Health Resources and Services Administration

Advisory Committee on Heritable Disorders in Newborns and Children

Meeting

10:00 a.m. to 3:10 p.m.

Tuesday, April 23, 2019

Committee Members

Joseph A. Bocchini, Jr., M.D. (**Chairperson)**
Professor and Chairman
Department of Pediatrics
Louisiana State University
Health Sciences Center in Shreveport

Mei Baker, M.D.
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Departments of Pediatrics and Genetics,
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University of Minnesota

Jeffrey P. Brosco, M.D., Ph.D.
Professor of Clinical Pediatrics
University of Miami School of Medicine
Department of Pediatrics
Deputy Secretary, Children's Medical Services
Florida State Department of Health

Kyle Brothers, M.D., Ph.D.
Endowed Chair of Pediatric Clinical and
Translational Research
Associate Professor of Pediatrics
University of Louisville School of Medicine

Jane M. DeLuca, Ph.D., R.N.
Associate Professor
Clemson University School of Nursing

Cynthia M. Powell, M.D.
Professor of Pediatrics and Genetics
Director, Medical Genetics Residency Program
Pediatric Genetics and Metabolism
The University of North Carolina at Chapel Hill

Annamarie Saarinen
Co-founder, CEO
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Scott M. Shone, Ph.D., HCLD(ABB)
Senior Research Public Health Analyst
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Beth Tarini, M.D., M.S., F.A.A.P.
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EX-OFFICIO MEMBERS

Agency for Healthcare Research & Quality

Kamila B. Mistry, Ph.D., M.P.H.

Senior Advisor

Child Health and Quality Improvement

Centers for Disease Control & Prevention

Carla Cuthbert, Ph.D.

Chief, Newborn Screening and Molecular Biology Branch

Division of Laboratory Sciences

National Center for Environmental Health

Food and Drug Administration

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Organizational Representatives
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Robert Ostrander, M.D.
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American College of Obstetricians & Gynecologists
Britton Rink, M.D., M.S.
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Susan M. Tanksley, Ph.D.
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Association of State & Territorial Health Officials

Christopher Kus, M.D., M.P.H.
Associate Medical Director
Division of Family Health
New York State Department of Health

Department of Defense

TBD

Genetic Alliance

Natasha F. Bonhomme
Vice President of Strategic Development Genetic Alliance

March of Dimes

Siobhan Dolan, M.D., M.P.H.
Professor and Vice Chair for Research Department of Obstetrics & Gynecology and Women’s Health
Albert Einstein College of Medicine and Montefiore

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National Society of Genetic Counselors

Cate Walsh Vockley, M.S., LCGC

Senior Genetic Counselor

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UPMC Children’s Hospital of Pittsburgh

Society for Inherited Metabolic Disorders

Shawn E. McCandless, M.D.

Section Head, Genetics and Metabolism

Children’s Hospital Colorado

C O N T E N T S

P R O C E D I N G S

CHAIRMAN BOCCHINI: All right. Good morning, everyone. I want to welcome to the second meeting of the Advisory Committee on Heritable Disorders in Newborns and Children for 2019. We will begin this meeting by taking roll call. All right, so we're going to start -- is that -- okay. Yes, all right, red means on. Okay. So, we have new microphones here, so it will take me four hours to figure it out. So, roll call for committee members first. Kamila Mistry, Agency for Healthcare Research and Quality Kamila Mistry.

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Mei Baker.

DR. MEI BAKER: Here.

CHAIRMAN BOCCHINI: Susan Berry?

DR. SUSAN BERRY: Here.

CHAIRMAN BOCCHINI: I'm here. Jeff Brosco.

DR. JEFFREY BROSCO: Here.

DR. JOSEPH BOCCHINI: Kyle Brothers.

DR. KYLE BROTHERS: Here.

DR. JOSEPH BOCCHINI: Jane DeLuca.

Dr. JANE DELUCA: Here.

DR. JOSEPH BOCCHINI: Carla Cuthbert.

DR. CARLA CUTHBERT: I'm here.

DR. JOSEPH BOCCHINI: Kellie Kelm.

DR. KELLIE KELM: Here.

CHAIRMAN BOCCHINI: Joan Scott.

MS. JOAN SCOTT: Here.

DR. JOSEPH BOCCHINI: Cynthia Powell.

DR. CYNTHIA POWELL: Here.

DR. JOSEPH BOCCHINI: Melissa Parisi.

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Annamarie Saarinen.

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH BOCCHINI: Scott Shone.

DR. SCOTT SHONE: Here.

DR. JOSEPH BOCCHINI: Beth Tarini.

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: And our DFO, Catharine Riley.

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: Now, for your organizational representatives, the American Academy of Family Physicians, Robert Ostrander.

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: American Academy of Pediatrics, Debra Freedenberg.

DR. DEBRA FREEDENBERG: Here.

DR. JOSEPH BOCCHINI: American College of Medical Genetics, Michael Watson.

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: American College of Obstetricians and Gynecologists, Britton Rink via webcast.

DR. BRITTON RINK: Here.

DR. JOSEPH BOCCHINI: Association of Maternal and Child Health Programs, Jed Miller.

DR. JED MILLER: Here.

DR. JOSEPH BOCCHINI: Association of Public Health Laboratories, Susan Tanksley.

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Association of

State and Territorial Health Officials, Chris Kus, by webcast.

DR. CHRISTOPHER KUS: Here.

DR. JOSEPH BOCCHINI: Child Neurology Society, Jennifer Kwon by webcast. Genetic Alliance, Natasha Bonhomme.

MS. NATASHA BONHOMME: Here.

DR. JOSEPH BOCCHINI: March of Dimes, Siobhan Dolan.

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: National Society of Genetic Counselors, Cate Walsh Vockley.

MS. CATE WALSH VOCKLEY: Here

DR. JOSEPH BOCCHINI: Society of Inherited Metabolic Disorders, Shawn McCandless.

DR. SHAWN MCCANDLESS: Here.

DR. JOSEPH BOCCHINI: Thank you. Now that we have completed roll call, we now need to approve the minutes of the prior meeting. Committee members received a draft of the minutes of the March meeting to review prior to this meeting. We incorporated revisions submitted by

committee members, distributed a final draft of the minutes to the committee prior to this meeting. Are there any further additions or corrections to be made to the minutes? Hearing none, we will proceed with a vote to accept the minutes as they have been distributed. This is a committee member vote. Mei Baker.

DR. MEI BAKER: Approved.

DR. JOSEPH BOCCHINI: Susan Berry.

DR. SUSAN BERRY: Approved.

DR. JOSEPH BOCCHINI: I approve. Jeff Brosco.

DR. JEFFREY BROSCO: Approved.

DR. JOSEPH BOCCHINI: Kyle Brothers and Jane DeLuca will abstain since they have just joined the committee. Carla Cuthbert.

DR. CARLA CUTHBERT: Approved.

DR. JOSEPH BOCCHINI: Kellie Kelm.

DR. KELLIE KELM: Approved.

DR. JOSEPH BOCCHINI: Kamila Mistry.

DR. KAMILA MISTRY: Approved.

DR. JOSEPH BOCCHINI: Melissa Parisi.

DR. MELISSA PARISI: Approved.

DR. JOSEPH BOCCHINI: Annamarie Saarinen:

MS. ANNNMARIE SAARINEN: Approved.

DR. JOSEPH BOCCHINI: Joan Scott.

MS. JOAN SCOTT: Approved.

DR. JOSEPH BOCCHINI: Scott Shone.

DR. SCOTT SHONE: Approved.

DR. JOSEPH BOCCHINI: Beth Tarini.

DR. BETH TARINI: Approved.

DR. JOSEPH BOCCHINI: Did I skip Annamarie Saarinen? Oh, Cindy Powell.

DR. CYNTHIA POWELL: Approved.

DR. JOSEPH BOCCHINI: Okay. All right. So, the minutes are approved as distributed.

So, I would like to now introduce you to our new two committee members. They are now joining us for the first time, Dr. Kyle Brothers and Dr. Jane DeLuca. They will serve on the committee through June 30, 2023. I would like to give you a brief introduction about both of them.

Dr. DeLuca, a Ph.D., R.N. is an associate professor in the School of Nursing at Clenson University, South Carolina. Dr. DeLuca is a pediatric nurse, academic scientist, and university instructor with special expertise in the field of heritable disorders who provides services for newborns and children at risk for hereditable disorders. She has a clinical appointment at the Greenwood Genetic Center in their Metabolic Clinic. In her practice, she cares for patients with inborn errors of metabolism. She has more than 15 years of clinical care experience with children and their families identified with metabolic and genetic disorders through newborn screening programs in New York and South Carolina in both urban and rural service areas. Her research interests include parents and family experiences of newborn screening. She is a board member of the Society for Inherited Metabolic Disorders. So, Dr. DeLuca, we welcome you to the committee.

Next is Dr. Kyle Brothers. Dr.

Brothers is an M.D., Ph.D. and is an associate professor of Pediatrics and the Endowed Chair for Pediatric Clinical and Translational Research at the University of Louisville. Dr. Brothers received his MD from the University of Louisville School of Medicine, completed his pediatric residency training, including a chief residency year in pediatrics, at Vanderbilt and his Ph.D. in Ethics and Society, also at Vanderbilt University. Dr. Brothers' research focuses on Policy and Ethics in Human Genetics and the Translation of Health Technologies into Clinical Care. Dr. Brothers is a practicing primary care pediatrician and serves as a Chair of the Ethics Committee at Norton Children's Hospital in Louisville, Kentucky. So, Dr. Brothers, welcome to the committee. We look forward to your contributions.

Next, we mentioned at the last meeting that we were working through a number of organizations that had requested becoming organizational representatives. I want to thank all of the organizations which applied. Two

organizations have been selected to join the organizational representatives for the committee. These representatives will be joining us in August, and at that time, we will introduce them and name the organizations.

Next, we have received a new condition nomination for the RUSP. The committee has received the nomination for including congenital cytomegalovirus infection. This was submitted by a nomination team led by the National Cytomegalovirus Foundation. The submission is currently undergoing initial review.

Our next meetings are listed on this slide. The next in-person meeting will be August 1 and 2, 2019, followed by the November meeting. All of the meeting dates have been set up through 2023, and these can be found on the committee's website.

So, today we will begin the meeting with a number of presentations. We will first hear a presentation on New Disorders Readiness Tool. We'll follow with a Draft Approach and

Timeline for review of the RUSP Condition Nomination Evidence Review Process. This is a continuation of the information that comes from our plan to review our processes to update them as needed to try and improve decision making if necessary. And then, we'll hear about the Systemic Evidence Review Process.

Next slide. And then tomorrow, we'll hear a presentation on Newborn Screening Pilot Studies. We will hear an update from the Ad-Hoc Workgroup on Interpreting and Presenting Newborn Screening Results, and then we will hear from two rare disease registries, the Cystic Fibrosis Foundation and the CF Registry as well as the Primary Immune Deficiency Consortium, which is collecting data on SCID and related Immune Deficiencies.

We'll then hear from our workgroups for the work that they will have completed this afternoon. And then, we will follow on with a presentation on what's on the horizon for the committee as we change leadership after today's

meeting.

So, I will now turn the presentation over to Catharine to go over the DFO slides.

DR. CATHARINE RILEY: Excellent. Thank you, Dr. Bocchini. First, I just want to say good morning to everyone here in the room and for all those joining us via the live webcast across many time zones. We appreciate you all joining us today. We have a full agenda today, and we're excited for the next couple of days.

So, I have my general set of announcements. This Advisory Committee's legislative authority is found in the Newborn Screening Saves Lives Reauthorization Act of 2014. This legislation established the committee and provided the duties and scope of work for the committee. However, all committee activities are governed by the Federal Advisory Committee Act or FACA, which sets the standards for establishment, utilization, and management of all Federal Advisory Committees. As a committee member on the Federal Advisory Committee, you are subject to the

rules and regulations for special government employees.

So, I have standard Ethics and Conflict of Interest reminders for the committee that I want to go over. I want to remind the committee members that as a committee, you are advisory to the Secretary of Health and Human Services, not to Congress. For anyone associated with the committee or due to your membership on the committee, if you receive inquiries about the committee, please let Dr. Bocchini or I know prior to committing to any interviews or presentation engagements.

I also must remind committee members that you must recuse yourself from participation in all particular matters likely to affect the financial interests of any organization with which you serve as an officer, director, trustee, or general partner unless you are also an employee of the organization or unless you have received a waiver from HHS authorizing you to participate.

When a vote is scheduled or an

activity is proposed and you have a question about a potential conflict, please let me know as soon as possible.

So, according to FACA, all committee meetings are open to the public. If the public wishes to participate in the discussion, the procedures for doing so are published in the Federal Register Notice and are announced at the opening of the meeting. For this meeting today, we have both public comments that are going to be presented in person and the committee received written comments ahead of time, and those were distributed to committee members before the meeting. Any further public participation will be solely at the discretion of the Chair and myself as the DFO.

Before I move on from there, do I have any questions from any committee members? Okay.

So, I wanted to go over just a few logistics for being in the HRSA Building. So, visitors, as a visitor, you only have access to

the pavilion, which is this room we're in, the cafeteria, restrooms, and the meeting rooms that we'll be in this afternoon for the workgroups. All other areas of the facility are restricted and do require an escort by a HRSA staff member, and there are no exceptions for this. If you need to leave and re-enter, you will be required to go through security again. Around lunchtime and the breaks, there will be a HRSA representative by Security in case you do need to leave and re-enter around lunchtime.

We also ask that you not take any personal photography or video in the building, in particular around the entrance area. If a HRSA staff member is taking pictures or directing you to take pictures, that's okay; but, with your personal camera, we ask you not take pictures or photography of the building.

In case of emergency, please exit through the front door, so those are at the main security entrance that you came in today, cross the street and meet in the parking pad to the

left. Your escorts will have a roster and ensure everyone is accounted for. If there is an evacuation, please do not take -- only take essential items. Don't take any non-essential items, as this may slow down evacuation.

That is for the logistics. For the fun news, you may notice that we're all wearing beads. You may have gotten beads when you came in. This, of course, is in honor of Dr. Bocchini, with this being his last meeting serving as Chair. He has often brought beads to us, being from Louisiana in celebration of Mardi Gras and other festivities. So, we wanted to wear these in honor of you today, Dr. Bocchini. So, with that, I will turn it back over.

DR. JOSEPH BOCCHINI: Okay. Thank you. I hope everybody got their beads. I think that's a very kind gesture. Thank you. We're going to now move to the first presentation, which is entitled New Disorders Readiness Tool. That will be presented by Yvonne Kellar-Guenther. Dr. Kellar-Guenther is a senior research scientist

at the Center for Public Health Innovation at CI International and a clinical associate professor at the Colorado School of Public Health. Dr. Kellar-Guenther is a program evaluator for NewSTEPs. As part of this project, she developed and administered the readiness tool to track newborn screening programs and their readiness for screening for new disorders. So, this is an important topic that we are looking forward to your presentation. So, thank you.

NEW DISORDERS READINESS TOOL

DR. YVONNE KELLAR-GUENTHER: Thank you. So, thank you for inviting me to talk to you guys today. I also find it as a very important topic, so I appreciate the chance to speak to you.

On September 1, 2016, NewSTEPs received funding from HRSA to help support states in getting ready to implement for three new disorders. Specifically, we were helping with Pompe, MPS-1, and/or X-ALD, and as you all know very well, these were recently added to the RUSP, right? So, Pompe was added four years ago, MPS-1

and X-ALD were added three years ago to the RUSP. And so, as part of our funding, one of the things that we wanted to do is we wanted to understand prospectively how long it actually takes to go from first activity to actually implementing statewide screening. Up until now, when things are added, we asked states to kind of guestimate how long it's going to take, and the scientist in me wanted to be more exact than that. And so, we created the readiness tool to try to get some of that information. And like all good tools, we created it, and then we got the Steering Committee to actually help us finesse it a little more, and we got some expertise.

So, in the readiness tool, we actually look at statewide implementation and readiness in four phases. The first phase is the approval or authority to screen. And so, this is getting authority from the State Board of Health, the State Newborn Screening Advisory Committee. It also includes approval to raise funding. Phase 2 is the Lab and Followup Logistics, so this is

lab readiness, followup readiness, IT readiness. Phase 3 is education, and we're talking about education for the general public, for the families, and for the providers. And then phase 4 is the actual implementation, and there's a couple of different ways that we measure implementation. We do pilot screening. We do screening for selective populations. But what we're really interested in is the statewide implementation. So, what's what I'm going to talk to you more about today is the statewide implementation.

So, as part of our funding, we had some research questions that we wanted to answer, the first being, how long does it take to implement statewide screening for a new disorder. So, again, from the first activity to when we actually had statewide implementation. And again, it was prospective data.

We were interested in looking at the timing for the readiness phases, because we wondered if some phases took longer than other phases in trying to get a sense of where screening

programs were spending time, and with that, we were also interested in where most of the time is spent. And you've seen in the readiness tool, I included that as one of the documents that you got, but this is not like a recipe where you walk through every step. It's really big chunks, right? So, were you able to get the machinery? Do you have followup protocols? So, we're talking about big pieces when we talk about time being spent.

So, we're also interested in understanding the facilitators and the barriers to actually getting statewide screening up and running, and so we gathered that data as well.

So, as I mentioned, one of the ways that we gathered data was with the readiness tool. We were very fortunate in that we were able to get data from 39 states. So, 16 of those states received funding from NewSTEPs to help with the rolling and the readiness, and they provided data. Two of those states were Peer Resource Networks, so as part of our funding, we had three Peer

Resource Network centers that provided support, and you'll hear a little bit about that throughout the presentation, but they also -- two of the Peer Resource Networks were able to provide prospective data on getting ready for at least one of the new conditions that we were looking at.

And then, again, as part of the funding, we held annual meetings. And so, we opened those up to everyone, and one of the things that we asked for is if you're coming to the meeting, could you fill out the readiness tool, so we kind of have a sense of where you're at. And so, 21 other states were able to provide data because they were able to attend these meetings. So, of the 39 states that provided data, 39 were able to provide us data on getting ready for Pompe, 38 on getting ready for MPS-1 and X-ALD, and then last June when we had groups come out, we actually added SMA, because that had been added to the RUSP. And so, we have data for some initial activities for 27 states. That's very new. I'm not going to focus much more on SMA other than

that. But just so you know, we have some of that early data.

So, when you look at this graph, what you're going to see, right, is the actual phases that states were in. So, when you look at the purple across the tops, those were the states that actually were able to implement statewide screening while we were gathering data. So, what you should think is, that's not as many states as I was thinking. So, what we know, we know a lot about in progress. So, a majority of the states that have provided us readiness tool data as of February 28th, between 50 and 58 percent are still in progress. So, that's something to think about. We're talking about conditions that were added to the RUSP four years ago, three years ago, and the majority are still in progress. The other column that is probably of interest to you -- it was to me -- is the not started. So, we have 10 to 15 percent that three to four years after being added to the RUSP haven't started for various reasons. But when we talk about readiness in statewide

screening, that's something that we need to probably dig a little deeper into.

In addition to the readiness tool, we also gather data from annual reports. So, the states that were funded, we asked them to provide us annual reports, and in that, we wanted them to talk about the facilitators and the barriers. And so, after the last round of annual reports, we went through and we qualitatively analyzed those to kind of identify what those things were, and what I'm going to share with you today is only things that came up by at least three states. And then of that 16, we wanted to dig a little deeper, so we did key informal interviews with 7 states. So, these are still awardees, but they were either fast on something, slow on something, or there was something in their annual report that made us curious, so we decided that we wanted to talk to them a little more.

So, before I share the data with you, all data has limitations, and I want you to go in with your eyes wide open. The last collection was

February 28, 2019. We asked everyone to give updates. We do not mandate it. We do not require it. So, we don't have updates necessarily from everyone, but we got from a lot. But that's also six weeks ago, right? And so, in that time, things could have shifted. Some states weren't able to provide us the actual start and end dates. We calculated the time difference by the start and end date, the date difference. But some states told us here's how long it took, and we went ahead and used that data. So, we used those estimates as well as our exact dates.

There are states that are screening for these disorders that did not provide readiness data for a couple reasons. They had done it so long ago, they couldn't remember, and it wouldn't be accurate, or they just -- they didn't need to, right? So, we're not representing everyone. We're really representing the 39 states that provided data.

And the facilitators and barriers are only coming from the participating programs. So,

when I share them, you're going to be like, wow, no one talked about the need for funding -- probably because we were funding them. And so, when we -- there's probably other facilitators and barriers that are missed. They're also reporting facilitators and barriers to a group that provided them funding, so they might be a little biased.

So, the big question. How long does it take to implement statewide screening for a new disorder? So, on these box blocks, there's a lot of information here, but one of the things that you'll notice is that while the means are different and the ranges are different, the medians are the same. And so, the median amount of time that it took to implement statewide screening for the 13 states that actually implemented statewide screening was two years, four months. So, when we talk about the Public Health Impact Assessment, the estimate we tend to get is one to three years. And so, for these 13 states, that holds true. That's accurate for the median. But what you'll also notice is for Pompe,

you have a much wider distribution of time that it takes. It gets a little tighter with MPS-1 and a little tighter with X-ALD. So, why is that?

So, one of my theories is that as you prepare for one, you might have steps you don't have to do again for another. And so, if you prepared for MPS-1, or sorry, if you prepared for Pompe, MPS-1 may be a little quicker. And all nine programs that had implemented screening for Pompe also implemented screening for MPS-1. So, it's possible that that's what's going on.

You also had four of the thirteen programs that actually implemented screening for all three new disorders. So, they did Pompe, MPS-1, and X-ALD. So, it's possible as they did some of those activities for the earlier ones, it made the other phases quicker.

This is a quote from one of our respondents in the interviews. They're at the high end, and they're like, "Our timelines are longer because we were the first program and had so much to validate before we could start our full

population pilot. So, it kind of speaks to getting some of that stuff done with the first that maybe benefits rolling out others. But it also speaks to the need for assistance, right? So, gaining assistance from other states was a facilitator to implementing statewide screening, which makes sense. But, if you're one of the early adopters, your timeline is going to be a little longer than if you're one of the later adopters. So, those states that are waiting might be quicker, because they're going to have resources that the states that started earlier may not have.

So, when we looked at kind of facilitators and barriers, nine states said that the collaboration between states makes it easier to implement statewide screening for new disorders.

So, as I mentioned, as part of a new disorder funding, we convened states every June, and these were states that some were screening, some weren't, but those sessions were built to

learn from each other. They shared things that were happening. They talked about questions that they had, and they could ask each other. And that was found to be very helpful. So, I think as we roll things out, that something to consider is how do we build those systems for states to work with other states and learn from other states.

Also, as part of the funding, we have these peer network resource centers, and that was mentioned as a facilitator by the nine states. They could go visit them. They could see what methodology they were using. They housed events that were really helpful for them in rolling out the statewide implementation. We did have three states say that one of the barriers to implementing statewide screening was limited information. Those are some of our early adopters. So, we just have to think about that as we think about states getting ready to implement statewide screening.

So, that picture is of one-third, right, of the states that we gather data from.

So, how do they compare to the other states that are kind of still working? So, if you look at the right side, that -- I guess actually your left, sorry -- we've got the 24 months -- sorry -- the 28 months median time that they took from the first activity statewide screening. But when you look at your right side, what you'll see is other states that are in progress are spending a similar amount of time. So, it's possible that all those states that are in progress have finished within the last six weeks, and then the time frames are the same. But that's probably not likely. And so, while we've got this median of two years and four months, my guess is it's going to go a little higher, right, as these other states -- the 50 percent that are still working -- are finishing. So, we have to remember that as we kind of look at this and gather information.

So then, another question, right, was how long does each readiness phase take? So, the first phase was authority to screen, and we had 25 states that had started and completed at least one

activity in this authority to screen. So, they talked to some committee, had gotten permission from some committee. Seventeen, or 44 percent of them, had received approval for funding. So, we've got more that are working toward the authority or have finished the authority then we have for the approval for funding. It took a median of 18 months to get through those phases, right, so, a year and a half. And this only represents the 13 programs that are actually implementing statewide screening. So, this is also the 13 programs that implemented statewide screening and the approval for funding is a similar time. You've got a median of 17 months, right, somewhere between 15 and 19 months to get that approval for funding.

When you start looking at the actual activities, so each activity with its beginning and end date, so this now includes everyone who's had at least one activity completed, you see that there's a huge variation. Some are getting things done in zero days, which kind of seems like it

might not be the case but if you have a mandate to screen, it turns out that's zero days. And of the 13 states that are screening, about half of them had a mandate to screen for at least one of the conditions. So, that's the other caveat with this group.

But these activities can take anywhere from zero days to close to three years, right? So, you see a large variety in how long the activities take. So, which activities are taking us a while? Well, on the high end, one of those is obtaining approval from the State Newborn Screening Advisory Committee that took a median of six months. The other -- there's two others -- the other one is obtaining approval from the State Budget Authority. That took a median of six months, and developing a budget took a median of five months. So, these are the -- when you look at kind of those high end, these are the subsets that are taking the longest.

This is a quote from one of my interviewees, and I know it's long, but I think it

really explains kind of the complexity of this process, right? So, "In our administrative code, we review all new disorders that come onto the RUSP and report back to the full Advisory Committee. That state-based committee will vote on recommendations and then send it to the Commissioner of Health. The Commissioner will then take it to the Board of Health and say that we want to change regulations." So, one thing that you see in terms of differences is some states need one group to say this is okay, some need multiple. The more you need, the longer it's going to take, right? "As soon as we get the Commissioner of Health to agree, that starts a process where you post notice of intent to change regulations, 30 days of comments, edit the notes based on public comments, go to Planning and Budget, the Attorney General, et cetera, and each one has to sign off." So, for this state, there's lots and lots of pieces that they have to go through. It's going to be really hard to do this quickly. Each approval step can take between 30

and 60 days. So, when we talk about maybe wanting to get things approved quicker, this is hard, because they have no room to compress. That 30 or 60 days has to stay there, and for this state, all those steps could take 18 months to a year. And on the outside, you think, wow, that's a really long time. But this last sentence is actually one of my favorites. "This process gives us time to systematically and carefully bring up a disorder."

So, I think one of the things we have to think about is faster may not be better, right? And so, there's something about this approval time that allows them to do the lab readiness, the followup readiness, right, the education. And so, as we talk today about kind of how quickly things take or don't take, let's remember that faster maybe isn't always better.

The other piece is that they're not doing the phases sequentially. They're doing them simultaneously. So, this allows some wiggle room for that validation for getting in equipment and those types of things.

So, how are we doing on lab readiness? So, the median time to actually have the lab ready is 21 months. This phase had the longest median time. so, when we look at all four phases or all three phases, this is the one where the most time was spent, which probably isn't a shock to any laboratorians in here. We had 23 of the states had actually completed at least one activity in lab readiness, so 59 percent. And again, we see some of them took zero days, and then this time, it's a little over three years, right, for some of those steps that take longer.

So, what are those activities that are taking the longest? Well, it took a median of 12 months to identify laboratory space, modify, and install the equipment. I don't know if you can make that faster, maybe. But that's the main time-consuming activity, which I think makes sense. And then you had a median of nine months to identify the needed equipment, so that might be something that could go a little faster. Nine months to develop a lab-staffing plan, and nine

months to train laboratory staff. So, equipment and staffing are kind of the big things that are taking time in the laboratory readiness. It turns out those are also your main facilitators and barriers. So, if you don't have the staff, it turns out it's really hard to implement statewide screening, and nine states out of sixteen mentioned lab-staffing shortages as being an issue. And so, they are also doing the other parts of their job while they are trying to get this up. So, you can see that lab-staffing shortages are kind of compounded, right? It's a really big issue. It's hard to overcome. And for the three states that were able to hire lab staff, they thought that that actually helped them be able to implement statewide and sooner.

Equipment, same thing. If you have it, things go faster. If you have to get it, things are slower, right? So, the ability to get the new equipment and assays were mentioned by six states as a facilitator. The inability to get the equipment or not having access was mentioned as a

barrier by another six states. Just because you have the equipment doesn't mean that you can start running, right? So, the other big barrier is actually getting the equipment up and running. So, that also takes some time. So, it's not a surprise that this is the one readiness phase that takes the most.

In terms of where we can help, one of the places is having FDA-approved kits. So, not having an FDA-approved kit and/or instrumentation was a barrier for three states. That might be something that can be done before they start statewide implementation. And then validating methodology. This goes back to that earlier comment of being able to collaborate and work with other states. They help with some of this validation. And so, having that system in place could be really helpful in getting states up and running.

So, followup -- so, followup took a median of 18 months to get ready. We have 20 participating states that had done at least one

followup. So, what you're seeing is the majority have done at least one step in approval authority to screen. You have a little bit of a drop for lab readiness. You have a little bit of a drop for followup. So, some states that are in progress haven't really quite hit the followup piece yet. But you have 51 percent of the respondents were able to talk to us about at least one activity.

So, while it was a shorter time in the median time to actually get followup readiness up and running, it's actually a little longer for each activity, right? So, instead of looking at a median of five to six months, we're starting to look at medians of seven to nine months. So, this is one of the stages where they actually have outside people who aren't doing newborn screening day-to-day help, right? So, when you're talking about long-term followup protocol -- when you're talking about identifying medical specialists, those are people outside of the State Newborn Screening System, and so that's my hypothesis as

to why it might be taking a little longer. But that's just a hypothesis. But their activities take from zero days to like three-and-a-half years. So, it can take a while for some of these activities.

The ones that are at the top -- the things that take the longest -- identifying medical specialist or treatment centers, and again, that's something that maybe could be approached beforehand that could maybe help the states be a little quicker in gearing up. It took nine months median time to develop and gain buy-in for short-term followup protocols and nine months median time to develop and gain buy-in for long-term followup protocols. And we've all had discussions on long-term followup protocol, so we understand. But these conditions specifically brought up some of those issues that I think we haven't had with some of the other conditions added to the RUSP.

Again, not a shock, staffing was a problem for followup as well, right? So, if you

have them, things go faster. If you need to hire, then it's a barrier, and it takes a little longer.

But setting up the followup protocols was identified as a facilitator by five states going through the process, working with those stakeholders, really helped get things up and running. So, that's something to think about as we think through the readiness.

And then, difficulty around establishing long-term followup protocols was mentioned as a barrier to implementation for three states.

So, IT -- so, for IT readiness, we looked at several different things. We looked at changes to the LIMs. We looked at changes to the followup reporting system. We looked at electronic ordering and electronic results reporting. So, my first caveat is when we looked at -- statewide implementation isn't the end for readiness. So, states were starting activities after they had statewide implementation of screening. The number one activity that they were

starting after statewide implementation for screening was IT readiness. And so, that's something to think about, and I don't -- that can mess up how in the followup it can, right, how things get reported out, how you share things. So, that's -- again, as we roll out new conditions, it's something we might want to consider.

In terms of the time that it took, again, this is for the 13 states that are screening statewide. So, you've got a median between six to nine months. So, that's following with what we're hearing with the other ones with the lab readiness, with the approval authority to screen. And again, we have half the states have started at least one IT activity. I think this -- these numbers are going to get a little higher potentially as they do more activities. But then, it's possible that as the states that are in progress for implementing, it could go back down, because it's possible a LIMs vendor might be able to help, you know, once you get it started. So, I

-- I can't predict a year from now if this will be higher or lower. I think it has the ability to kind of go both ways.

For the actual activities in each phase, you're seeing the median of five months. And again, I think this is going to shift. We don't have a lot of data, right? So, this -- I think this will shift a little as we go through.

In terms of the activity that took the longest amount of time, it took a median of eight months to describe and develop specifications for the LIMs. So, that's the one activity that's taking a lot of time.

So, onto our final readiness phase, which is education. So, for the 13 programs that are implemented statewide screening, you've got a median of 10 to 14 months to do education. This is -- well, sorry, let me get to that in a second. Only 16 participating states have started and completed one education activity. You have 13 states that are screening statewide or implementing statewide, and you have 16 that have

started at least one activity. It may be that they don't need to do education, which I don't know if that's true or not. It may -- this is the second most frequent one that started after implementation. So, that's just, again, something to kind of look at and think through.

In terms of the time it takes, this is like followup, where it might be quicker overall because we're maybe not done yet. But it's -- each activity is taking a little longer in terms of median time. But again, this is an activity where you bring in stakeholders, you bring groups together to help with education. And so, it might just take longer for those activities that involve people outside of the Newborn Screening System.

So, those activities that take the longest? Nine months median time to initiate an education strategy for family and general public. So, this is where they're actually from scratch starting to build education materials. Nine months median time to identify and modify

education materials. So, this is -- it's out there, they just have to go find it, and this is for the general public, sorry. And then nine months median time to identify, again from scratch, measures to track the impact of provider education materials. So, those are the activities that are taking the longest amount of time.

We didn't have a lot of facilitators and barriers around education. But I think it's because we didn't have a lot of states that were working on these activities when they were doing the reporting. So, the one that came up was the facilitator's input from various stakeholders in education was identified as a facilitator. It's possible if we were to go back, we'd hear more things about education.

All right. So, our final thoughts. We know a lot -- about a third of the states have provided readiness tool data, and what I feel is we have kind of an outline, right, of what's there. But I don't think we have a clear picture of what's there, because we haven't heard from

two-thirds, and there are states out there that chose not to come to the meetings that we held, so they did not provide readiness tool data, right? We have states that three to four years after the RUSP haven't started. We don't know why. We don't know what's happening, right? So, what we have is we might be throwing the ball backwards, but we don't know it yet, right? So, that is my -- my caution to you.

So, as with every good project, you need a village, and this is my village. So, I have to give a huge shout out to Sarah McKasson, who did all of the figures that were lovely on this, and then Kshea, Sikha, and Jelili for their leadership on this project. So, thank you very much.

DR. JOSEPH BOCCHINI: Yvonne, thank you for that excellent presentation. Clearly, this is an important subject, and you have really excellent data to begin looking further into this and getting more input from other states. I think this is great. So, let's open this to -- for

discussion and questions. And so, I'll open it to the committee members first, and, operator, if you'll open the lines for the organizational representatives for their turn and asking questions or making comments.

So, in speaking both here in-person and on the phone line, please state your first and last name each time you ask a question or provide comments to ensure proper recording. So, I see Sue Berry first.

PUBLIC COMMENTS

DR. SUSAN BERRY: Hi. This is Sue Berry. Thank you for all the work that this entailed. I know -- do you have any insight into what I might call the leaders? What elements were in common for people who were able to implement rapidly and who have already done so and can -- are there things we can learn from them that will facilitate more rapid implementation for people who are following along doing this work?

DR. YVONNE KELLAR-GUENTHER: So, yes and no, do we have insight on the leaders, right,

because some of the leaders that are so far ahead didn't provide data because it's -- it's been too hard. So, I would say the 33 percent who provided data is the insight that we kind of have here. It's interesting that half of them had an outside mandate to screen. And the one where I shared -- I shared the quote about all the different steps, that state, in the middle of all that, had a mandate to screen and all of a sudden they went from their 18-month to their 6-month window, and so they got it done, but they can talk to you about the costs of getting it done. So, do I have insight as to what it took? Really, it's just kind of what I shared here, because it's the third that's done it. So, I don't have more insight versus what I have here.

DR. MEI BAKER: Mei Baker, committee member. This is very well done. I just wanted to be sure I understand it correctly. Because when you talk of readiness, it's multiple aspects, and it doesn't happen sequentially, right?

DR. YVONNE KELLAR-GUENTHER: Right.

DR. MEI BAKER: So, when you talk about the timeline, how do you define? You said like what took the longest -- you used -- how do you do that?

DR. KELLAR-GUENTHER: So, the time -- when we give the time from the implementation, we take the very first date of the very first activity. And I didn't say it in here, but usually that's approval to screen, but not always, right? Sometimes it's getting the equipment. And so, but whatever that very first date was that they gave us, we took that, and then we used the statewide implementation date as -- as the end date for that part. For those that are in progress, we took the very first date that they provided and then February 28th, because that was the last day that we asked for data.

DR. JEFFREY BROSCO: Jeff Brosco. I have actually two questions. You said you started the clock ticking when the first activity by state?

DR. YVONNE KELLAR-GUENTHER: So, for

each state, there -- they have their own clock, and their clock was for the fist activity -- the first date that they gave us, because we had -- they had to give us a date started, and a date completed. And so, if the first date started was what their time -- their clock started, and then the statewide implementation or February 28th was their last day.

DR. JEFFREY BROSCO: Why didn't you use the start date of when it passed onto the RUSP?

DR. YVONNE KELLAR-GUENTHER: We do have some where we actually looked on when it's on the RUSP, and that's in the materials that I gave you guys specifically. We started it because we were looking at for a state to gear up, because that's what they do in the Public Health Impact Assessment, so that's kind of what guided how I looked at it. But I do have dates actually from the RUSP. Here. I can tell you. The median -- the median time for Pompe it was nine months after addition to the RUSP, but those are people who

started before, right? For MPS-1, it was seven months after addition to the RUSP, and for X-ALD it was -- the median was one month prior.

DR. JEFFREY BROSCO: So, I think this is a really important thing for looking at your results, because if you don't use a uniform starting time, like the day it hits the RUSP, it's really hard to know how to interpret the data. So, for example, in Florida, we have a log that says within 18 months of reaching the RUSP, we have to make a decision about whether to add or not. So, if you asked our team when do we started, well, is it first time we send out a notice about the first meeting? Is it the time when the team -- this Newborn Screening Advisory Committee first meets? It is, you know, when would that start date be, that would dramatically change. You know, I'm guessing if you allow every state to define starting point, it might be hard to tell how -- what those meeting times means.

DR. YVONNE KELLAR-GUENTHER: Right.

DR. JEFFREY BROSCO: I just recommend

at least maybe also looking at it from the date it hits the RUSP, and it's a little bit more uniform.

DR. YVONNE KELLAR-GUENTHER: So, right. And we did -- we did do that in the report that we gave you guys. But I think that we were trying to look at -- what drove the question for me is when we asked states in the Public Health Impact Assessment, how long do you think it will take, and we actually asked, how long do you think it will take after you get approval to screen, which is an 18-month, or right, time frame for some of them. So -- so, that's why it drove for me. But absolutely, and we can do that. We have that information, so it's easy to redo those runs.

DR. JEFFREY BROSCO: I'm sorry, one other question, Jeff Brosco still. Did you hear anything about opportunity cost? What I mean by that is if you look at state labs and providers and everyone else, they're basically full-time busy all the time.

DR. YVONNE KELLAR-GUENTHER: Yes.

DR. JEFFREY BROSCO: And if you said,

okay, we're going to add it within six months, as you mentioned some states do, is there any opportunity cost or things that don't get done that people have to give up in order to quickly get a new thing on? Because, as Susan points out, we love to think that as soon as possible you get a new condition on, but there may be some cost in that as well. Do you have any data on that?

DR. YVONNE KELLAR-GUENTHER: Yeah. So, that came up in the interviews. The biggest cost is you lose staff, and then there was -- so that's one, and then they talked about -- they weren't as specific -- but they talked about other -- other things kind of falling by. So, you -- you pull people off to work on this, and so now they're not working on their regular screening. And so, you do have some opportunity costs in terms of timeliness, not a lot. I mean, the labs -- the ones that are there that they're doing, they try very hard to keep at the level that they're at. But the biggest overall was staff morale and loss of staff. So, it's hard for staff

to be busy all the time and feel like they're getting nothing. And then, it was very difficult to train for screening for the new condition, because they were so busy doing the other pieces, so.

DR. SCOTT SHONE: So, Scott Shone. I just want to come back to Jeff's comment before I come to what I wanted to say. I think it's -- starting with the RUSP date is, I mean, it's a different question altogether from RUSP to when they would start their own implementation process. It's easy in Florida and California because you have a law that states that. But, in other -- in all the other states where there's a diverse process to get from RUSP to perhaps moving forward with implementation, the -- that -- it is, I think, a study question onto itself is the time from RUSP to -- to moving forward with implementation. But as I said in the webinar, we shouldn't just assume that every state, once it's on the RUSP, is starting looking at implementation, because it might not be, and they

might not ever. I mean that's -- again, I just want to make sure that we understand that it's the recommended uniform screening but not the required uniform screening. So, I think that's a good question to look at, Jeff, but I think in the scope of what -- what this process looked at is what are the barriers to once a state moves -- actively moves forward with implementation to the time to get it going. And I think it's come up with the Public Health Systems Impact and, Yvonne, I appreciate you bringing that and sort of the question around that.

But, I wanted -- first, what I wanted to say is I wanted to thank you for this work and also acknowledge it's National Medical Laboratory Professionals Week, so all of our friends and colleagues in the labs as well as the Followup Teams who make this happen, and obviously the high achievers.

So, I think it's crucial to understand that -- and this sort of goes along with what Jeff said -- is that once a law is in

place or there's a mandate, it doesn't mean that everything just follows through quickly, and I think breaking this down helps realize that, and I think as -- as anybody looks toward implementation in this state should think about a mandate is nowhere near enough and that we need to work in the system to help break down the barriers around staffing, around budgeting, around training, around education, and it seems as though it's a little hard because what Mae said, the data is presented sequentially, and a lot of these things overlap and there's some other things here.

So, two questions. One, some intangibles I think that we probably didn't talk about like champions within the state, within the programs that might help push this forward. So, is there an assessment around that and the role that those types of people play, and whether they're internal to the program or just pushing on the program.

And two, the reality is, what can we control, and how much does the process change?

You gave an example of this is a 30-day process and that's it versus where can perhaps the committee make suggestions or recommendations to help process improvement to -- to benefit the states that are moving forward with implementation?

DR. YVONNE KELLAR-GUENTER: So, I have a couple things. If we go back to the RUSP conversation, I think the people who start earlier show optimal median time rates, so it's something to think about. I think to your point of quickly, one of the quotes that I didn't use was from followup staff, and they said, "Okay, so you might be able to get the test up and running, but if the followup system isn't up and running, what service are we doing to the family if we have a positive result or if we have a false positive?" And so, I get that kind of goes back to the opportunity cost, I think, as well.

In terms of what can be done, right, so there are -- throughout here are things, right, I think that connection to other states is huge,

and I -- I do not think that should be minimized. I don't know how to incentivize other states. I, you know, this is probably the nicest field that I've ever been in, people want to help, and so I think it's there. But I think, again, opportunity costs. If you say, hey, we did it first and now everyone is coming to our door, so that's another thing, right, to think about. So, how do we that -- those collaborative efforts, equipment, and having FDA like when we're thinking about things added to the RUSP, where are we at with FDA approval? Because for some labs, that's -- that's a stopper, right? And so, you kind of have to think through that. Those followup protocols, we don't talk about that a lot, but a lot of these new conditions are becoming more and more -- making followup more and more blurry, and I think we have to think about how we're going to support that, and again what can be done that I think can then transfer to all states.

Education. There is stuff out there that people can kind of take and use, but not

everyone takes and uses it, right? And some things that we don't have for education, which is near and dear to my heart, is we have no way to measure the impact, right? So, you -- one of the steps was to actually measure the impact of the education. Hardly anyone started that, which, as an evaluator, makes me sad. But it makes sense because they don't have the tools to start this. So, is that something that -- that can be out there, that we can do, that we can kind of help them with that piece so they don't have to come up with it in addition to getting the lab up and running, in addition to getting the followup going.

I think the approval authority to screen is where you have the least room. There can be some support, right? APHL provides some support to states in getting through that process. But I think that it's the lab readiness, the followups, the IT, education where there's the most room for help to kind of get the process going along with the caveat that if you're system

isn't ready, right, and you've pushed it through and you're screening, but you don't know what to do with the kids, just because you're screening and you've checked a box, you're still not really doing what you need to do. So, thinking about that there's a minimum time that states need and what is that. Did that answer your question, Scott? I know.

DR. CARLA CUTHBERT: Well, I think Scott got pretty much what I was going to be asking about. My name is Carla Cuthbert, and I am from CDC. One of the things that I think jumped out at me when you were speaking, I really appreciated your -- your entire talk was about not having room to compress. And so, my big question again as a federal person is, where can you compress some of that activity? And, you know, with all the states that we fund, we know that it takes time to be able to get through all of the red tape within their programs to be able to buy equipment, to get it placed, actually do all of those things, and I'm -- so, again, I really

appreciate Scott for asking that.

To what -- to what Jeff said, I -- I smiled when he said, you know, can we compare this to when the -- when the condition was added to the RUSP because what we often get as questions from Congress is what can you do to get conditions implemented within states within one year of implementation? And it's like, you know, and you have to be -- obviously, you have to help educate them about it. It's not that they don't want to, but here are all of the things that need to happen, and I think that what you've provided us is a very, very nicely documented way that we can answer that question to really help -- help them understand that this is not something that can be done, you know, as soon as the Secretary says yes, do. We can't just make it happen immediately. So, I really, thoroughly appreciate what you guys have done here.

DR. YVONNE KELLAR-GUENTHER: Thank you. And we were talking earlier, the slowest time is one year, four months. So, no one did it

in a year, and so I think that's important also to kind of share. So, a year for our recipients anyway was not achievable.

DR. BETH TARINI: Beth Tarini, just a quick question. So, a year for the recipients.

DR. YVONNE KELLAR-GUENTHER: Well, so for the 13 states that had implemented screening.

DR. BETH TARINI: And received an award to do so, federal --

DR. YVONNE KELLAR-GUENTHER: Not all -- not all of them received funding from us. That doesn't mean that they didn't receive funding from other sources, right? So, I don't know if they received funding from CDC or other places. I just know that not all of the 13 states were awardees from NewSTEPs projects.

DR. BETH TARINI: So, my question is, we talk about -- at a higher level, we're talking about compressing time for the -- the people you have information on, which we are saying are the higher achievers, right? There are some highest among the higher and, you know, you do what you

can do. You don't have the data from the others. So, there's this concern I have that in terms of return on investment, we're sniffing at the margins, right? Can we get a month here, a month there, a month there? Meanwhile, I wonder if there is something amongst this group that makes them more similar to each other than they are to the other groups who are not implementing, and then the -- to make an assumption that the lessons learned from them will help improve the time amongst the other group or groups if you want to use an early adopter conceptual model like you are alluding to, I think that's reasonable. Then, the question is, are early adopters from a conceptual model much different than the middle and then the lag from that just basic assumption.

So, I think we should also be very -- not only careful to not generalize, but there are a lot of babies who aren't represented by this and whose time lag is longer to get screened, and whose requirement or whose -- I should say -- affected intervention to get them screened may be

entirely or somewhat different from what we see here.

Now, you've done what you can do, but -- but I urge us as a committee to say what can we do to get the data from the other states and identify from those states what are their big barriers, because they may not be the same as these.

DR. YVONNE KELLAR-GUENTHER: Right, and what I would add onto that is can we continue to get more data from the states that have provided data, and it's voluntary, but any support of like wow, this is great data, and it helps us with decision-making, we could have more, would help us get that data, right? And so, I think we know a lot about the middle of the in-progress. I'm really hoping that these 39 states will continue to give us data.

DR. BETH TARINI: And I'm also recognizing that there could be data submission fatigue, right?

DR. YVONNE KELLAR-GUENTHER:

Absolutely.

DR. BETH TARINI: -- data timeliness, we ask them for data on general operating procedures for the NewSTEPs.

DR. YVONNE KELLAR-GUENTHER: Absolutely.

DR. BETH TARINI: We're now asking them for data on how long it takes. So, at some point, continuing to ask for data -- I'm not saying any which way of the intervention -- without support -- taking without giving is going to become a problem.

DR. YVONNE KELLAR-GUENTHER: Right.

DR. BETH TARINI: Now, we give -- we, as the feds and committee -- give in other ways, but that's a balance I think that needs to be attended to.

DR. YVONNE KELLAR-GUENTHER: Right. And I think knowing would help you guys in decision-making would help us then look at the data so that it's not just data to report data because I like analyzing data, it's -- it's

actually data that's meaningful. And so, if you have guidance on questions that you have, I would be happy -- our group would be happy, I'll volunteer -- to kind of look at this to see if we can get more data. But, yeah, just to have it is probably not.

DR. JOSEPH BOCCHINI: Okay. I have Annamarie, then Jeff, then Natasha, then Sue, and then Melissa.

MS. ANNAMARIE SAARINEN: Hi. Annamarie Saarinen, Newborn Foundation Committee member. I really enjoyed your talk, and I really am so appreciative of the lens that you're putting on this. But, to answer some of the questions that are being raised here, I'm going to do my usual thing which is sort of hyper-simplified, which is to say if you get questions asked at the CDC of Congress that are what do we do to implement things in a year after they're on the RUSP, well then, the short answer is that it's probably not the RUSP anymore. It's not the Recommended Uniform Screening Panel, it's the

Required Uniform Screening Panel -- I guess that's still a RUSP with a different R. But, until there are not the variables at the state level, there -- it will never be a smooth pathway. So, what you're talking about until then is incremental improvement and I think there are these different stakeholders, if you are going to go after more data, that you would need to start bucketing into, if you haven't already, meaning some stakeholders you're reaching out to are going to have the -- the easy answers when it comes to what are the policies in each state with regarding to moving forward with something that's on the panel.

So, you showed us, like here's an example of, it took six months to do this once it went on the RUSP, and it took six months to do that because we had to go get authority from our legislature or we had to do something else with our State Department of Health. Now, we know what some states have put into statute that when something is on the RUSP, that's an automatic trigger, right? It's like, if it's on the RUSP,

we don't have to go through the process of having something legislatively mandated on our state to add it to the panel. But that's only a handful of the states. So, it's just -- there's all sorts of variables here. I know I'll harken back to, you know, ten years ago when I went to my first meetings of this committee, and the comments from the families and the advocacy groups around how is it okay that my baby was born 15 miles on the other side of a border in Wisconsin and died because they didn't get an early diagnosis because we didn't have screening, but they had it six months earlier and my baby would have been alive if they'd been born 15 miles away. Do you guys remember this? Mei, you remember, right? And then we hear it -- for ten years, we've been talking about this. So, those things that are putting other states behind either by function or by choice really, really matter to Beth's point. They really, really matter on what babies are at risk in these states.

So, I'm not sure that I have the

answer to what this committee can do, but there are -- there's been research done, and I point to Dr. Gross, if he's around somewhere -- I just saw him in the crowd a minute ago -- but what he did in terms of looking at states that had implemented via the mandate versus states that were moving forward with some screening without their -- all of their ducks in a row, per se. Like, that was really interesting research. So, there's some stuff out there for you, some models that you can look at, and I just am really grateful that you've put something out there for us to all think about and act on hopefully.

DR. YVONNE KELLAR-GUENTHER: That came up in the interviews, like some of the newborn screening programs said that we are one of those states that's a little later and they understand the inequity. The other thing, though, that came up is that one of the states can't do pilots, like they have to -- once it's on there, they have to go to full statewide implementation. And so, then they're running it, and what's

happening is they're validating on the first set of kids that come through, which also causes another set of problems. So, I think as we think through is there this one date that everyone has to start, the equity, let's not forget that having other states that have started is helpful, right? If we all start at once, I -- I can see both sides of the argument. As a mother, I would like every state to screen for everything, right, for my child. But, if everyone is starting at the same time, is that going to take longer than if we have some early adopters? So, do we promote some early adopters and then bring everyone up to speed at the same time? I don't know. There's a lot of -- I think there's a lot of discussions for us to have. But there are -- there are things -- when we go too fast, there are problems, and I don't -- I don't want to lose that in the discussion as well. And so, you want the screening to go well when it goes. But I agree that there's a lot of ways we can look at this.

DR. JOSEPH BOCCHINI: So, I've got a

number of people, so I'm going to go to Jeff, Natasha, Sue, Melissa, Mike, and then Beth will have the final comment, because then we'll have to move on. But this obviously is an important subject that I think the committee has opportunities to weight in on and perhaps do some of the things to help states get through things once someone -- a condition is added to the RUSP. So, Jeff.

DR. JEFF BROSCO: So, just a quick comment. So, this research is really helpful for us in a whole bunch of ways. But it also leads into our discussion later this afternoon and going on, which is to agree that we don't, as a committee, include all the variables in our decision about the RUSP. It's legitimate for a state to say wait a minute, you didn't think about cost effectiveness or you didn't think about public health opportunity costs, so we have to do our own look at that. So, it's agreed that we expand our criteria and think about the RUSP including everything, it should be easier for

states to say look, they've done all that work, we can just put it up and get going.

DR. YVONNE KELLAR-GUENTHER: Yeah, I would agree with that.

MS. NATASHA BONHOMME: Hi. Natasha Bonhomme, Genetic Alliance. A lot of what I was going to bring up, Annamarie actually covered. But are there -- kind of what are your next steps around this? Like, are you planning on publishing this, are you planning on pulling some of this information out? Because I think there is still that -- even with this -- well, with this data, there still is going to be that desire to have that so then what should we do, what should be the strategies. So, yes, just because there is a law that's implemented at the state level around, you know, timelines from RUSP to state implementation, though that's not a slam dunk, maybe that's a step -- is that a step in the right direction or multiple steps in the right direction? I just worry about when -- and I don't you are necessarily implying this -- but, you know, the

idea of like faster isn't necessarily better, but if there are things that move us in a direction that is faster and not just for faster sake, but because you have the support or because now -- I'm just saying there's a lot here, and I think we in this room are lucky enough to be able to hear this data, but there are people outside of this room who are making decisions and also driving decisions that this would be helpful for them in -- in their efforts around having conditions either added or -- or expanding screening programs.

DR. YVONNE KELLAR-GUENTHER: So, to answer your question, the funding for this is -- we're -- we've -- it's over soon but NewSTEPs has other funding. So, I have no authority, but what I would say what I would love is I would love to continue to gather the data and try -- because I don't -- I don't want to publish on a picture of one-third of the states. I want to have more data to have a fuller picture. There's our team -- the CPHI Team has talked about do we do survival analysis? So, we're having these conversations,

and if there is interest and support, I would be thrilled to spend more time looking at this to try to get a little more data to have a fuller picture, and I would love to publish. I'd say right now, I would be wary to publish, because I feel like we have a very incomplete picture. But I would be thrilled if we could get more data and be able to do that, and I -- I don't want to say that slower is the ideal. I believe there is places [sic] and I believe in this data, we have places that we've identified where we can speed things up, but I think it's exactly your point. You just want them to be able to do it well, and so how do we support them? So, what can we do for followup, which I think isn't thought about a lot when we bring a condition onto the RUSP. How do we make sure that when something is called out, it -- it's -- there's support there, and we're not doing a disservice to the family? So, I'm not about slowing it down, but I'm also not about making it six months to a year, because I think that that has opportunity costs. So, I think

there's a huge picture around this that we need to kind of think through, and I would love nothing more than to spend more time with this data and try to get some of those answers. Serious, I would love nothing more. So, this is -- this is really important to me, and I started this because I hear the discussions that newborn screening programs are having, and I hear about the opportunity cost, and I hear all these things, and so it's like how do we make informed decisions versus guesstimates. That -- that's my main goal. So, does that answer?

MS. NATASHA BONHOMME: Yeah, yeah. And when I say publish, I really mean get it out there, and that can mean anything from peer review to even just these things that I think many of us in this room know, but isn't getting communicated out in terms of what are those challenges and barriers, and also the solutions. You know, even on the education front, you know, there -- there are things outside of state programs that help support education. So, you know, that would be

part of that strategy list that I'm talking about.

DR. YVONNE KELLAR-GUENTHER: Right. And I don't know if, but I had a bigger report, right, because there's a lot of information there. But absolutely, I think that there's more -- there's more in the data that we have that we haven't been able to present here, but there's more in the data of questions that we can answer. So, I think that we have a really nice start to answering, and I'm really excited about the SMA, because that's really recent, and so that data is very clean. People are remembering things, because it's been so new. So, if I have permission to continue to ask for data, and if they're not hating me, I would love to have, you know, maybe every year or something, if I could get another update in June something to try to move the -- make the picture clearer.

DR. SUSAN BERRY: Hi. Sue Berry. So, I want to come back to a little bit of what Annamarie was talking about, which is the variability between states and when I am watching

the scene see is sort of a two-edge sword when legislatures weigh in. We have the risk that legislators will weight in with the most heartfelt and kind intent in adding things to the RUSP that make it unfair for everybody, if you will, because again, you have that border problem. Sometimes without any evidence whatever about the utility or suitability of adding a test, on the contrary, sometimes states are required to seek legislative approval to go and add something that has been vetted thoroughly by the RUSP, and that takes sometimes years to get through legislatures. And so, I don't have any solution for this, but I know it's an important confounding variable for many of these when legislative action is required or takes place and moves into this arena.

DR. MELISSA PARISI: I want to thank you for this work and in particular for breaking it down by different phases. I think that's really critical. And more of a comment, I guess than a question, there may be differences that are also predicated on the particular conditions.

DR. YVONNE KELLAR-GUENTHER: Right.

DR. MELISSA PARISI: So, for example, we know there was a lag in adoption of SCID because that was a brand-new technology being incorporated.

DR. YVONNE KELLAR-GUENTHER: And these are all mass spec.

DR. MELISSA PARISI: Exactly but with SMA data, since that's also a condition that for many states, they're choosing to multiplex with SCID, there may be a reduction in the amount of time for the phase 2, the laboratory readiness, because the equipment issues may not be as significant. So, I do think that -- but there may be other issues with SMA2that may produce delays with regard to adoption. So, I just think that it's important to keep those nuances in mind and to break it down by phase, because I think that's really critical.

DR. YVONNE KELLAR-GUENTHER: Yeah, and I think a thing to think about is as new conditions are added that maybe need new

technology, because we were too late for SCID. Is it worth without burdening the states -- is it worth going through this again to kind of see? But, yeah, X-ALD, as you see, is very tight because they are able to use -- it's an approach that they've used for something else, the multiplexing. So, yes. That's why we try to compare across the three, but then they're all mass spec, so.

DR. MICHAEL WATSON: So, it sounds like you need to look at what the best practices might be across those phases in the states that move more rapidly, and then I think there's also some features of states that you're going to have to capture. Some states, you know, contract out a laboratory service to another state.

DR. YVONNE KELLAR-GUENTHER: Yep. That was usually the zero days was the outside lab contract.

DR. MICHAEL WATSON: Yeah, and when new technologies come in, it's not all that uncommon that they might contract out with

somebody else. Some states do other states, and that could really contribute a lot to the differences between states.

DR. YVONNE KELLAR-GUENTHER: And none of the 13 states that were screening were regional labs, right, which influences other programs. So, absolutely. And I think that we definitely need to do some comparisons across. Well, actually, I kind of lost -- but yeah, I agree with you that we need to -- we have some of that.

DR. MICHAEL WATSON: You probably can't fix the state legislative processes, but education and lab.

DR. JOSEPH BOCCHINI: Oh, Beth has withdrawn her question. So, that will conclude this session. Yvonne, I want to thank you very much for the work that you've done, your presentation, and I think it clearly has generated a significant amount of discussion, which potentially by continuing this could lead to better understanding of how to move this process forward more quickly and more uniformly.

DR. YVONNE KELLAR-GUENTHER: And we would love to help with anything -- any insight we can provide into the process. So, thank you for letting us.

DR. JOSEPH BOCCHINI: All right. Thank you. Next on the agenda is public comments. We have received requests for making public comments from eight individuals. We will hear from four of them today and four of them tomorrow. So, first up is Dean Suhr from the MLD Foundation. Dean.

MR. DEAN SUHR: Good morning. I'm Dean Suhr from MLD Foundation and Rare Army, two separate entities that I'm involved in. Dr. Bocchini, thank you for your service. I know we're going to talk about that later, but the leadership is well respected.

One other comment from the previous discussion, which we tried to slow down or defer, but we're measuring on states, and we all represent states, but I think we also need to be pragmatic and look at number of births as the

denominator and what percentage of births are we addressing as we're looking at this. So, I will be looking forward to that.

I wanted to report briefly on the RUSP round table, a meeting that we've been having since 2015. We had our seventh session yesterday. We typically do that in front of this Advisory Committee meeting. It's a broad swath of people from all different parts of the ecosystem. We're not formally chartered. This is an initiative that the foundation put together independent of our disease just to provide a discussion forum in kind of a free-flowing format. The conversation yesterday was -- was very good, very broad, and I just wanted to touch on a couple of those -- the items that we discussed. You'll hear a little bit more about this tomorrow and some of the comments, but Newborn Screening Saves Lives Act was a topic of discussion. That is the authorization for this committee, including both funding and charter. The current proposed legislation has not been introduced but should be introduced over the next

week or so. It does include an increase in funding, but as you all know, authorized funding versus appropriated funding are two different steps of the process. So, as advocates we'll be involved in that.

We did discuss yesterday the varying opinions from industry as well as other participations in the ecosystem and different thoughts and priorities relative to how simple that legislation should be, and through that discussion, I think made some progress so that we should be well-aligned as we go forward.

We had a long discussion about pilot studies, and I just wanted to highlight two points on that. Melissa Wasserstein -- Dr. Wasserstein up in New York is about to launch a 13-disease consented pilot study that is partially funded by the NIH. It's a -- the next phase of a study that she completed about a year and a half or maybe two ago, and she's expanding that. Very exciting study for a number of reasons, most significant being that 13 diseases are being investigated.

The other thing that I think was very unique about that is that the primary funding is coming from the NIH, but on a 3-to-1 ratio against that NIH funding, there is industry funding supporting it. So, we're getting a change in how some of these projects are being created and moved forward. No one industry is dominating that funding. No one industry has a particular control over a disease. They obviously, you know, have interest in the general space, so, that collaboration we talked about.

There's a similar study going on with DMD launching in a similar time frame at a different set of hospitals and facilities.

We talked a bit about stability, bottlenecks, and risk, kind of the terminology that settled at our meeting, and I should say that we're not unique. We don't have a special control over this agenda. You all are addressing some of these things here today. But that was a very active discussion.

And we talked particularly about

something related to terminology. We started talking about long-term followup. And I bet if we asked each one of you and we kind of went around the room a little bit and asked what does long-term followup mean, it means something different to all of us. And so, I encourage you to think about that a little bit as you go through discussion. It's one of those broad buckets and categories, but it means something different to a lab, to a parent, to a policy-maker, to a public health leader, and it's not just following up on newborn screening, it's following up on a child and how do we -- how do we become better at overall improving clinical care of which newborn screening is a starting point.

We discussed -- and just two things really quickly here. We discussed two other things that I wanted to comment on. One was children, which is in the charter and the scope of the name of this committee, but it's actually not in the authorization. So, it's not as simple as just saying well, you should jump off and take

care of children. But, part of this was a conversation about spinning off of the bottlenecks, which is are we overburdening what happens in day one or day two or day seven of life, and the newborn labs and the -- the timeliness and so on that goes on, and what might be better tested for, screened for, at some age of childhood? And, of course, as you all know, it's very complicated, but I think we want to plant that seed and certainly that's of interest to a lot of folks within the ecosystem.

And the last one was a -- just a comment that somebody made, which again, you know, it's part of just being able to sit around and talk. One of the folks that was there said, Wilson-Jungner criteria comes from the '60s. It was developed for adults. We've adapted it to newborn screening, but it's probably one of the few things if not the only thing -- I'm not a medical professional -- but it's one of those things that has not changed in the 51-plus years since it was adopted. It's one of the few things

in health policy that hasn't been updated and revised. And so, we had some discussions around that, but just plant that seed and a little food for thought for all of you.

So, our next meeting will be before the November meeting, and we look forward to sharing more information then. Thank you.

DR. JOSEPH BOCCHINI: Dean, thank you very much, and thank you for the work that you and the group are doing.

Next up, we have three individuals who represent the Homocystinuria Network America, Danae Barke -- I hope I'm close with that pronunciation -- Elizabeth Carter, and Margie McGlynn. So, if you'll please come forward.

MS. DANAE BARKE: Good morning and thank you for the opportunity to speak to committee, whose mission it is to protect the health of newborns in this country by identifying and recommending best practices in newborn screening. Our goal today is to describe challenges with one of the conditions on the RUSP

-- homocystinuria. My name is Danae Barke, and I'm the co-founder and executive director of HCU Network America, a patient advocacy and support group founded for this complex disease in 2016 to help patients and families. I'm also a patient with classical homocystinuria, so I know first-hand the impact this disease can have on your health and quality of life. I was born before newborn screening, and I was -- it was introduced in my state and I was not diagnosed until I was 10, after my younger brother was diagnosed due to dislocated lenses. It was very hard at that age to adjust to the low-protein diet that led me to having a blood clot when I was 24. Fortunately, my health is much better today, and I now have a 1-year-old daughter, who was screened for homocystinuria at birth.

Currently, newborn screening for HCU occurs nationwide and individuals identified at birth have the opportunity to be managed through a low-protein diet and supplements, and if compliant with treatment, most of these individuals avoid

consequences of HCU including dislocated lenses, near-sightedness, cognitive deficits, blood clots, and strokes.

Unfortunately, even with newborn screening, many cases are missed. In fact, literature suggests at least 50 percent of patients with classical homocystinuria are missed by newborn screening primarily due to the laboratory methodology and algorithm used to screen. Methionine is used as the biomarker instead of homocysteine. Studies have shown that cut-off levels are set too high to avoid false positives and/or the infants do not have high enough levels at day one or two to be detected by this biomarker.

We have met with many of the HCU patients who were missed as they or their parents came to us for support once they were diagnosed. We have documented their stories to share with you. We are aware of 21 patients across 12 states over the past 32 years, all of which were missed after newborn screening was implemented in their

state. We found 14 who were missed over the last 10 years, and we realized we have only scratched the surface. One of these cases is a little girl from Montana who had a stroke at age 3 that led to her diagnosis. We were devastated to hear from a family in North Carolina, who had a little boy diagnosed at age 5 due to displaced lenses who unfortunately suffered a blood clot on the way home from a baseball game last November and died after a week in the ICU. You will hear from another -- you will hear next from a mother of a little boy missed by newborn screening.

So, that is why we're here today on behalf of the patients and families whose lives were negatively impacted despite everyone's best intentions in implementing newborn screening to ask for your support in helping improve the process so all individuals with HCU can benefit from the charge of this committee -- effective newborn screening that enables early identification and life-saving treatment. With your help, we are confident that improvements can

be implemented nationwide and all individuals with the HCU will have the opportunity to benefit from the excellent health care the metabolic community is able to provide to help patients avoid the consequences of HCU and help them have healthy and productive lives.

MS. ELIZABETH CARTER: Good morning. I would like to ask all of you and invite you to imagine something. So, if you would, please close your eyes and visualize with me. Imagine that you are on the beach with your family. You hear the sounds of the waves, feel the warm sun on your body and the sand between your toes. The best part is that you hear the laughter of you two precious little boys, ages 5 and 2, as they experience the magic and excitement of the ocean. These are memories in the making.

Now, please open your eyes. Two days later, this is your reality. Everything has changed. This was the day that turned our world upside down. This was the day that our sweet, bubbly, full-of-life Elliot, at 2 years old, was

put into a medically induced coma and placed on the ICU floor of the Children's Hospital where he would remain for 29 days. Elliot was having seizures with no outward signs and doctors could not figure out why. They would later find out that the seizures were a result of a series of blood clots in the veins throughout the brain, which ultimately resulted in Elliot having a stroke. I will never forget the words spoken to us by the doctor on July 15, 2018. "We want you to know how serious this is. We don't expect to lose Elliot to this, but you need to know that we could." I can tell you that at that moment, I'd never felt more hopeless or afraid.

It would be what seemed like an eternity but was really just 11 days after Elliot was admitted to the ICU that doctors were able to pinpoint a cause for everything. Homocystinuria they told us. It's a rare genetic condition, and we think that that's what Elliot has. As grateful as we were for a diagnosis, because it meant that we could move forward with a plan, we found

ourselves wondering that if HCU were a genetic condition, why had we never heard of it.

Fast forward to today. We now know that my husband and I are both carriers for this rare condition called HCU. We've also learned that when Elliot was a newborn in the hospital, homocystinuria was something that he was screened for, but unfortunately Elliot was missed at newborn screening. I don't like to live my life with what ifs, but I often find myself wondering how differently things may have turned out for Elliot and for our family if we had known in the beginning that Elliot had a serious condition. We could have prepared. We could have given him the medications that he needed, and we could have avoided almost losing him.

Thankfully, Elliot is doing wonderfully today. In fact, he's better than ever. I call him Elliot 2.0. He is happy, full of energy, and as feisty as any 3-year-old should be. We were lucky, and we are very, very blessed.

My hope now is that there are medical

advancements that continue to be made so that Elliot may live the most normal life possible. I hope and pray that no family has to go through the experience of losing a child to this condition. I know all of you are passionate about detecting these conditions in newborns to give them the best chance of early treatment to avoid the potentially devastating effects of the disease. I hope you are able to develop improvements to make sure that all HCU families can close their eyes and imagine their Elliots in scenes on the beach and not in the ICU. Thank you.

MS. MARGIE MCGLYNN: Good morning. My name is Margie McGlynn, and I thank you for the opportunity to speak at this very important forum. So, I am the president of the board and the co-founder of HCU Network America, and I committed to founding this organization in honor of two sisters I lost to homocystinuria at a far-too-young age. My sisters were 6 and 2 when they were diagnosed, and I was 4, but I can remember it like it was yesterday. For the next five years, I watched

them progressively deteriorate, suffering from seizures, blood clots, stroke, cognitive deficit, osteoporosis, et cetera until they died within six months of each other -- first, my 9-year-old sister of a pulmonary embolism, and six months later, my 14-year-old sister of a stroke.

I can only imaging being a mother today how that felt to my parents to lose two children who they loved and cared for so much. And, as Elizabeth said, my hope is that no family in the future ever has to lose a child to HCU like mine did. Were my sisters born today, they'd have the opportunity to be screened and hopefully to have their disease detected so that they could then have the opportunity for treatment to help them live longer, more productive lives. We also know that there are new medications being developed that will make this an even easier disease to manage in the coming years.

So, we as a patient advocacy organization, believe that the best long-term solution is to have a primary screen of

homocysteine instead of methionine. We are advocating across many stakeholders to create awareness about this condition, and we also are trying to support the ideal solution through our global grants process where we're offering a grant for someone to overcome the technical issues involved in screening for homocysteine. But in the short term, we urge this committee to make it a priority to have a review of the success and results with newborn screening across the United States and to accelerate the development and adoption of better laboratory screening approaches that may help.

One such approach has recently been described in a publication from E-HOD, the European Network and Registry for Homocystinuria where they recommend a second-tier test being done. First, lower the methionine cut-off level, and then use the second-tier test to assess both homocysteine and MMA using the same dried blood spot. This enables better detection not only of CBS-deficient homocystinuria but also of

methylation disorders and cobalamine defects. And it also avoids the impact of false positives on families. We know that the CDC has been working on methods to detect both homocysteine and MMA and the CDC is supporting the adoption of second-tier screening methods through both hands-on training as well as technology transfer. So, we hope that the committee will support the CDC effort.

So, on behalf of the HCU community and especially those families who have had someone missed by newborn screening, we urge the committee to evaluate this issue as soon as possible and determine how best to move forward and to have a new solution implemented hopefully in the next few years. We have the same goal as the committee to have all individuals with HCU detected at birth and given the best chance to lead a healthy and productive life. We thank you for your passion and commitment to newborn screening. We are here to help in any way that we can. Thank you.

DR. JOSEPH BOCCHINI: First, let me thank the three of you for your willingness to

share your personal stories, and thank you for your advocacy. We certainly appreciate you bringing this to the attention of the committee, and we will look into this right away. Okay. Thank you all very much.

Okay. All right. In the interest of time and trying to stay on schedule, we're going to break now for lunch, and I will then begin this afternoon promptly at 12:30, and I'll make my brief presentation on the RUSP Condition Nomination at that point, and then we'll move into the afternoon session. So, Catharine, anything? No. Okay. So, if you'll all make sure you're back here promptly by 12:30, we'll begin the afternoon session. So, thank you very much.

LUNCH BREAK

[Off the record at 11:30 a.m.]

[On the record at 12:30 p.m.]

DR. JOSEPH BOCCHINI: All right. So, welcome back everyone. We'll begin the afternoon presentations. So, first we'll need roll call. Kamila Mistry.

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Mei Baker.

DR. MEI BAKER: Here.

DR. JOSEPH BOCCHINI: Susan Berry.

DR. SUSAN BERRY: Here.

DR. JOSEPH BOCCHINI: I'm here. Jeff Brosco.

DR. JEFFREY BROSCO: Here.

DR. JOSEPH BOCCHINI: Kyle Brothers.

DR. KYLE BROTHERS: Here.

DR. JOSEPH BOCCHINI: Jane DeLuca.

DR. JANE DELUCA: Here.

DR. JOSEPH BOCCHINI: Carla Cuthbert.

DR. CARLA CUTHBERT: Here.

DR. JOSEPH BOCCHINI: Kellie Kelm.

DR. KELLIE KELM: Here.

DR. JOSEPH BOCCHINI: Joan Scott.

MS. JOAN SCOTT: Here.

DR. JOSEPH BOCCHINI: Cindy Powell.

DR. CINDY POWELL: Here.

DR. JOSEPH BOCCHINI: Melissa Parisi.

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Annamarie Saarinen.

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH BOCCHINI: Scott Shone.

DR. SCOTT SHONE: Here.

DR. JOSEPH BOCCHINI: Beth Tarini.

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: And Catharine Riley.

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: And for our organization representatives, Robert Ostrander.

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: Debra Freedenberg.

DR. DEBRA FREEDENBERG: Here.

DR. JOSEPH BOCCHINI: Michael Watson.

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: Britton Rink by webcast. Jed Miller.

DR. JED MILLER: Here.

DR. JOSEPH BOCCHINI: Susan Tanksley.

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Chris Kus by webcast.

DR. CHRISTOPHER KUS: Here.

DR. JOSEPH BOCCHINI: Jennifer Kwon by webcast. Okay. Natasha Bonhomme.

MS. NATASHA BONHOMME: Here.

DR. JOSEPH BOCCHINI: Siobhan Dolan by webcast.

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: Thank you. Cate Walsh Vockley.

MS. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: And Shawn McCandless.

DR. SHAWN MCCANDLESS: Here. All right. Thank you all. So, we're going to open this session just by reviewing a couple of things.

RUSP CONDITION NOMINATION AND EVIDENCE REVIEW PROCESS: DRAFT APPROACH AND TIMELINE

DR. JOSEPH BOCCHINI: As you know, we embarked on a review of our current processes from

the acceptance of the nomination packet through the systemic evidence-based review, the decision matrix, and then review -- how to review conditions that are currently on the RUSP to reevaluate them on some ongoing basis, and we had an expert advisory panel that met to discuss the entire review process and based on our presentation in March, you heard who was there and efforts that were made, and you'll hear more about that shortly.

Next slide. So, what we decided was that the first step in our review would be the Systematic Evidence Review because that -- any potential changes to that would then inform the need for potential changes in the decision matrix and possibly in the nomination packet that we ask individuals and organizations to put together. So, we've come up with this timeline. And so today you'll have the first presentation of the Systematic Evidence Review and some of the data or some of the recommendations and considerations that were being made for that, and we would like a

really good, solid discussion on that, feedback from the committee, which would then help inform the next steps to bring that Systematic Evidence Review into -- into full focus.

In August, we'll look at portions of the Systematic Evidence Review. We've talked about the potential for adding values to the review, the potential for cost assessment and modification of cost assessment, population-level modeling, public health system assessment, and these will all be part of the August meeting for further discussion by the -- by the committee, and then working towards a final decision about alterations of the Systematic Evidence Review and alterations to it.

In November of 2019, a discussion will take place about the decision matrix and a review of the conditions that are on the RUSP with some, again, feedback from the committee about what potential changes would be beneficial based on what we've done before.

And in February of 2020 at that

meeting, to then review the initial nomination package and to make sure that the changes that we've considered and brought into the system might inform what might need to change in the nomination packet to help make things work effectively when a condition is being evaluated.

And then at that point, we hope to be able to confirm all the final changes to the process. And so, that's the timeline that -- that we've proposed for going forward.

Next slide. So, today, as I mentioned, the goal is to focus on the Systematic Evidence Review, and what additional types of information should be included in the evidence review to help make the committee's effort more successful in being able to get to the point where we determine that there's a benefit for the child who may have a condition that we are looking at.

Next slide. So, here are some of the topics that are going to be talked about. Case definitions, planning to consider them at the start of the review, the need to standardize

terminology regarding primary and secondary targets, and incidental findings. Pre-specifying outcomes and the use of intermediate outcomes. The range of treatments that might be included in a systematic review and how to grade the evidence. And identifying and synthesizing unpublished evidence and other potential sources of data.

So, with that, I'm going to turn this over to Dr. Powell and Dr. Kemper. They are going to make a presentation about where we are with the Systematic Evidence Review, and then they will lead a discussion on approaches to assessing and reporting the evidence with particular attention to identifying the type of data and information the committee would like to see included in the evidence review. As you are listening to their presentation, please be thinking about ways in which the methods used, and the data included in the evidence review can be modified from what we're doing currently to better inform the committee's decisions and deliberations. Also, be thinking about case definition would include, how

outcome measures can be identified and graded, and the various types of treatment that ought to be included in our evaluation. Additionally, consider how we best can synthesize and utilize gray literature which Alex will define for us.

And then I would like each of the workgroups to take what they've heard today and include some discussion about those -- these issues in your workgroup agendas so that tomorrow, you can bring back things that may have come up from the workgroups that might help inform a subsequent discussion on where we need to be heading with this Systematic Evidence Review.

So, with that, I'm going to turn it over to Dr. Kemper and let him lead the discussion.

EVIDENCE REVIEW PROCESS

DR. ALEX KEMPER: Thank you very much for teeing this session up. So, I just want to take a step back. We really see this process that we're going through as an opportunity to look back at the previous evidence reviews that we've put

together to inform the decision-making process that the Advisory Committee is involved with and think about what are the lessons learned, how can we strengthen the process, how -- what are the things that we could do to make sure that we best inform the Advisory Committee around, recommendations.

So, as Joe mentioned, a couple of months ago, we had a large in-person meeting to go over things and try to think about alternative methods moving forward, and that was discussed a little bit in the webinar that was held last month, although obviously it's really difficult to get any sort of meaningful feedback on a webinar. And so, what we're going to be doing over the next few meetings is talking about the lessons that we've learned from looking back and thinking about how we can do things better moving forward. But this is really going to be a dialogue. We really want to solicit as much feedback as we can.

So, Dr. Powell is going to help me facilitate a discussion with members of the

Advisory Committee and the organizational representatives. But that doesn't mean that we're not interested in getting feedback from, you know, others who attend this meeting in person or via webinar or who otherwise have an interest in the process, but just to help make it feasible, that's what we're going to focus on today. However, you know, certainly I'm open to feedback and then more importantly, in August, there's going to be a larger public comments section to give feedback on the kinds of things that we're talking about.

So, I'm going to lay out a lot of topics for everyone to think about. But again, it's a work in progress, and we really look forward to hearing what everyone has to say. So, I'm going to go ahead and get things moving and then periodically, I'm going to open things up, and then between me and Dr. Powell, hopefully we'll be able to draw out your thoughts.

So, as I go through here, the key issue that I want everybody to think about is how to best synthesize the available evidence to

inform the Advisory Committee. So, this is about, you know, filling in or solving the puzzle. So, this presentation is about the Evidence Review Process. It's not about the decision process. But, as Dr. Bocchini talked about, we are going to revisit that decision-making process.

So, this is what I talked about before that in March 2019, we provided just a summary where we talked about the in-person meeting where we really dug into issues of the nomination, the Evidence Review Process, and decision-making, and at that time, we also considered how to periodically reassess conditions that are already on the Recommended Uniform Screening Panel.

But today my objective is to think about ways to strengthen the Evidence Review Process and use that to ultimately develop a manual of procedures.

So, as Dr. Bocchini mentioned, we have a summary report that's going to be due in March of 2020, and you've already seen the outline

for when we're going to present things. So, I'm not going to go through that again. But just to highlight, that our Evidence Review Group is continuing to engage with the Advisory Committee in between meetings to think about how to move things forward and, of course, we're interested in feedback from others.

So, this again is -- the goal today is thinking about the Evidence Review Process, so I will be the first to acknowledge there are a lot of thorny and complex issues, and we're not going to resolve all of them today. But I do think that it's important that we discuss them.

So, everybody okay on the plan? Any questions so far? Okay. I got a thumb's up from Dr. Brosco, which is always reassuring.

So, this again is the conceptual framework that we use whenever we look at newborn screening, and the key things to take out of this as we look at what's the difference between what might happen with newborn screening compared to what would happen with usual clinical case

detection, and all of this lives within the broader public health system. So, as everyone in this room knows, I believe, there are three components to the evidence review.

So, we look at the effectiveness of newborn screening, so how well does newborn screening detect those kinds of cases that you would want to detect.

Secondly, we look at the benefits and harms of newborn screening compared to what might happen with usual case detection. So, again, we're not looking at just what happens through newborn screening, but what's the incremental benefit or what are the harms associated with newborn screening.

And then finally, we also look, and there was a nice robust discussion earlier about the public health system impact, but we do look at the impact of expanding newborn screening on public health and the health care system.

So, one thing that I don't think that I've been as clear about, but we need to keep in

mind -- let's see if this animation works -- woo, it's always a miracle when that happens -- is, right. So, that's the DeLorean from -- from Back to the Future. The reason I put this up is we need to also keep in mind the time horizon so, you know, when clinical cases might develop, you know, what the time difference is between picking up cases through newborn screening and when is it that we expect the benefits or harms related to newborn screening to occur. And I think it's really important that we keep in mind this -- this issue of -- of timing of things, because it could have an impact on how you view the overall impact of newborn screening. I'm going to periodically bring that up.

The other thing that I will remind everyone is that we've really tried to optimize the Evidence Review Process given the time constraints that are put on us in terms of the nine-month window. So, we really try to focus on those things that we think are going to be most important for the -- for the Advisory Committee,

and you'll see how that's going to come up for today.

So, we're almost to the participation component of this, and what I'd like to do is first of all, prepare you for -- for where we're going. So, there are a series of things that I want to make sure that we get through today. One is talking about issues of case detection. The second thing is what we expect in terms of the key outcomes. How do we know what kinds of things that we should be looking for? The third thing is related to treatment in terms of what sort of treatment should we include. The fourth thing is related to assessing the peer-reviewed evidence and how do we really evaluate the quality of what's out there. And then the final piece is related to the gray literature. How do we identify and assess unpublished evidence? And so, that's where we're going. These are the big topics I want to make sure that we hit in the next hour or so.

So, let me begin by talking about

case definitions. So, one of the challenges that we faced in prior reviews is what defines the condition detected through screening when potentially affected individuals might be asymptomatic and then you begin providing interventions so that they may never develop what we typically think of with the condition, right? So, what we want to do is make sure that we understand what it is that we're screening for so that we can evaluate what the benefit of detecting through newborn screening is versus usual case definition.

In general, there are three ways that we've gone about doing this. So, you can look at the genotype, right? But there might not be a clear genotype/phenotype correlation, or there might be incomplete penetrance or variable expressivity. So, although it's like a, you know, as a general pediatrician before I got involved in this, I might, you know, think that there would be, you know, greater predictive value by looking at the genotype. What we've learned is that

that's not always the case.

The second way is we can look at biochemical manifestations of the condition, right? But the problem is there's pseudodeficiency, there can be changes of biochemical profile over time, and so going directly from some biomarker associated with the condition is saying, you know, this is -- this is what the child or individual has is complex.

And then, the third thing, and I alluded to this before, is related to clinical, right? So, the clinical signs or symptoms might not emerge, right, when they're -- when they're asymptomatic and early treatment might alter the course of the condition significantly. But it's clear that when we do this evidence review, we have to have a clear notion of what the case definition is.

So, I'm going to put up one more slide about case definition, and then I'd like to open it up. So, actually two more slides.

So, the first is, I propose that we

really need to standardize the terminology that we use in terms of primary target -- that thing that we're really going after. Secondary targets being those things that, you know, we would like to identify through screening or at least we're considering whether or not there is benefit through the evidence evaluation, and then incidental findings, which are things that wouldn't be targeted at all. But there are all sorts of challenges related to understanding the condition, agreement about the goal of screening, and this has come up before in terms of issues of identification and carriers or late-onset disease, right? So, there were a lot of conversations, for example, around Pompe disease.

And then, one of the things that's been made clear to me by those who are involved in public health is that the case definitions that we use when we do these evidence evaluations or when the Advisory Committee makes the recommendation has significant impact on State Newborn Screening Programs in terms of what they're looking for in

the reporting requirements and that kind of thing. So, I will just say that -- I will be the first person to say that as a clinician, I like things to be binary. It's easier for me to think about that. But it's clear that that's not the case. Look at congenital hypothyroidism or cystic fibrosis that things are not, you know, easily able to separate into condition, non-condition. But all this has significant implication for evidence review.

So, I have -- but I'm not going to put it up now -- some suggestions about ways that we could move forward with this. Dr. Powell, I'll hand the microphone over to you if you want to solicit questions from the Advisory Committee or others.

DR. CYNTHIA POWELL: All right. Thank you, Dr. Kemper. We'll first take questions from the committee members or comments from committee members and then turn it over for questions from the organizational representatives. Sue Berry.

DR. SUSAN BERRY: This is Sue Berry. I want to hone in a little bit on that secondary target comment that you made. I recall the original paper that sort of outlined the suggested parts for the RUSP. What the secondary targets were were stuff that came along for which we had limited evidence, and that was pretty much it. It wasn't that we were trying to get them. It wasn't that they were in any way desired, necessarily, as targets. It's just that they were other things in the MS/MS basically and we've subsequently ended up with other secondary targets -- things like discovering children with Down syndrome and T-cell immunodeficiency when we're screening for SCID.

But I think we ought to be really careful about having it misunderstood that secondary targets were targets in the first place. They were -- they were ride-alongs, and the implication for some reason that they carry the same weight in some ways as what is the primary target is something I think we should be careful about because it's a very high burden and the

information is not very good. So, I think we want to be -- I love the idea of standardizing terminology. I want to make sure that we remember where we came from on it, and that when we talk about what a secondary target is that we are very careful not to give it more importance in some ways than it deserves. I don't know how else to put it.

DR. ALEX KEMPER: So, can I just -- just ask one additional question, just to make sure I understand? So, for the Evidence Review Process, do you think that we ought to be looking at the secondary targets if you know what the secondary targets are or just focus on the primary target and not think about the secondary targets?

DR. SUE BERRY: So, this is Sue Berry again. I would argue that you have to essentially take care -- you have to account for them, if you will, in the Public Health Impact. I don't think there is a special need to define the evidence of utility for screening for them because they're not -- you're not going to -- they're going to come

along whether you do that evidence review or not, and I think our decision-making is, I think, more based on the primary target with, if you will, I don't know how else to put it, the burden that the secondary targets may also bring, because that -- that makes it more complicated. It gives you information that will be hard to deal with. You have to decide, for example, the secondary targets might be so terrible that you really need to think hard about your primary target. I mean, that's an exaggeration, but it could happen.

DR. CYNTHIA POWELL: Jeff Brosco.

DR. JEFFREY BROSCO: It's Jeff Brosco. I'm following up on what Sue said. I would say it even stronger than that, that we should really be focusing entirely on whatever the primary target is, and that primary target -- I think we've talked about it as a group -- might be, in part, defined by the group that's proposing the candidate condition and saying here's what we think we should be screening for, in part because this is a public health mandate for states. When

you start including secondary targets, late-onset things, and incidental findings, it's very confusing for state labs -- now, what do we do with the information? I think if at the federal level we make it very clear that our recommendation is for the primary target and only the primary target, it makes it easier for states to say we're going to use our resources that way and not go down the line with these other things.

DR. CYNTHIA POWELL: Mei Baker.

DR. MEI BAKER: Mei Baker, committee member. I think it doesn't matter if you put a primary or secondary. When you have a target, it means we intended to find them. I think that's -- that's important. If this target is subjected to all the review process, I personally want to avoid there is a first, I mean, primary and secondary. If something comes along that's not avoidable, we need to assess the pros and cons, you know? I think a week back or two we talked about the SCID. So, it's why I still have trouble with incidental. I like to use our intent. For example, when it

comes to SCID screening, we use TREC assay and we knew you will have DiGeorge. But I'm talking about [inaudible], we said that's fine because no harm done. But when it seems to happen, but I still don't want to say this is our secondary target because we are not targeting them, and we made it very clear, we are not identifying other DiGeorge because of your status ratio.

So, I think if we really want it clear, I wouldn't use a primary target and secondary target. It just -- the disease condition we are looking for, but we also know technology, the method that you use, you may have unintended results and then we need to assess, it's our intent, it's good or harm. How much harm can weigh in in terms of the decision-maker?

DR. CYNTHIA POWELL: Beth Tarini.

DR. BETH TARINI: I agree with Mei. I think target suggests intentionality, and then when you start talking about intentionality -- when you hear intentionality, then the primary and secondary gets washed away. So, I -- I do think

that that's true, and I think that the issue that Jeff and Sue brought up of the primary disorder we're screening for is important because not only is there the harm, but there's like the piggybacking and the whitewashing of how the -- and also we get an extra boost to the -- to the intended disorder, because we can find all of these good things. And that -- that line of discussion tends to, I feel, insidiously pervade our discussions sometimes, like, well, it's not idea, but look at all these other things that might be -- might be there. So, I think the cleanest break and the most specific break is necessary between this primary/secondary piece, and that it should just be the intentional target. I think the language that Mei points out is important as well.

DR. CYNTHIA POWELL: Scott Shone. Any comments or questions from organizational? So, Debra.

DR. DEBRA FREEDENBERG: So, I just wanted to point out two things. One is that what

we're calling secondary targets or secondary conditions, a number of those conditions can be fatal in the newborn period just as -- will do you in just as well as the primary targets. And so, I think we need to recognize that although we may not be maximizing our screening for these, if we detect them, the child does need treatment intervention, and some of that can be life-saving for some of the conditions.

And then the other point that I was thinking about as we were talking was that I'm not certain we really know what the definitions of these conditions are anymore because we've changed the natural history of some of them. We've gone to late-onset. Every time we add a new condition on, we estimate the number, and that's not the number we see because there are all these milder forms or asymptomatic forms that we don't know if they're ever going to be symptomatic, you know? And then we're also changing our paradigm in terms of long-term monitoring when we have conditions that we can identify in the neonatal period, but

again, we don't know their age of onset.

So, what I used to think was very clear and very clean now is kind of getting a little more muddy for me and I suspect for a lot of other folks as well.

DR. CYNTHIA POWELL: Robert Ostrander is next.

DR. ROBERT OSTRANDER: Yes. I want to jump back from the secondary target to the very first question, and that is the case definitions. I mean, obviously, you can get muddied in all of this and never make a decision and a declaration. But I think we should pick a declaration. I think the thing that didn't get mentioned here that is just a very root issue, and especially if you step outside of the genetics world, is the notion of not diagnosing with a screening test but diagnosing with a confirmatory workup, and I think -- I would propose whatever category it falls into, I think part of the evidence review should be determining is there -- is there and what is the confirmatory workup and then that will be the

case definition. And it may fall into this, this, or this, but you've got to define -- you've got to make a case definition in order to gather new knowledge and to decide whether you're going to intervene or not. And a very simple way to do that is to use your confirmatory test for your case definition. It may land you in any one of those three categories, but that would be my -- my thought about approaching this and then, you know, some of the data. If you case define with a confirmatory test, some of the patients are going to be asymptomatic for the rest of their life, but because they've met the confirmatory test, they are an asymptomatic case as opposed to not a case at all. So that -- it seems to me that in order to tighten it up, that might be one way you could do that and also make it uniform.

DR. CYNTHIA POWELL: Mike Watson.

DR. MICHAEL WATSON: So, I almost feel guilty about having used the term secondary conditions when we did the Uniform Panel.

DR. ALEX KEMPER: I wasn't going to

bring that up.

DR. MICHAEL WATSON: I appreciate that. But, you know, what they were was things that were part of a differential for whatever the markers were that were used to get at the primary condition, and it was never the intent that the newborn screening program had to worry about them, because they didn't get identified until the primary marker sent them off to the diagnostic world to figure out if they had the target of screening or not, and if they didn't, they were not going to tell people that they found a disease -- it wasn't the one they were looking for, but they found something that they needed to deal with whether it was asymptomatic, presymptomatic, it didn't matter about urgency because it was all in the hands of the diagnostic people to sort it out. And if it had -- if it was an emergency, they were going to treat it emergently based on the market -- on the marker. But it's gotten really confused more recently when, I think, Genomics really drove the next level of confusion when the President's

Commission on Bioethics sort of defined what they consider secondary and what they consider incidental, and it actually fits better into the way that the world of medicine uses those terms. And, you know, they're very common in radiology where an incidental finding is something you see in the course of looking, you know, if you're looking at somebody's heart and you see a tumor, you know, in a lung, then you tell people that you saw an incidental finding. Secondary findings in Genomics were the things that took additional work. So, those other genes that we think are important to tell people about, you know, were things that required additional work to -- to look at them and cost and other things, and I think they set -- I think they've set the definitions now that are much more in line with the way organized medicine uses these terms, and people will probably understand what we're talking about better if we align ourselves with the language that's being used more broadly in medicine.

DR. CYNTHIA POWELL: Natasha

Bonhomme.

MS. NATASHA BONHOMME: I'm Natasha Bonhomme. To this discussion about primary and secondary, I think this is a really critical issue when it comes to education. The fact that it is muddy for those around this table who are the experts in this, I mean, how do we expect the public to really even be able to understand this? And I know that at different times, there have been concerns about counting of conditions and things like that, but I think if we could find a way to have some clear definitions around this and what -- what is -- I hate to say it -- what is newborn screening, you know, what are we doing? But, you know, what is this distinction, and I think what Mike was just talking about is a very clear one, and if that is what is decided, that would be helpful. But that this isn't just a -- a technical issue or a terminology issue. This isn't helping people really understand what is newborn screening as a whole system. So, it's really critical, and it really does impact how

those of us who are doing education and trying to support screening in general as well as all the different components of it, how we're able to talk about that.

DR. CYNTHIA POWELL: Shawn McCandless.

DR. SHAWN MCCANDLESS: Shawn McCandless representing the Society for Inherited Metabolic Disorders. Others have spoken eloquently about the point I wanted to make, but I think -- I wanted to emphasize that the original intention of the secondary conditions was just as Mike alluded to -- it was things that you couldn't avoid because they would turn up in the differential diagnosis. The use of the term secondary target has caused confusion for Advisory Committees that I've served on as well as for state laboratories and has led to a number of states identifying secondary targets as actual targets of newborn screening, and that, I think, is not helpful to the -- to the purposes that we're trying to accomplish.

The second thing is I just want to also reemphasize what Sue Berry very wisely said, which is that the -- these additional conditions have potential implications for the public health benefit, both as Debbie Freedenberg said, potentially positive but also adding cost to the system. And so that -- that seems to me the right place to consider them, but I agree with other speakers' comments that the primary focus should be on the primary focus, which is identifying those conditions that meet whatever criteria we determine are appropriate for newborn screening to be on the Recommended Uniform Panel.

DR. CYNTHIA POWELL: Jed Miller and then Deb.

DR. JED MILLER: Hi. Jed Miller, AMCHP. One of the slides talked about risks and benefits of newborn screening compared to usual case detection, and I'm kind of curious about how much attention is typically paid to the usual case detection and characterizing it, and, I guess, our confidence and our ability to discern what that

really means. And I'm thinking about -- we're talking about a lot of, you know, things -- the scenario where children are asymptomatic, but even if you're floridly symptomatic, there are a lot of steps to getting to care and to getting, you know, diagnosed and then lab testing. So, I'm curious about that aspect of things, because there seems to be a lot of assumptions that come into that usual case detection.

And I think back to our meeting last year on discussion about GAMT deficiency. One part of the meeting seemed to put a lot of confidence in the ability to detect that condition in terms of infrastructure with registries or labs, you know, reporting, and then it was interesting because that was in contrast to hearing some of the personal stories and public input about children who went through, you know, different experiences and were diagnosed at later ages. So, I'm just curious about how much attention is typically given to usual case detection and if that's something that warrants,

you know, a certain level of attention.

DR. ALEX KEMPER: So, let me just answer that question first. I'm not going to talk about GAMT, per se, because that, you know, never came to us, and I don't want to, you know, go into an area that we haven't looked at. But when we do do the evidence review, we look very hard to find out what's out there about how cases are usually found, because that really gives you a sense of what the incremental benefit to newborn screening is, and that's, you know, if we do this decision analyses comparing what might happen with, you know, if you were hypothetically to screen the four million babies born in the US each year versus what happens with usual-case detection. The amount of evidence that we can find related to what normally happens is, like everything else, variable. If you think back to when we were looking at X-linked adrenal leukodystrophy, for example, everyone said, oh, you know, the issue there is that these boys are presenting in, you know, in adrenal failure, and that's what's

leading them to be diagnosed. But although clinicians and, you know, experts in the field that we spoke to repeatedly told us that that was a common presentation for boys with X-linked adrenal leukodystrophy. It was really, really difficult to actually find out how often that happens. But I will say that from an evidence perspective, we tried to look at both sides, and when we're not able to find what we think is high-quality evidence -- I'm going to dive into that in a little bit -- but we try to make that clear to the Advisory Committee so that you can weigh that in your decision-making process. So, I'm sorry, Dr. Freedenberg.

DR. CYNTHIA POWELL: Debra, why don't you go ahead, and then we have Mei Baker, and I think then we'll --

DR. ALEX KEMPER: And then I have a couple of questions for you all based on what I've heard.

DR. DEBRA FREEDENBERG: I just want to sort of share an experience in that whether we

designate something as a primary or possible secondary does have public health impacts. So, for instance, my state expanded to include the secondaries not too long ago. So, part of that impact with that was that we could provide resources to a child in need, with a child with cobalamin A but we could not for cobalamin C, because cobalamin C was a secondary. So, there are other implications down the road as well in terms of state resources that are available, because [inaudible] were linked to things on the newborn screening panel. At the first -- at that time, it was the primary. So, that's just another aspect of it, not that I don't think that focus should be on the primaries, but just there are lots of arms out there.

DR. MEI BAKER: Okay. Mei Baker. A few -- two parts. One is given this discussion, I just want to emphasize on my comments basically moving forward. I think Mike and Shawn have eloquently described the history, what's the purpose. So, I think going forward, I would like

to see avoided is secondary condition, this kind of thing.

The secondary part, it's -- you mentioned the biochemical marker. Going forward, I don't know how you utilize this setting, but I suggest getting a little bit of detail, because when you talk about chemical markers, I would think what is the function of consequence? So, this marker actually is quite good, and I think we should -- this is almost golden standard in my opinion, when you talk about Medium-chain acyl-CoA dehydrogenase deficiency, you have an elevated C8, that's the consequence of deficiency. But in recent years, the condition we are screening for, we use enzyme activities. That's why we got in trouble with pseudodeficiency, late-onset, all these kinds of things. I think we need to distinguish them. I think that's important.

DR. ALEX KEMPER: I just want to reflect back on this very rich conversation. I'm glad everything is being recorded, because I'm going to have to reflect back on some stuff. But,

you know, there is this tension between primary and secondary targets and what we ought to do specifically around the evidence review process. I like the point that Dr. Tarini brought up, which I hadn't thought about it in this way, you know, this notion of intentionality. But, well, you brought it up. You amplified it. It takes a village. It takes a village.

But from an evidence review perspective, it would be great if we could tell you everything that happened downstream of newborn screening in terms of all the -- the benefits and harms and really summarize everything regardless of, you know, the path that an individual took following newborn screening, it -- it sounds like if I'm understanding it correctly, there are sort of two streams of thought in here. One is looking at everything that one might want to intentionally screen for, and that might include late-onset disease versus really focusing only on the primary target of screening and then how back into an understanding of what the public health burden of

looking at both primary and secondary targets. So, there's a little bit of a tension as I think about it, but it may be that I misunderstood that, and we don't need to resolve all this, but is that correct?

DR. JEFFREY BROSCO: I think you heard us talking about that there are those issues. But, I mean, at least I feel pretty strongly that if we think something is worth screening for, it should be part of your evidence review, and if we don't, then we shouldn't make it part of the evidence review, and it shouldn't be part of our deliberation. So, I could see us drawing a bright line.

DR. ALEX KEMPER: Do you mean as a burden?

DR. JEFFREY BROSCO: Well, that would be if you're saying that if you screen for something and you find this, but how is the burden come in then? It's a secondary condition the way Mike described it maybe, but is lab reporting is against the intentionality question they raised

before?

DR. MEI BAKER: So, I -- I agree with everything you said. It's -- if you use screening for condition -- I'm kind of repeating myself -- but you know you can avoid to find something else and then when you assess this is something else, do harm, do good, even because the harm is -- it's really enough where maybe it would not even screening for the first -- the original condition. That's -- I think that's an important thing. Everything, like Jeff said, if you think about the condition, they showed a subject with two other reviews.

DR. CYNTHIA POWELL: Beth Tarini.

DR. BETH TARINI: Beth Tarini. I think that they can be separated because, although people may not want to hear this, ultimately you could suppress, right? You could say -- can you not on some level say we're not going to -- I mean, the laboratorians in the room can say we're going to suppress this because this information is not going to be useful rather than have it -- take

it on its own merit of what you can do to avoid screening if you need to, if you think the burden is too great, if there's no treatment available for what you find, and you don't want to give it, and then deal with that on a separate issue rather than this is what I mean, it starts to back itself back into the primary target decision, when, in fact, there are other ways potentially to deal with it.

DR. ALEX KEMPER: Yeah. I would say that that's true for some conditions, but not other conditions. So, just moving forward thinking about how we're going to handle it, and I'll show you how I and others have sort of come to it. But if you take like late-onset disease for some conditions, they may look, you know, exactly the same on the screening.

DR. BETH TARINI: Well, I was thinking two separate conditions. So, now you've brought up another issue. Is this incidental within its -- is this unintentional within the primary disease itself, in which case I would call

it this is a disorder of X, you know, of X enzyme, which presents primary and late, or is this a disorder of one, for instance, enzyme as well as this secondary target over here, which is a completely different disorder? So, there are separate concepts. I think they both can occur. I think you probably have to, yes, conceptually dig it out a little more. They'll have, therefore, different -- different interventions.

DR. CYNTHIA POWELL: Shawn McCandless.

DR. SHAWN MCCANDLESS: I think it's really important for this group to be extremely careful about the terminology that we use, and again, for newborn screening, what we're -- the evidence review is directed toward a specific condition, and we get -- we start overlapping markers and conditions, and they're -- it's very important to be very clear that they're separate issues, and the condition that's being considered for the evidence review, the decision, I think, is based on whether there is a test that can identify

it in a presymptomatic phase and whether there is evidence that -- that treatment that's initiated during that presymptomatic phase changes the outcome. And that that makes the job easier for the evidence review, because it actually doesn't matter what the current practice is and good we are at picking the kids up when they're symptomatic, because the whole point of screening is their evidence that treatment before symptoms begin is better than after symptoms begin.

The other reason to be very clear about that we're discussing a condition as opposed to a marker is that once you've identified that a condition is potentially appropriate for newborn screening, you then look at the marker that you're using, and that gives you the opportunity to define secondary markers for ratios of metabolites or some other method to further enhance the specificity of the newborn screening test and to reduce the number of false positives, which are often a very significant burden on the health care system and particularly on the families who are

dealing with them.

DR. CYNTHIA POWELL: Kellie Kelm.

DR. KELLIE KELM: Yeah, Kellie Kelm, FDA. I actually really agree with that statement, and I think this comes up in a lot of other places as well. We talk about wanting states to actually, for example, put it on the websites or something, what they're screening for deliberately, right? We talked about that a lot lately, and it's come up in a lot of different things, you know, are you screening for carriers, are you screening for this and that, and states make different decisions about what they're screening for. And we know that it can be different from state to state.

And the other thing that I think about, as you mentioned, you know, for example the methodology since we only add a condition and we don't define the method is that methods change and that obviously, maybe even as we've talked a lot about going back and reassessing some of the conditions, you know, we may also want to, based

on the technology -- maybe not now, but in the future -- go back and -- and redefine things, because like right now, I think, SMA was -- we defined it as homozygous of, right, very specific, and that may change obviously if testing changes in the future. But for now, we define it that way. But I definitely think that, you know, it would be very helpful here if we can define it as closely as we can. But then, obviously, we've talked a lot more about defining things in other spaces as well, and I think that that would always just be helpful for transparency too.

DR. CYNTHIA POWELL: Kyle.

DR. KYLE BROTHERS: I don't want to be perceived to be the person against precise terms because I think it's very important. I just think, you know, you've seen one genetic condition, you've seen one condition, right? They're so unique, the stories are so different about the inheritance pattern, the technology. Some of them, you could suppress certain kinds of results, certain technologies that's not really

possible. So, from the perspective -- I just don't think we can solve the language problem that this field creates. I mean, it's just an inherent problem in the field.

So, I wonder from your evidence review, it might make sense to define a bucket of information like implications or other implications to consider or something like that, and all of those things go in there, and it would be helpful to know what information is available about that, but going back to Jeff's comment, I think it's really about we have a primary condition that evidence review should focus on that, and we also need whatever information is available about other implications that should be considered in the decision.

DR. ALEX KEMPER: So, I -- I'm sorry, is there someone else?

DR. MEI BAKER: Mei Baker.

DR. ALEX KEMPER: Oh, I didn't see you, ma'am. I'm sorry.

DR. MEI BAKER: Mei Baker. I have a

quick comment. Just to follow what Shawn was saying, method, marker, and conditions. But I think we are in the situation -- the condition itself seems to get complicated quickly. So, the example is the Pompe. So, I think the intention is infantile Pompe, but to later on say I think what we know now, people can argue both sides, but to me, in our state experience, after close to 19,000 screenings, we have 13 late-onset identified and zero infantile what you say. You know, I think we maybe need to -- I think in the group we talk about it, in the forward, not just condition, even condition in the subtype, we need to take into consideration.

DR. ALEX KEMPER: That's a great example. So, I was, you know, I didn't have the foresight to know what everyone was going to say when I put together these slides, so I apologize for the broken Ouija board. So, I did -- as I was putting these slides together and with the help of others -- put together some draft ideas, and obviously I'm going to go back and revise this.

But the key thing that I'd like to focus on is that in the nomination package, you know, the more clear about what the intention of screening is is going to help us, and defining these case definitions as we go into things, whether or not they reflect primary or secondary targets, just making sure that we know what information will be most helpful. And so, we'll continue to focus on that as we had, although maybe do a better job upfront to clarify what the goal of screening is, and then continue as we've done in the past in terms of cataloging incidental findings as they are reported in the various studies, but not focusing on the larger impact of the incidental findings.

So, I think what I'm proposing here is just a little more clarification in the report that you would get, along with some pushing upfront in terms of working at the time that a nomination package is handed off to us to understand really what it is that the goal of screening is. Does that make sense? Jeff's

giving me like a maybe.

DR. JEFFREY BROSCO: I think you should probably go on.

DR. ALEX KEMPER: Okay. Well, that was easy. So, let's --

[Cross-talking.]

DR. ALEX KEMPER: I wrote this before anybody said anything, so.

DR. SUSAN BERRY: Okay. All right. So, I'm just going to say one more thing.

DR. ALEX KEMPER: I have plausible deniability.

DR. SUSAN BERRY: What I -- this is Sue Berry, and what I'm going to refer to as what I call the iceberg effect, that almost no matter what you do in terms of making a good case definition, that almost no matter what we think we're going to find, that's not what we find, and if you don't build that in from the beginning with the idea that you're going to do all this ascertainment, no matter how you define it, you're going to misinterpret what you're going to see.

DR. ALEX KEMPER: And that gets to the whole spectrum issue that we've talked about, I think, in every single report. Okay. I'm going to move on to -- let's do something easy. Key outcomes. So, I would say that a goal of ours that we've had, and this is an area that I would like to force us all to thing about, is prespecifying what the expected outcomes of interest are, to make sure that we're clearly working to identify and cataloging them. And when I talk about the expected outcomes, I'm thinking about both benefits and harms. But obviously we're going to continue to be open to new outcomes of interest that are identified during the review process.

So, in terms of benefits that we've looked at in the past, mortality, we've looked at some components of morbidity, we've looked at length of life, we've looked at ventilator-free survival, we've looked at different measures of neurologic and motor function, which by and large are focused on issues of mobility and

communication.

In terms of harms -- this one I sort of captioned, and we've tried to consider -- and the reason I say that is harms can be -- are often times incompletely reported. So, there's all the harms that we've talked about in the past related to screening. Aaron Goldenberg has been very helpful for us in terms of thinking through, so pain or other adverse impacts from screening or diagnostic testing, false positives, and false negatives, and then after diagnosis, earlier exposure to treatment, to adverse effects, and the psychosocial harms of uncertainty of outcomes. So, that's a very high-level look at harms, and we have harms more broken out in -- in other reports that we put together for the Advisory Committee.

So, what I'd like to do is just think through other benefits and harms that are of interest. So, there are these intermediate outcomes, and those are often times reported, but it's difficult to know what the link is sometimes between these intermediate outcomes and patient-

centered outcomes. So, when I talk about a patient-centered outcome, let me be clear that I'm talking about something that individuals feel, right? So, you know, within, you know, different areas, you know, different ranges, you may not sense, you know, that your -- your biomarker has gone up. If you think about like lipid screening, you know, I may not notice when my cholesterol has gone up, but I might notice, you know, cardiac events related to my lipids.

So, also imaging findings are another good example. So, like MRIs and the scores that we've seen done on MRIs for conditions that affect white matter. So, how do we think about these intermediate outcomes, and should we pre-specify them?

There are issues of quality of life. So, when I think about the impact of preventative service, you know, ultimately, I'm interested in two things: length of life and quality of life. But quality of life is a notion that's difficult to get to, and it's often times not reported in

the kinds of studies that we have available to us. And then there's this larger issue that we have not delved into because our mandate has been on focusing on benefits that accrue to the individual being screened and not the family, but there is this importance issue of avoidance of the diagnostic odyssey, diagnosis in other family members, if there is, you know, screening of other family members that happens as a result of identifying something in a newborn. And then issues of ability for families to develop plans for the future.

Now, there are a lot of other outcomes to families, and I don't mean this to be an exhaustive list, but I do want to just put that up there as something that we haven't specifically considered and just get feedback on. And then, what I can say is that when we do our literature, you know, we -- we don't do primary research, right? So, we can only describe what's been included in previous research. So, let me put that out there first and just remind you all that

it's beyond the scope for us to develop new evidence on outcomes that -- that haven't been previously described, and by that I mean haven't been described in -- in the scientific literature.

So, that's a lot of stuff there, and I'll just open it up now for thinking about benefits and harms and also the degree to which -- I didn't highlight this and I should have -- if we should have a list of outcomes that we always look for. And you can even imagine, because they -- they do this in other evidence systems where you have a priority list. So, you know, these are the lists of important outcomes, and these are the ones that are most significant, and these are the ones that are less significant to making a decision. Should we have a standing thing like that, that we then tailor to specific conditions, or do we kind of start the way we've done things in the past, which is, you know, convene experts and look at the nomination package to figure out what sort of outcomes we want to make sure that we explicitly look for. So, let me open it up.

DR. CYNTHIA POWELL: Beth Tarini.

DR. BETH TARINI: Beth Tarini. The -- so, the issue of outcomes to the family -- while we have not, as a committee, dealt with it, it has some up in the literature Dr. Alexander brought this up -- I think in the early mid 2000s maybe when he published it in Pediatrics, this idea of the benefits to the other. I want to put out there that, you know, we often talk -- it came up today -- about the -- the Wilson-Jungner Criteria -- should we be using it, should we not. The -- the one thing I think we shouldn't forget is -- and Dr. Brosco brought this up -- is this is a mandatory test that has a specific legal standard, and that legal standard needs -- that legal standard needs to be taken into consideration when we talk about the rationale for why we decide to recommend a test be screened. Now, I always say you -- you build the system and you go according to the system you build. If we want to change that system or add a new one, that's completely reasonable and an option. But the outcomes for

the family raise concern given the constraints, and I don't think we have any legal -- we have ethics. But I don't think we have any law expertise on the committee of what that means in terms of mandatory testing for children. One can see what's happening with the vaccine issue at large, so I just want to raise that point. I think it's important.

DR. CYNTHIA POWELL: Jeff Brosco.

DR. JEFFREY BROSCO: So, Beth, one way we can have our cake and eat it too, right, is something that Alex and I have talked about, which is if you -- if we set up ahead of time and said here are the things we, as a committee, really care about. First is about mortality, quality of life, and key morbidity, and say this is what's really most important to us, then you might have a second- or even a third-tier of things that are also interesting and could be important, and by setting out ahead of time, we start slowly to solve this problem of we never have evidence about quality of life because if you're thinking about a

candidate condition, you might say, oh, that's what the RUSP criteria are, we should include a quality of life measure in our next pilot study. So, we can begin to solve that evidence issue, and I agree that we don't want to -- I would not want to switch so we're doing things on the RUSP simply to avoid the diagnostic odyssey, but if that were something that came out of it, and the last way to sort of put that in is when groups are putting a forward candidate condition, if they said we've surveyed families, and for them, one of the outcomes that's really important is X, Y, and Z, that's helpful for them to put forward, and we can see where that falls in our tier system.

DR. BETH TARINI: I agree. My concern is quality of life can be -- I understand quality of life can be measured for a wide group, but this will affect the entire population. So, if get -- if my child is born and my -- the mandatory testing is based on quality of life, it needs to be a quality of life that I agree with, since you're removing my parental rights in order

to test the child. So, I don't think actually quality of life, I think quality of life is -- is potentially a gray area, because if you don't -- your quality of life may not meet the standard or one's quality of life of a legal requirement of a mandatory test. I get -- I'm not sure. Clearly, diagnostic, I mean, what is the metric of quality of life which says that you can mandatory test a child at birth? I don't know the answer. But I think there is something that needs to be discussed. Am I not clear?

DR. CYNTHIA POWELL: Kellie Kelm.

DR. ALEX KEMPER: So, actually, can I -- because I think you might have had two quality of lifes in there too, the family or the parent quality of life and then the child's quality of life, which are distinct things too.

DR. BETH TARINI: Certainly. I mean, I guess the one issue is the family, and the second is the quality of life, be it for the family or the individual themselves. So, you're right, it needs to be stratified. I mean, I --

this came up, I think, implicitly with the conversation about SMA, that there were some people -- I'm surmising -- that felt uncomfortable that the quality of life was there to make it mandatory. I don't know that. But -- but when I voted on it, I voted on it on mortality, because we didn't have this discussion to day what is the threshold of quality of life that we feel is -- is uniformly agreed upon or of a standard of which we think it can be used in a mandatory test.

DR. KELLIE KELM: Well, to tack onto that before I get to my point, I mean, I guess since the states are the ones mandating the testing, we may have to get input from the states in terms of what they may have in terms of -- and if anybody has any language that pertains. But I'm going to guess that I'm not sure if there's one at the federal level that we could even point to.

But I was just thinking about some of the more recent conditions that we've gone through in terms of some of these things, and I think I

know a lot of -- we have a lot of intermediate meetings while you're working on evidence review, and you sort of ask us a lot of questions, and I think if I recall for some conditions, they assess mortality, but then they'll also assess things like cognitive, you know, in a study. They're doing it in a way that it's measurable or definable or a six-minute walk or, you know, which is, you know, you can tie that to mobility, for example, or other things. So, obviously, a lot of times, I think these things will just automatically come out, because you'll say these were measured and we'll be able to capture them. I mean, I think it would be difficult if they weren't somewhat captured in a way that we could say was -- that was an outcome that -- that we would want to sort of -- and I think that's sort of the difficulty, is how do we -- so as evidence review, how are you going to present that without actually having the evidence measured, and sometimes all you're going to have is mortality. I think when it was SMA, we just -- we didn't have

very much. It was a very small amount of data in the population that we were thinking about treating asymptomatic babies. And so, in some ways, we just sort of have to define explicitly what we have so at least it's there and say that this was measured, or, and this wasn't, and maybe this is important. But right now, it just wasn't measured.

DR. ALEX KEMPER: If I can just add on to the complications you were talking about. There's an issue of the time horizon, too. So, there may not, you know, often times the studies we find are of such short duration that it's hard to know, you know, did it change the child's quality of life, because, you know, if you're just looking at six months or one-year outcomes, it's hard to make, you know, inferences about what's going to happen down the road.

DR. CYNTHIA POWELL: Jeff.

DR. JEFFREY BROSCO: So, none of this really solves anything, but it is worth pointing out that there's a lot of researching work going

on in quality of life measures, right? So, the National Academy of Medicine and others like the Vital Signs project are trying to say well, there's sometimes disease-specific quality of life measures, asthma is a great example, but then there are also more general ones. And so, there is, you know, not a simple thing, and I want to separate that out from outcomes for the family, right? That is different from quality of life measures.

DR. CYNTHIA POWELL: Kyle Brothers.

DR. KYLE BROTHERS: This is Kyle Brothers. I don't want to be dismissive of quality of life measures. I think they can be quite useful, especially in research settings, but for -- conditions have their own unique set of complications that have implications for quality of life, but I would rather us, if we're going to set a priority, let's set what is a specific complication that we're worried about, and what's, you know, what's the frequency of that. That is a more approximate, it's easier to look at, and we

can set it as a higher priority. But I think we don't want to be too wholistic because quality of life for children is defined as perceived quality of life from the perception of the parent, which, there's just a lot of action going on there. It's difficult to really know what's going on. So, I'd rather for us to set a second-tier and say first tier of things like morbidity and mortality that are sort of universally recognized, and the second-tier is a set of complications or concerns that are specific to this condition that we can measure the frequency of them, and then I'd like to see quality of life -- perceived quality of life as reported by the parent -- being a lower thing -- not, it's not irrelevant, I just don't think it's a top priority.

DR. CYNTHIA POWELL: Shawn McCandless.

DR. SHAWN MCCANDLESS: Two thoughts that I think are in complete agreement with what Kyle just said. The first is that I think it's also important to remember that often times, the

treatment that we give to prevent mortality or intellectual disability actually has a significant deterioration -- causes a significant deterioration of quality of life and so that has to be -- if we're going to assume that quality of life is an important measure, it gets even muddier when one considers that possibility.

The second thing is that I think reflecting on what Beth has said about the -- and Jeff -- about the mandatory nature of newborn screening programs. It seems to be that it really does make sense for things to be kept very simple, that the primary goal of a newborn screening program should be to intervene pre-symptomatically when that will prevent death, intellectual disability, or permanent physical disability. One could add a few other things, maybe, but at the end of the day, if you can't show that what you're going -- if it doesn't matter whether you identify the condition pre-symptomatically for those three criteria, what would be the justification for newborn screening -- for mandatory universal

newborn screening?

DR. ALEX KEMPER: And so, if I can try on that point, that would also argue for having the kind of prespecified list as well, the investigators and advocacy groups and funders and that kind of thing could look at when they're setting up outcomes for the various studies they're putting together related to newborn screening. Is that fair to say?

DR. SHAWN MCCANDLESS: Yes.

DR. ALEX KEMPER: I love consensus.

DR. CYNTHIA POWELL: Robert Ostrander.

DR. ROBERT OSTRANDER: Robert Ostrander, AAFP. I'm going to push back a little bit on some of this discussion, and I absolutely think that if we can't show a medical benefit for screening, you know, that should be a -- an exclusion, I mean, we shouldn't approve something simply because of the family life and quality of life measures.

But I got pulled into this world 20

years ago, I guess, when NICHQ did a learning collaborative on Children and Youth with Special Health Care Needs, and one out of three people at learning collaborative were parent partners, and their priorities were very different from the clinicians in the room, and I really wonder if we shouldn't, as part of our process between now and 2020, think about convening some parent partners and finding out what they say about benefits and harms, because the thing that I learned long before getting into this newborn screening community was that what the parent partners were telling us then is the diagnostic odyssey was a huge deal, that children and families, I mean, these are -- this is family-centered medical home not payer-centered medical home like we're doing now, but family-centered medical home and to separate the benefits to the child and benefits to the family -- the immediate family is artificial, and the things that we heard that were very important were avoiding diagnostic odysseys, getting plugged into a coordinated medical home-

type situation where right from the start, you are hooked up with people who understood your child's special conditions, you had a relationship with them, so they understood your expertise as a parent, and you knew who to call on your bad days so that on your good days you weren't sitting there wringing your hands, what if my kid gets sick today. And I think we'd be doing a disservice to the people that we're here to serve if we don't find out what they -- what benefits they think are the most important and somehow take them into account. Now, we always tend to value and prioritize things, and this is a huge issue with governmental management in health care right now. We tend to prioritize and value things that are easy to measure as opposed to what might or might not be most important, and I think we have to resist that temptation to say we're not going to deal with this because it's really hard to measure, and I think we probably can, and I think Jeff touched on it. There are general -- there's general information about chronic conditions in

kids with special needs about what's important and what we can measure, and I think we probably can measure just in general kids who are extreme versus kids that are usual case, what is -- how -- what's the difference in the timing of the start of the diagnostic odyssey and the duration of the diagnostic odyssey. What's the timing from the establishment of medical home and, you know, how quick do they get into surveillance? I don't think we should discount that at all, and I don't think -- I don't think you can de-link the family from the patient.

DR. CYNTHIA POWELL: Beth.

DR. BETH TARINI: Beth Tarini. I want to be clear. I believe we could have an evidence base for quality of life. I believe we could create an evidence base for family outcomes. I raise the concern of where that bench -- where that line is that allows us to invoke parens patriae and have a mandatory screening test. That's not to say it can't be a secondary piece of once one meets the, you know, you can now be a

mandatory test outcome evidence-based, you cannot use this secondary -- I'm calling it secondary -- but, this additional evidence base and look at it for does this give us more benefit than this disorder? It doesn't seem like we have -- have needed that, because we have -- it -- it doesn't seem like we've thought that there's been too many disorders added so that we have to distinguish among two if both meet the medical outcome, because we're barely scraping by, it seems to meet the medical outcome.

That being said, I think again, there is an evidence base. It can be broadened and developed for quality of life. It can be done for outcomes. The question I have is, do we intend to continue to do so under the mandatory requirement and the legal requirements that has at the state level. That's all.

DR. ALEX KEMPER: Annamarie, were you --

MS. ANNAMARIE SAARINEN: Annamarie Saarinen. So, this has been such an interesting

discussion, and I really didn't want to take up extra time again. But I think what you're trying to decide here is what's the threshold and what's the criteria for how we look at things during evidence review and move things forward, and if that's the case, I really go back to Jeff's suggestion of like how -- is there -- is there a very standardized way that we can incorporate language in the nomination process and in the review process that does consider the -- the parental -- the exact things that -- that you just mentioned, Dr. Ostrander, the diagnostic odyssey, the real parent-family experience and what their priorities are and that they're -- that we're weighing those and recognizing those, and it's not just clinical evidence, and I will point to -- we have a baby in Minnesota that was picked up by screening -- and I'm sorry to use another congenital heart disease example -- but this baby died two days ago after spending ostensibly 630 days that she has been on the planet in the unit. She never went home. She had multiple congenital

heart surgeries to try to repair her very complex heart disease, but what I do know -- because I know the mother -- is that they wouldn't for a minute have not wanted to have known that their baby had a heart defect and then been sent home and she died one or two weeks after birth, because that would have happened had it not been picked up for the screening test. But those two years -- many of them on a ventilator -- I think many of us from a clinical perspective would argue what kind of quality of life was that for their child. But I really like us all to continue to think about those things as we put forward these uses of language that can be more -- I don't know -- help us to a better job of measuring what moves forward.

DR. ALEX KEMPER: And so that -- that's actually a great point for me just to remind everyone too that this particular topic sort of blurs the line between evidence review as well as the decision-making process. We're going to revisit both of those issues in the future, so

it's not -- obviously, we're not coming to consensus now about anything. But I -- I, you know, did hear that the, you know, Advisory Committee is interesting in digging into these issues more and that there are clear things that everybody would agree that the evidence review ought to look for, because they're so fundamental to what would allow something to be on newborn screening, but have it consider these other things is still a work in progress.

So, I have -- can I just -- yeah?

DR. CYNTHIA POWELL: I'm sorry. Is there anyone on the phone who has any comments?

DR. ALEX KEMPER: Okay, hearing none. So, from an evidence standpoint, we're going to continue looking at the full range of benefits and harms as we've done in the past. One of the things -- actually this goes to your comment before -- is we really need to make sure that we're clear about the comparison groups, and when we're talking about differences in morbidity or mortality, you know, what is that difference

compared to? We didn't talk about this too much, but I will raise the issue of the time horizon again. So, again, we're not going to be able to resolve this, but this is a question for the Advisory Committee. Is there some minimal period of time that you want to wait for before you know what the outcomes are? So, if you look at something where you just have six-month outcomes, for example, how much does that -- how much does that help you versus, you know, is there some threshold? Then again, it's a complicated issue, and it's going to depend upon condition, but I'm going to raise that as something that we're going to need to talk about. And then, of course, we need to, you know, it's my last point is it's just a work in progress.

I do hear -- maybe because I want to hear it -- but that there's this interest in coming out with some sort of tiered list at least as a way for us to -- to begin to think through those issues. And so, again, I'll follow with that as well as everything else that I have here.

All right. Should we move onto another topic? I'm looking at my timekeeper too. How much more time do I have? I've lost track. So, they'll light that when I've run out of time.

So, let's talk about treatment. So, treatment is complex as well. Typically, when we have done our evaluations, we've focused on the FDA-approved indication when there's, you know, a new drug that's available for treatment like nusinersen would be a good example of that. One of the challenges that we have is, how should we consider therapies that are in development? How should we consider supportive therapies, so non-targeted supportive therapies for an affected individual or maybe some sort of, you know, supportive therapies for the family? And the final point that we're wrestling with is how should availability of the treatment be weighed in the evidence review component, or is that something that's for the impact assessment side of things? At what point do we look at whether or not treatment is available?

So, I'm going to open this slide up for comments.

DR. CYNTHIA POWELL: Shawn.

DR. SHAWN MCCANDLESS: Regarding therapies in development, when we -- those of us who have lots of gray hair or little hair left who have been involved in lots of clinical trials know that they don't always work, and we always tell our potential subjects in our clinical trial that if we knew that it worked and if we knew that it was safe, we wouldn't have to do the clinical trial. I think it would not be wise to make decisions about newborn screening based on therapies in progress. I think there needs to be confirmed documented efficacy of the treatment.

That doesn't necessarily mean FDA approval, but there needs to be a body of evidence confirming that the treatment or the therapy is safe and effective.

DR. ALEX KEMPER: So, one of the examples of this going back to the SMA examples, as we were doing the review, more and more

information came out around gene therapy, although certainly those studies weren't, you know, fully available. But, you know, that's an example of the kind of thing that we struggled with during the review process.

DR. SHAWN MCCANDLESS: And I would just say that that relates to the -- to the time horizon, that if it's -- if the data about the therapeutic efficacy and safety are premature, then it seems to me that making a decision using those data is premature.

DR. ALEX KEMPER: Other thoughts about therapy? Maybe we have like a postprandial low, I think. Anything else there? Yeah, Kyle.

DR. KYLE BROTHERS: I was just going to comment on the idea of incorporating things like supportive therapies and issues like that. I completely agree. I think FDA approval is probably not the -- the right standard, especially as we're not -- we're unlikely to keep adding in more common conditions. Likely, the conditions that we add are going to be less common, and

that's just going to continue to compound the complication there. So, I agree with keeping an open mind about whether FDA approval is, in fact, the standard. But I would like to see some evidence that it works.

From the perspective of supportive therapies or other types of things, I think it makes sense to tie the tiers of treatment with the tiers of the outcomes. So, therapy or some other intervention that improves one of our lower-tier outcomes is probably not relevant or it's less relevant. But, if we can -- if there's some sort of intervention that helps with one of those higher-tier outcomes, then that really starts to be where I think the importance comes in.

DR. ALEX KEMPER: That's great. I hadn't really made that connection with the tiers. But I think that will be helpful in the evidence review process moving forward.

DR. CYNTHIA POWELL: Sue Berry.

DR. SUSAN BERRY: So, I'm going to throw another spanner in the works, as they say.

DR. ALEX KEMPER: Very British.

DR. SUSAN BERRY: Availability -- yeah, very British -- availability of treatment can be a relative thing. Available to whom? Is your insurance company going to pay for that $500,000 therapy? Is the therapy available only to people who have a certain mutation but not others? These are all going to be things I know we're going to struggle with, and it's only going to get more obvious with time, because many of the therapies that are going to emerge are going to be extraordinarily expensive and very specific in their targets.

UNIDENTIFIED FEMALE SPEAKER: [Inaudible, speaking off mic.]

DR. SUSAN BERRY: Same. So, will that be something else? I'm going to put it under availability is more than just -- is there a treatment at all, but how available is the treatment to individuals and what's the burden on society if we have those treatments?

DR. ALEX KEMPER: And that gets to

accessibility and so forth.

DR. SUSAN BERRY: Um-hum, access is maybe another -- another piece that deserves to be in this is access beyond availability.

DR. ALEX KEMPER: And should that be part of the evidence review process?

DR. SUSAN BERRY: Well, I -- I suspect if you're thinking about -- we had, you know, there's always this conversation you have. You spend a half a million dollars on this and you could give five hundred thousand children vaccines. It -- it's a relative value thing, and I'm not sure that there's a price that -- a price tag that we place on good outcome. But if we don't even bring it up, I think we're irresponsible.

DR. CYNTHIA POWELL: Kellie Kelm.

DR. KELLIE KELM: Kellie Kelm. I think that we have considered it, just not formally. I mean, I think, obviously for SMA, we knew that Spinraza was out there, but we didn't really know a bunch about coverage at the time,

and I'm sure that it may have changed. But we haven't really talked about that. That was also after we were talking about SCID at the time, I think everybody had to go to Duke for the process, but then we knew that kids on Medicaid, right, weren't going to probably be able to travel and get it covered. So, you know, we all sort of knew that in the back of our minds, but I guess we could more formally think about it and capture it and consider it in our decision-making. I think it's obviously easier, for example, if it's something available in Europe that that you can't get here or something like that. But I think, you know, we'd have to -- that would be something new, because we didn't consider the cost of Spinraza in our discussions. We just said it was available and we said that that was -- that checked the box. So, I think it could get more difficult, but I don't know. We seem to avoid it most of the time.

DR. CYNTHIA POWELL: Deb Freedenberg.

DR. DEBRA FREEDENBERG: I was just going to say that if you're considering therapies

in development, for most of those, we really don't know the long-term outcomes. They haven't been around for a while, and I don't know how you assess their efficacy outside of the short term that the studies done -- that were needed for FDA approval. You know, they're phase 2 or 3 stuff. I'm not certain how you would weight that, because you really don't know five or ten years down the line what the outcome is going to be. I mean, you know what it is if they're not treated, but you don't know what -- what it's going to look like.

DR. ALEX KEMPER: I guess the duration of therapy or duration of outcomes and that kind of thing, which like when we looked at SMA, we only had really a year or two worth of data.

DR. DEBRA FREEDENBERG: Right, and you may be changing the more severe disease into something that's a more chronic -- needs more chronic management.

DR. CYNTHIA POWELL: I think for the sake of time, Alex, do you want to go ahead?

DR. ALEX KEMPER: Yeah. So, basically, this is just basic, this slide says it for now. We're going to keep doing what we're doing. So, what I do want to do -- how much do I have left, another ten minutes? Yeah.

So, I'm going to go through quickly some slides just talking to you about our plans for assessment of the peer-reviewed published evidence, and this requires less weigh-in from you all. But I do want to be clear about this, and this comes from the in-person meeting that we had and some other work related to GRADE, which is a standardized process for evaluating the quality f literature. So, things that we're going to summarize for screening treatment studies include the number of studies and observations for each study design, summary of findings, consistency or precision, estimates of potential reporting bias, overall study quality, body of evidence limitations, applicability, so do these things apply to babies that might be picked up through newborn screening, as well as a summary of overall

strength of the evidence and there are different ways -- GRADE has one way -- but different ways that have been developed for putting these into tables and moving forward, I think that we really ought to just mirror what they do.

So, when we think about questions related to adequacy of the evidence for screening and treatment, we're going to be looking at specific questions. Do the studies have the appropriate research design? So, are they clinical trials, population-based observational studies, and so forth? To what extent are the existing studies of sufficient quality? The key to that is whether or not there's a comparison population. To what extent are the results generalizable to newborn screening? How many and how large are the relevant studies, and are they precise? For example, are the intervals appropriately narrow? How consistent are the results of studies? So, if you have, you know, a handful of studies and they're all finding disparate things versus the same things, then your

level of certainty about it would be different. And then, are there additional factors that would assist in drawing conclusions? So, does it make sense? Does it fit into our understanding of the disease?

What I put up here is the ultimate rating of quality of evidence used by GRADE, which breaks things into high, moderate, low, and very low. But the interesting thing is that GRADE doesn't really have a process for assessing the kind of small case series that we often times use. It's just -- it's just not there. Interestingly, it does seem like they're trying to develop methods to do that, but we're just not there yet. So, you know, clearly, we will be able to assess the quality of evidence for the trials and observational studies where they find them. We're obviously also going to keep our case series, but we're just going to have to summarize their quality in a more quantitative way instead of being able to assign it a quality rating.

With that, I'd like to just touch on

the gray literature as well. So, there are two areas where we've really used the gray literature. One is around the accuracy of screening and the process for diagnostic confirmation. So, you know, some of these previous reviews such as like I have Dr. Caggana and her team on speed dial on my phone. That's an example of unpublished literature, but, you know, sort of up-to-date related to screening outcomes. And because we've looked at conditions where the treatment is still in development, we've looked at gray literature related to that. So, I have here examples of gray literature including newborn screening program data, documents that have been submitted for drug approval -- that's what I mean by regulatory documents -- study protocols, and research that's in progress, which important to recognize is that there's a bunch of different places where you can find the gray literature ranging from trial registries or information submitted to the FDA, as well as conference and abstract proceedings, as well as talking to authors and study sponsors and

looking at other registries. So, some gray literature is, you know, we have methods where we can find them through searches of electronic databases and other things where we have to reach out to individuals and figure out how we're going to get things.

We had very helpful comments from one of the directors of GRADE, who says that when they look at gray literature, they have a standardized form that gets sent out broad and wide for individuals who might have relevant unpublished data to submit. We've not done that before, but it makes the most sense in terms of really being able to catalog what unpublished data are out there and also to have a more formal way of requesting unpublished data.

So, in terms of assessing it, there's obviously the data that we get directly from the newborn screening program, I consider to be the lowest-risk of bias, and by that I mean, you know, that's just, you know, following through the algorithm in terms of how many babies were

screened and how many babies tested positive and negative, and who ended up in the diagnostic confirmation process and what their outcomes are.

But, you know, for the other parts of gray literature, there's not easy ways to assess the risk of bias. So, let me just end this part by saying that we're going to continue to review the registries and so forth, and I think that we ought to mirror what's been developed for GRADE in terms of developing a standard way to collect relevant literature from those in the field. I think it's -- it'll just be a more transparent process, not to say that it will not be free from risk of bias, but I think it's just a more replicable process.

So, let me just open things up to questions and thoughts about the assessment that I just went through.

DR. CYNTHIA POWELL: Kellie.

DR. KELLIE KELM: I just -- Kellie Kelm. I just want to -- I understand the lowest -- your statement about the data from newborn

screening labs, then obviously the caveat from generally what is that literature or even trying to get information from drug trials where they tend to be silent is often you only hear about the positive things, that things that are negative or even neutral, we often can't get that information or they just don't make it available, and that makes it extremely difficult to understand the quality of it.

DR. ALEX KEMPER: I would say I'm especially concerned when we look at conference proceedings, and it's, you know, especially when you just have an abstract, and it's really hard to figure out what went in there and sometimes we get all excited and we find out that what's in there is really different than what was in there.

One of the things I jumped past that I'd like to ask you about is when I was talking to Dr. Bocchini, apparently the Advisory Committee on the Immunizations Practices uses data submitted to the FDA for approval of vaccines, but I'm not sure what your thoughts are about us being able to get

similar stuff that's been submitted to the FDA for approval.

DR. JOSEPH BOCCHINI: So, let me just add to that a little bit. What sometimes happens is that it's sort of like a drug that's been licensed by FDA, vaccines are licensed by FDA, but the studies that were done -- that were submitted to the FDA for that licensure have not yet been published. But the manufacturers are often willing to provide that data to ACIP workgroups confidentially to review that information so that they can prepare for a decision at the time of licensure about a vaccine recommendation. And I just wonder whether that's a similar process that could potentially be utilized here if a drug has been -- the trial data has been submitted to the FDA, the FDA is looking at the packet or has already decided to license the product, whether that might be helpful to the committee to have that data.

DR. KELLIE KELM: Kellie Kelm. I -- I actually -- yeah, I don't know -- if you've seen

it -- talk a little bit more about specifically the method and how you do that -- how you communicate with the agency and the companies and see whether or not that's possible, because I currently don't know of the way to do that. But you might want to use that and see if we can -- if we can do that. So, because yeah, they -- obviously there's information that winds up in, for example, the drug label. There are post-approval commitments like some of the studies, I think, for SMA that we talked about in the post-year was a post-rule commitment and I don't -- I think in a lot of cases, they may not actually need to provide that publicly at all, and, you know, there may not be a decision actually as to drug label or not, and that depends. So, that might be something where we might want to talk to the agency and say hey, you know, we know in the letter you've obligated the company to do this, is there some way for us to get that data? But maybe we can talk about how the other committee communicates with them and see if that's possible,

because I don't know.

DR. CYNTHIA POWELL: Beth Tarini.

DR. BETH TARINI: So, I -- when we went to the SMA review and started to use the gray literature, I thought that this would be our way sort of to help fix the issue of not having enough data. And then, I became concerned that we didn't know what we didn't know, and so -- and that -- there were two issues. There was that, and there were others that knew something we did not. Now, we could have a conversation about whether or not in that meeting when the public comment period raised data about cases we knew nothing about and whether or not that was data we should have had access to or couldn't because of the way the trial was being done is one piece. The other is I think if we use gray literature, especially that around ongoing trials, that we have a sense of what we are getting and what we're not getting, so at least we know what we have may or not be complete, so -- so we don't make that assumption.

And then, I think we -- we don't

delude ourselves that just because it's being done in a trial that it will one day undergo the rigor of peer review, because my understanding is we've not yet seen the SMA data in peer review format, which I'm not saying does or does not make it less valid, but it certainly underlies an assumption if we assume it is always going to go to peer review and then we'll have this secondary validation coming.

So, I'm not saying we shouldn't use it, I'm saying we should be clear about what we're getting and what we're not getting, and what assumptions we're making based on it. And I think your forum will be helpful in that regard, and I think the more we become familiar with it, these kinks may eventually be worked out at least to some degree.

DR. CYNTHIA POWELL: Shawn McCandless.

DR. SHAWN MCCANDLESS: Shawn McCandless for SIMD. Just to follow up on that and the earlier point, if one were going to get

access or ask for access to FDA data, I think it would be unwise to use that before the FDA had made a decision about a novel therapy because one would hate to initiate newborn screening based on our interpretation of the data that the FDA is looking at and then later have the FDA decide that -- that there's not -- that there's not going to be an approval for that drug. That puts us all in a very awkward position.

DR. ALEX KEMPER: Point well taken.

DR. CYNTHIA POWELL: Dr. Bocchini.

DR. JOSEPH BOCCHINI: Yeah, I'll just say it's typically after the FDA has made the approval so that compound is licensed and yet that data is not in the literature yet. It's been submitted, and FDA has utilized that data, but it has not yet been published.

DR. CYNTHIA POWELL: Alex, do you want to have the last word?

DR. ALEX KEMPER: Thank you. No, no. this is really helpful, and it's a work in progress to be continued, and I appreciate

everyone's level of engagement.

DR. JOSEPH BOCCHINI: So, now this meeting gets turned over to Catharine.

ACKNOWLEDGEMENTS FOR DR. JOSEPH BOCCHINI

DR. CATHARINE RILEY: Well, thank you, Dr. Bocchini. So, as you can see on the agenda, we wanted to reserve some time this afternoon to acknowledge Dr. Bocchini's many years of service as the Chair. So, we've put together a series of activities for the remainder of the meeting to honor you and say thank you. Before I introduce them, I just want to take this opportunity to personally say thank you. It's really been an honor and a privilege to work with you, and I truly value your wisdom, your passion for the field, your compassion for the populations that we serve, and I could go on. But I want to get to the actual festivities, so.

I would like to invite Alaina Harris up to the podium. So, Alaina is one of the HRSA staff members that has actually known and worked with Dr. Bocchini the longest, and if you don't

know Alaina, I wanted to take this opportunity also to acknowledge and highlight the incredible work that Alaina does for this committee. So, I want to say these meetings would not run the way they do without the hard work of Alaina. So, many, many thanks to her as well. So, with that, I will turn it over to you for the festivities. Thank you.

MS. ALAINA HARRIS: Great. Thank you. That was very nice of you, Catharine. Yeah, thank you for that kind introduction. So, Alex, do you want your -- okay. Now we can begin. As Dr. Riley noted, I have known -- part of our staff to have known Dr. Bocchini since the beginning of his time on our committee with myself and Jill here at the time, and I just want to say that at the time that I got to know him, Dr. Bocchini and I were basically just young children, right? So, today we'd like to honor Dr. Bocchini's Chair as -- I'm sorry -- tenure as Chair of the Advisory Committee on Heritable Disorders in Newborns and Children, and I just want to let you know since

Dr. Bocchini is from Louisiana and every February, he brings the committee Mardi Gras beads, that's why we're wearing beads today to celebrate them. So, I hope everybody has them and if not, I'm not a member of the Mardi Gras krewe, so I'm not going to throw them your way, but you can get them like out at the registration desk. Okay, now then. Over the next hour, we are going to have a number of people who have been impacted by Dr. Bocchini's leadership to acknowledge the work that he's done for the committee as Chair, and I'd first like to call on Joan Scott, the Director of the Division of Services for Children with Special Health Care Needs to say a few words on behalf of Dr. Bocchini, and we need you up here too.

MS. JOAN SCOTT: So, Dr. Michael Warren who is the Associate Administrator for the Bureau was unable to be here today. So, his loss is my gain, and so I get to make this presentation on behalf of the committee of HRSA and HHS to the benefit of all the nation's children. You have led the committee since 2011, and over the last

eight years, your dedication has been incredible. You have, over those eight years, led the committee through a lot of very difficult and important discussions, not just about conditions that get added onto the Recommended Uniform Screening Panel but how the committee does its business and how we can improve newborn screening through the nation to benefit all of our children, and you've done that work and led this committee not just with skill and expertise but with compassion and wisdom and kindness, and those are the qualities that we will remember you best for.

So, on behalf of the committee and HHS, I'd like to present this to you and what it says is the Advisory Committee on Heritable Disorders in Newborns and Children to you as the Chair from 2011 to 2019, you have made a difference in the lives of newborns and their families with your wisdom, compassion, and generous spirit. Thank you for your many years of service in leadership to help the nation's infants and children. So, I want to give this to you, and

we have a little letter of commendation to go, and we can ship this to you, so you don't have to carry it. Thank you, Dr. Bocchini.

[Speaking off mic.]

MS. ALAINA HARRIS: Perfect. Okay. In the meantime, we are also going to hear from some committee members and some organizations reps who would like to say a few words. So, first up is Cindy Powell. And you can sit at the table if you want to or get up here, whatever.

DR. CYNTHIA POWELL: Thank you. Well, I certainly would like to thank Dr. Bocchini for sharing his wisdom and advise to ensure a smooth transition as we change committee Chairs. I think I mentioned to you on one of our first phone calls after the announcement was made that I was the incoming Chair that, you know, you have such a low-key approach but enable everybody to speak their mind and, I think, feel that they've participated in the discussions and final decisions being made, and I think, you know, my two years serving on the committee, that's not an

easy thing to do. I will continue to value your input as we go forward, especially as we have to consider some conditions for which you're extremely knowledgeable. And so, you know, we look forward to that, and although I know you still will have a lot of other responsibilities at your university, you know, understanding a little bit better now what the tremendous amount of work that you do behind the scenes and in between the meetings, I hope that now that you won't have to do as much of that, that you'll be able to spend more time with your grandchildren and enjoy Louisiana basketball and other activities. So, to use a common phrase from Louisiana, Laissez les bons temps rouler.

MS. ALAINA HARRIS: Next up is Dr. Brosco.

DR. JEFFREY BROSCO: So, you're probably going to hear themes from all of us about your style of leadership, because I think all of us have learned so much from, you know, there are different ways that you can lead a group, and I

think that yours is characterized by being clear, being calm, and being compassionate, right? So, we've had so many discussions over the years where someone thinks this and someone thinks that, and we're all over the place. At the end, you've done a wonderful job of sort of pulling it together and being clear about who we are, what matters to us, and where we're going. And we've also had some discussions that have been less than calm. There's been a lot of emotion, a lot of real deepfelt ideas about where we have to go and what we have to do next. And because of your calm presence there, it's always helped like we're still in control, things are not falling apart. We're having an appropriate discussion. We're coming back to a good place. And the compassion I think we've all heard and seen every time, and one of the things I've noticed is that I don't think there's ever been someone who has come to the podium to give a public comment that you haven't met with them afterward and talk to them, and it's so obvious that it's general caring. It really is

a wonderful example for all of us. So, thank you, Joe, for all that you've done for us.

MS. ALAINA HARRIS: Dr. Shone.

DR. SCOTT SHONE: So, Dr. Bocchini, I echo what Cindy and Jeff just said in terms of your -- your patience and your calm leadership. Throughout my time working with you both on the committee and prior, I always felt that you valued my opinion, my perspective, and what little experience I did bring to this topic, especially when we didn't agree on a topic, and I appreciate you always calling on me, even when I know you hoped my mic didn't work. And in response, I think you routinely challenged me with some controversial and difficult topics at times. But I appreciate you helping me reflect on newborn screening, the system, my own personal views, and how they -- how they overlap. I also appreciate in return us continuing talking newborn screening as a system as opposed to a test. And I'll just end by saying being on this committee was a career bucket list item for me. I was able to achieve it

a little earlier than I ever anticipated, and I appreciate you helping to facilitate that. And it's really been an honor to serve on this committee under your leadership. So, thank you very much.

MS. ALAINA HARRIS: Dr. Beth Tarini.

DR. BETH TARINI: So, I'm going to echo much of what was said. Dr. Bocchini, I can remember sitting for many years in the Chairs of the organizational representatives and, you know, having the opportunity to feel that the Chair of the committee who is focused admittedly so on the committee also cared about what the org reps thought and also allowed the org reps their opportunity to offer their perspective. That meant a lot to me. That's not how committees that can go hierarchically, if you will, often function. But I think that was emblematic of your leadership. So, I appreciate that. And I also appreciate the same care extending outside of the confines of the conference room when you would come up and see how I was doing and ask me about

what had transpired in my life in the interim. So, in my time as an org rep to a committee member, I felt that same level of respect and grace, and so I thank you for that, because I think that speaks a lot about your character.

MS. ALAINA HARRIS: And now, we're going to hear from Sue Berry. Is she here?

DR. SUSAN BERRY: Wow, that's a lot to follow, people. And I ended up writing some things down because I -- it's easy to get off task. But I -- I really just want to say thank you. Thank you for kind and respectful management of our discussions and for always listening, making sure everyone can be heard, for making the formality of these meetings almost seem normal, which is a difficult task indeed, and for always being compassionate and an attentive respondent to the families and others seeking the attention of the committee. That has been so key to the example that you -- you make for all of us. It's not always easy to herd this particular group of cats, but you keep us mindful of the goals, which

are the children and the families, and the persons affected with these conditions, and for that, we should all be grateful. And I just appreciate all you've contributed to the advancement of care for this people. So, thank you.

MS. ALAINA HARRIS: Next up, we're going to hear from Scott Grosse.

DR. SCOTT GROSSE: So, I came up with one word to describe you, avuncular. What does avuncular mean? Like an ideal uncle. Dictionary definition, someone who is affable and kind and supportive of those who are younger or less experienced, and you have manifested that to me personally and to many, many others. Thank you.

MS. ALAINA HARRIS: Next up is Natasha Bonhomme.

MS. NATASHA BONHOMME: A part of me just wants to say ditto to everything that's been said, but I won't be -- I won't be that short. I really just want to say thank you so much for really everything that you've done. You really have brought a type of leadership that comes from

kindness and empathy to this committee, which I really appreciate, and you know, you don't only say that families are important, but your actions, your being when families are speaking really show that, the way that you've followed up with families both after they've spoken here as well as families or advocates I've sent your way to say can you explain a little bit more about the committee and really have a conversation with them, all the way to just a couple of weeks ago giving up your Saturday to come and speak to a group of advocates. It's -- it's been impressive and inspiring to me, and so just thank you for that, and kind of on behalf of the different groups that we represent that attention and that respect hasn't gone unnoticed. So, thank you.

MS. ALAINA HARRIS: Next up, we're going to hear from Andrea Matthews, who was a member of our committee back in the day. She is not able to be here, so she has sent us a video, and if I can figure out how to get out of here. Yes, it was.

MS. ANDREA MATTHEWS: Hi, Dr. Bocchini. I just wanted to take a moment to say thank you for all the work that you've done on the committee and the great work leading us all to take care of the nation's babies. I want to personally thank you for making me feel welcome and always making me feel a part of the conversation. All that you do, you so fiercely led this committee and kept that babies and the families at the forefront. So, thank you so, so very much. I wish you all the best.

MS. ALAINA HARRIS: That's cute. All right. While I'm getting the slide set back up again, we are going to hear from the ACHDNC Chair Emeritus -- is that the right way to spell that -- say that? Dr. Rodney Howell.

[Speaking off mic.]

DR. RODNEY HOWELL: I was told to write something, which I did. I'd like to make some comments about my dear friend, Joe Bocchini, but I'm also commenting a little bit about the committee since it seems an opportune time to say

a few words. I'm very pleased to be here today to recognize Dr. Joe Bocchini for his outstanding work as Chair of the Advisory Committee on Heritable Disorders of Newborns and Children on this occasion of your last day as Chair. It was my great pleasure to serve as the Founding Chair of this committee during its first eight years, and I am very much aware of the enormous amount of time and effort that Dr. Bocchini has devoted to this important work. He has exemplary diplomacy, which is essential to this position, as he and the committee have found now, and his leadership and judgment have been responsible to the advancement of this committee. His leadership has provided the committee to add many additional important conditions to the Recommended Newborn Screening Panel.

It is also important -- very important for me at this time to emphasize the extraordinary value of the work of this committee and its distinguished leader in assessing the current state of our life-saving and life-changing

Recommended Uniform Panel. This could not have been possible without the very hard work, effort, and talent of all the staff at HRSA. It is clear that lives every day are saved as a direct result of the work of this committee.

As I travel around the world as President of the International Society of Neonatal Screening and work in many different countries on their newborn screening efforts, this program established by the United States is recognized as the standard for all the rest of the world. The -- we must also recognize the foresight and support of the United States Congress and our Presidents for developing and funding the Newborn Screening Saves Lives Act, and I think we're obviously thinking about that at the current time.

I wish to extend my very best wishes to the incoming Chair of this committee, and I'm sure that she will continue to provide outstanding leadership. We find ourselves at a time when there are many new life-saving drugs and programs which will provide the possibility of saving even

more babies when coupled with effective newborn screening. At such a time, we must discover and employ new patterns to carry out excellent evidence reviews, conduct pilot studies of panels of conditions instead of single conditions in order to increase the number of conditions for which newborn screening is extended to the lives of even more babies. I comment Dr. Bocchini for his outstanding leadership of this committee and feel assured that the vital committee will continue in its excellent work. Thank you very much.

MS. ALAINA HARRIS: Thank you so much, Dr. Howell. Next up, I'm going to call on a couple of people. If you just want to go ahead and come up to the microphone now. Marci Sontag, Alex Kemper, Michelle Puryear, Jelili Ojodu, and Nancy Green. Come up here.

[Speaking off mic.]

All right. So, we're going to hear from Dr. Sontag.

DR. MARCI SONTAG: Dr. Bocchini, I'm

going to be short and sweet. It seems hard to believe that you've been the leader of this helm for eight years. You have guided us and this committee and really the whole community through some tough discussions and some controversial decisions, and you have done so with professionalism and humor and grace, and I thank you for that. I think we've all learned so much from the grace that you've shown to this committee and this community. So, thank you very much for your leadership, and you will be very much missed.

DR. ALEX KEMPER: So, Dr. Bocchini, it's great to be able to come up here and make my remarks. So, let me begin by saying that many but not all of you may not know that in addition to the work that he's done on the Advisory Committee, Dr. Bocchini is one of the longest-serving Pediatric Department Chairs and he's also an Infectious Disease expert, and as I mentioned earlier too, he previously served on the Advisory Committee on Immunization Practices. So, with your infectious disease background in mind, I

appreciate the opportunity to inject my comments about you, and it only gets worse. So, I think we can -- I'll agree that your time spent leading the Advisory Committee has been spore-tacular, that you've maintained the culture -- culture, see -- of respect for individuals and for the importance of evidence while also serving as a booster for public health through evidence-based recommendations. It's great to work with you because you make the importance of newborn screening contagious. I know that others in this room, including those who staph -- I'll say that again -- the Advisory committee feel the same way. I don't need to cell anyone in the room about your importance to newborn screening, but I'd like to add on personal note that you're really a fun guy. It's not -- I can keep going, right -- so, it's not a strain to put together these comments to thank you for your time and I'm sad that your time as Chair has come to the end. The time just flu by. And although we're excited to work with Dr. Powell when she becomes the next Chair, the fact

that you're agreed to offer to stay on to help us really augers for the future -- that's -- I thought that was pretty good. So, it's really -- it's hard for me to capture respect for you in these measly words, so I just want to say a deepfelt thank you.

Dr. Michele Puryear: Hi. So, before I came here, Joe knows this, I was part of the National Vaccine Program. And I'm not sure why Marina Weiss put an infectious disease representative in the Newborn Screening Saves Lives Act of 2008, but she did, and I thought of Joe. I -- I don't know if you know this, but I had received a grant from CDC to write about or educate physicians on risk communication about vaccines, and I -- somebody introduced me to Terry Davis, who worked with Joe, who was a health educator, and she said, "Screw physicians. What you need to do is educate parents." And she was a health literacy expert, and that was -- that began my relationship with Joe. So, when I saw infectious disease representative, I knew who to

nominate for this committee because he came with a view about family centeredness, understood the importance of families, of course, and understood the importance of education. And so, I'm going to miss you. Anyway, good luck. Hugs to Terry.

DR. NANCY GREEN: Well, Dr. Bocchini, actually I had -- I was wondering if I could make a comment about the discussion about harms. But, since I have the opportunity, I promise I won't do that. I just -- you got me, yeah. It's hard to do. Anyway, I wanted to thank you. You know, it never fails to strike me how much the workings, the personality of a committee really does come under the influence of the Chair, and we've had two very different styles, having been on this committee or associated with the committee for a long time, and your style has just been marvelous, and really -- as has Dr. Howell's -- and, you know, it's been very thoughtful and I think if I reflect on the -- the theme of the committee over your tenure, I would say it's thoughtful, which is, you know, really quite a remarkable aspect of

this committee and how it's gone and where it's going. So, thank you very much, and we'll talk about harms another time.

MR. JELILI OJODU: Dr. Bocchini, thank you so much for your leadership over the years. We, as a community, certainly appreciate everything that you've done. A number of things come to mind when thinking about your leadership, how you are able to show empathy as a number of folks have echoed, and I don't want to echo a number of things that have been echoed already, but it's remarkable. No one will accuse you of not giving them an opportunity of not only speaking their minds but being able to share their thoughts as well. So, thank you selfishly for allowing us, the newborn screening community, to be able to have a public health impact as part of everything that is being done here. I know that, as Joan Scott said, that there have been a number of things that we have worked behind the scenes to make sure that a number of voices get heard, and we certainly appreciate it. And then, to Dr.

Powell, congratulations. We look forward to working with you, and thank you for many years of service, Dr. Bocchini.

MS. JANA MONACO: Thank you. I'm glad I got a moment to just say how much I appreciate your leadership with this committee on behalf of all families and parents who need a voice and who can't be here, and I know they would if they could. But as you know when you're dealing with rare diseases, especially these kinds, sometimes, like me, just to drive up the beltway can be a little bit of a challenge. But through it all, I think you came into your position right when things were really tumultuous at our home with Stephen and having a lot of his surgeries at the time, but through it all, you have been such a profound voice. You continued what Rod did, and you definitely made families' voices very important, and you listened. And I'm such a proponent of families and patient- and family-centered care, and you exhibited that here, and I always appreciate that. I hope that my

children will always be a reminder for there can never be complacency, because one of my fears as I've watched as a parent over the years and seeing the changes in newborn screening, the expansion, and all the babies that are caught and thriving and living life, sometimes I fear that the Stephens of the world are going to be forgotten or the capacity of these conditions and what they can do might be forgotten. So, thank you for letting them be a reminder of where we never want to go and where we want to look forward to and for the rest of those conditions that are just waiting. Thank you for tweaking everybody's brains and getting everybody to think and really look within themselves and what's out there and enabling us to take what textbooks say and what families say and trying to bring them together. So, I wish you all the best and I thank you, and I just have the utmost pride and gratitude to this committee and for the families that don't even know it exists but they're benefiting, and that's why we're all here. So, thank you, and good luck, and I look

forward to meeting you, Cynthia. Thanks.

MS. ALAINA HARRIS: Those were really nice, which obviously makes sense. So, I also want to let you know, Dr. Bocchini, that we have made you a scrapbook, and it includes photos from over the years that you've been a member of this committee and Chair of this committee. It also includes previous committee members' notes to you, including Dr. Don Bailey, Dr. Charlie Homer, and Dr. Ed McCabe, who also submitted their thoughts to you -- about your service here. We've also included notes and pictures of people in the audience today. FYI, if you have not had a chance to thank Dr. Bocchini in the scrapbook, we're going to keep it out there with the Polaroid camera and some notes for you to do. So, do that please. But there's a lot in here too.

All right. And then just be -- also, we've got cake. So, maybe I should have started off with that. So, I hope you all stick around to have some cake after this part until the workgroup meetings start at 3:30. And I do just want to

say, Dr. Bocchini, thank you. I have a personal thanks for you. I'm sorry, okay. My personal thanks to you for your compassion with -- with me and other people and also for your service to the families, clinicians, the laboratorians, policy makers, but especially to newborns and children in our country. So, I am just so grateful for having known you since we were children and for being part of your tenure as the ACHDNC Chair. So, thanks. And now I'm turning it back over to you.

DR. JOSEPH BOCCHINI: All right. Well, first of all, I'm overwhelmed, so I just want to thank you all for all your kind words and, I mean, this is really very special to me. I want to tell you that this has been a real honor and a privilege to be a part of this committee, and I am so happy that Rod and Michele are here today, because I wouldn't be here without them. And I will tell you that following the Inaugural Chair of this committee, who did so much to establish the way it worked and to make it so successful was a real -- kind of gave me pause, because the only

thing I could think of was don't mess this up because Dr. Howell had really established the way this committee operated and established with Michele how effective it has been, and so my task was really to build on their success and to kind of grow the committee based on things that were changing in the newborn screening community and so I took on that task knowing that if I messed up at all, Dr. Howell would call me. So, I figured that I'd be okay.

So, I do want to say that I agree the committee has many accomplishments over these past years, but I don't view them as mine. I view them as the committee's accomplishments, and I think if I was able to play a role in making things happen, it was because my goal was to enable everybody to weigh in and use whatever we could put together to make the best decisions about whatever topic we were dealing with, and I think my goal always is to consider what's the right thing to do, and then to find the way to do that. And I think one of the most important things, because as a federal

committee working with states, working with different stakeholders and different groups, it's really important that we work together and that we collaborate and that we try and find ways to understand what the -- what issues each group is facing and find ways to try and overcome them together. So, I think one of the main things that I think is important to me was developing collaborations and building on relationships and working together in such a way that we would accomplish what we -- what we wanted to over time.

I've got to thank a lot of people. I mean, I think Dr. Howell, Dr. Puryear, I mean, both of you were really essential in building this committee, but also giving me this opportunity, and I really thank you both for that, because it think that -- that's been a good part of what I feel has been really fun and -- and really rewarding for me. And there's another term in Louisiana, it's called lagniappe, and so when you -- when something happens and it's good and then you get something extra, that's lagniappe. And

so, these eight years have been lagniappe. So, I really appreciate that.

I think Dr. Howell said it best. There's no better group of people to work with. I think that. So, from the beginning with Dr. Lu, Dr. Warren, and then Joan Scott, Debi Sarkar, Catharine Riley, Alaina Harris -- these are skilled professionals who are passionate and committed to their work, and the reason these committee meetings run so well is because of them, and I think that they've been very effective in -- in building what we need to make this -- this committee work. So, I owe a great deal of thanks to all of you for everything that you have done.

Committee members, I mean, this is a wonderful committee. I think the expertise that's demonstrated across the table here is just incredible. I mean, between public health, laboratorians, clinicians, all the people who are on this committee, the different federal partners, everybody has contributed effectively to decisions that are made by this committee. And, Annamarie,

you're one of the long list of families -- representing families who have really given -- and Jana is another one who have given great depth to this committee and an understanding of the real focus of what we're going, which is the newborn infant. And so, I think that's been really a very special part of this committee. So, it's really the work that you've done that has made this committee so successful, and so I need to thank you all for doing that. You have provided support. You've provided guidance. You've provided advise, and most importantly, your expertise to help make decisions work.

I also think that the organizations representatives have played an incredible role in the effectiveness of this committee because you each have brought a perspective that has been important. In many cases, it's included the public, like with Natasha over the years, and the different organizations that are relevant to have relevant interest in newborn screening, and I think that's really helped the committee. Many of

you have participated in discussions that the committee has had and have helped frame some kinds of things that the committee has done. You've worked on the workgroups, and so, I think that's all been very beneficial to us, and I think it's a good model for how a FACA committee should operate and how it can be effective in reaching its goal.

And it's really interesting that we've certainly seen a tremendous change over the last eight years on how based on in part the work of the committee and understanding of things, as things have changed, that there are more resources being put into understanding how to bring a condition up for newborn screening, how to provide research opportunities, pilot study opportunities, and other things that have all been part of what this committee has considered important and necessary to bring a condition forward. And so, that's been a really nice transition to see. So, I think that's been really another good part of -- of the -- of the committee.

Cindy, I think you're a great choice

to continue this committee. I think you have all of the skills needed to continue this in a Dr. Howell tradition, and so I'll look forward to helping you in any way I can, but I think that you will put your stamp on this committee and move it forward in a very nice way. So, I think the future is really strong for this committee and this -- and in meeting the mission that it has.

And lastly, I've used this quote in multiple talks that I've given about newborn screening because I think Dr. Howell wrote this in an article that -- that he published a number of years ago, and I think this is a key thing is that we need collaborative efforts between parent advocates, advocacy groups, professional organizations, investigators, Federal Advisory Committees, and state public health programs. These are needed to successfully improve the health of newborns and children to newborn screening. And that's what we're all about. And so, Rod, this is still as true today as when you wrote it.

Again, I want to thank you all very much. I'm overwhelmed. Thank you.

[Applause.]

DR. CATHARINE RILEY: Okay. Good afternoon. This is Catharine Riley. So, thank you all for participating in the festivities. And like Alaina mentioned, there is cake, so please stick around for a bit and partake in that. I'll be putting a slide up here in a minute that lists the workgroup -- where the workgroups are meeting. For those of you that don't have that information yet, we'll get a slide up that has the room numbers if you'd like to join one of those meetings. I would also like the committee members and org reps to stick around just for a few minutes. We're going to try to get a couple of group photos if we can before we disperse to the workgroup meetings this afternoon. And then, of course, we'll be back for day 2 tomorrow, so we look forward to seeing everyone again. Thank you.

[Whereupon the meeting was concluded.]