019 which means that they're both completing four years of work on the Committee. Dr. Brothers during his time served as a Chair to Follow-Up and Treatment workgroup. He served as a member of the Nomination and Prioritization workgroup, taking on reviews of condition nomination packages. Kyle, I have to thank you for your service, your immeasurable contributions. I feel a sense of loss in thinking about you not sitting on the Committee and providing your insights. I've only shared the chairs with you for a very short period of time but you've meant a lot to me in terms of thinking about the work of the Committee, how we need to think about ethics and responsibility to the public and I thank you for time. Thanks, Kyle.

Jane? And we have something for you. I have something for you.

[Applause]

DR. BROTHERS: It feels weird to be departing the Committee right now. I feel that we're at a pivotal time. We have a lot of questions before us that are, you know, fundamental to the way the

Committee works. The conditions that are being considered are ever rarer, creating difficult questions we've been discussing today, we've been hearing about today. What's the evidence of benefit, of incremental benefit from early screening, etc., all sorts of these critical issues so I do hate to be leaving as we're having those active conversations. Maybe if I left a year from now we'd still be at a pivotal point. But I do, I just want to thank everyone for including me in the community that I have sort of not--didn't live my life in as some of you have but it's really been wonderful getting to know the advocates and parents, the members of Committee and you, Ned. So I thank you so much for having me as a part of the group. It's really been wonderful. Thank you.

DR. CALONGE: Dr. DeLuca, throughout her term has served as the chair of the Education and Training workgroup. Dr. DeLuca also served as a Committee liaison to the Evidence Review Group and has been a key contributor to this element of the Committee's work over the past four years. Jane, I have to thank you again for your commitment, the ongoing, great quality of work that you've provided, Committee discussions and support for Committee decisions going forward. The issue about training and education as key to the success to the Committee and I think that your leadership has really helped HRSA,

helped the Committee and helped all 50 State programs to think about how to best incorporate training and education to assure the success of the program moving forward.

So I wonder if you would be willing to come up and take a nice little piece of class from—

[Applause]

DR. DELUCA: Thank you, Ned and hi everybody. The appointment to the Advisory Committee was very important for me personally. I've worked in newborn screening for many, many years in the front line, in terms of taking care of patients and families that have been identified through newborn screening.

I feel like I'm a COVID baby because a good part of my being with the Advisory Committee was through COVID and I feel like the Committee persevered, you know, through that. And like Kyle, also feel like there's change afoot, you know, in terms of what the Committee is doing and what's going to be happening in the next few years which I feel is really, really important. I want to thank the families and my fellow Committee members and just thank you very much.

[Applause]

DR. CALONGE: Thanks, Jane. And finally we have someone leaving us who is not termed out and so I have to acknowledge Kellie Kelm who is our representative from the FDA and a very valued

colleague.

Dr. Kelm joined the Advisory Committee in February of 2009, officially the member with the longest tenure on our Committee. She served as a chair for the laboratory standards and procedures workgroup for many years. She has provided years of support to this Committee and helpful information about the FDA's work on newborn screening. She has recently taken on a new role as the Deputy Officer Director for the Office of Gastro Renal OBGYN General Hospital and Urology Devices so she'll rotate off.

And I know that I am speaking for both people currently on the Committee and people who were on the Committee in the past in thanking you for providing service and more than ten years. When we don't exactly know you're going to rotate off, it takes us a while to get your recognition ready and delivered but it is coming and I'm wondering if you could come up and make a couple of comments.

DR. KELM: Thank you. You know it's hard to believe. It started I had a nine-month-old and now he's finishing his freshman year of high school so, it's been quite a journey. And Ned, I want to thank you. I'm obviously from the FDA side and not a newborn screening side but everyone has been so welcoming and it's just been just a wonderful learning experience and great interacting with so many of you over the years and getting a lot of help

since this is not, I just wanted to be a part of it.

And Susan and I wound up with timeliness and lots of other challenges, a lot more things going on than I think we expected and I hope that it's just been wonderful to just be a small part of it. And as Kyle said, it's going to be challenging, and it has been the last 15 years and it's going to be exciting to see where it goes so, anyway. Thank you very much.

[Applause]

DR. CALONGE: That brings us to the end of day one and we will begin promptly at 9:30 a.m. tomorrow. I wish you all a good evening and we'll adjourn the meeting for today. Thank you.

(Whereupon at 4:25 p.m., the meeting adjourned, to reconvene on Friday May 5, 2023.)