Health Resources and Services Administration

Advisory Committee on Heritable Disorders in Newborns and Children

Webinar 10:00 a.m. to 2:09 p.m.

Friday, March 22, 2019

Present

ADVISORY COMMITTEE MEMBERS

Joseph Bocchini, Jr., M.D. (Chair and Moderator) Professor and Dr., Department of Pediatrics, Louisiana State University

Mei Baker, M.D. Professor of Pediatrics, University of Wisconsin School of Medicine and Public Health, Co-Director, Newborn Screening Laboratory, Wisconsin State Laboratory of Hygiene

Susan Berry, M.D. Professor and Director, Division of Genetics and Metabolism, Department of Pediatrics and Genetics, Cell Biology & Development, 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

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Cynthia 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, Newborn Foundation

Scott M. Shone, Ph.D., Senior Research Public Health Analyst, Center for Newborn Screening, Ethics, and Disability Studies, RTI International

Beth Tarini, M.D., M.S., FAAP, Associate Director, Center for Translational Science, Children’s National Health System

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Agency for Healthcare Research & Quality

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Health and Quality Improvement

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Carla Cuthbert, Ph.D., Chief, Newborn Screening and Molecular Biology Branch, Division of Laboratory Sciences, National Center for Environmental Health

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Robert Ostrander, M.D., Valley View Family Practice

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C O N T E N T S

P R O C E E D I N G S

Dr. BOCCHINI: Thank you. Good morning everyone, and welcome to the first meeting of the Advisory Committee on Heritable Disorders in Newborns and Children for 2019, so welcome. We will begin this meeting with a roll call of the members and of the organization representatives.

So, first agency for Healthcare Research and Quality Kamila Mistry. Mei Baker?

DR. BAKER: Here.

DR. BOCCHINI: Susan Berry?

DR. BERRY: Here.

DR. BOCCHINI: Jeff Brosco is seeing patients and he will join us in a little while. Carla Cuthbert?... Kellie Kelm?

DR. KELM: Here.

DR. BOCCHINI: Michael Warren?

DR. WARREN: Here.

DR. CUTHBERT: Carla Cuthbert is here, Dr. Bocchini.

DR. BOCCHINI: Thank you, Carla.

Cindy Powell?... Melissa Parisi?

DR. PARISI: I'm here.

DR. BOCCHINI: Annamarie Saarinen?. Scott Shone?

DR. SHONE: Here.

DR. BOCCHINI: Beth Tarini?

DR. TARINI: Here.

DR. BOCCHINI: And Catharine Riley?

DR. RILEY: Here.

DR. BOCCHINI: Now for our organizational representatives, American Academy of Family Physicians Robert Ostrander will join us later. American Academy of Pediatrics Debra Freedenberg?

DR. FREEDENBERG: I'm here.

DR. BOCCHINI: American College of Medical Genetics Michael Watson?

DR. WATSON: Here.

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

DR. MILLER: Here.

DR. BOCCHINI: Association of Public

Health Laboratories Susan Tanksley?

DR. TANKSLEY: I'm here.

DR. BOCCHINI: Association of State and Territorial Health Officials, Chris Kus?... Genetic Alliance Natasha Bonhomme?

MS. BONHOMME: I'm here.

DR. BOCCHINI: March of Dimes, Rebecca Abbott?

MS. ABBOTT: I'm here.

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

MS. WALSH VOCKLEY: I'm here.

DR. BOCCHINI: And Society for Inherited Metabolic Disorders, Shawn McCandless?...

All right. Well, thank you.

Next on the agenda is the November minutes. Okay. So committee members received a draft of the minutes of the November meeting to review prior to this meeting, the incorporated revisions submitted by committee members and distributed a final draft of the minutes to the

committee prior to the meeting. Are there any further additions of corrections to the minutes?

Hearing none, we will need a vote for acceptance of the minutes. So once again, Kamila Mistry?... Mei Baker?

DR. BAKER: Approve.

DR. BOCCHINI: Susan Berry?

DR. BERRY: Agreed.

DR. BOCCHINI: Carla Cuthbert? Carla, are you on mute?

FEMALE VOICE: She was disconnected, I think.

DR. BOCCHINI: Oh, she was disconnected. Okay. Kellie Kelm?

DR. KELM: Approve.

DR. BOCCHINI: I'm sorry, was that Kellie? Okay. Thank you.

Kamila Mistry? Melissa Parisi?

Dr. PARISI: Approved.

DR. BOCCHINI: Cindy Powell?... Annamarie Saarinen?... Michael Warren?...

DR. WARREN: I approve.

DR. BOCCHINI: Scott Shone?

DR. SHONE: Approve.

DR. BOCCHINI: Beth Tarini?

DR. TARINI: Approve.

DR. BOCCHINI: All right. Thank you. The minutes are approved. Okay. All right.

Next on the agenda is the new workgroup members. As you know, we asked for submissions for individuals who were interested in serving on workgroups. And so, first I want to thank everyone who submitted applications to serve on workgroups. We received many excellent applications, and I selected twelve new workgroup members. And on the next slides, you will see the individuals who were selected. We encourage those who are not selected this year to please apply again next year at the next opportunity.

So, the following individuals were selected to serve on our workgroups. For the Education and Training workgroup, Sylvia Mann, Maa-Ohui Quarmyne, Samantha Vergano. So, we welcome the three of you to the Education and

Training workgroup.

Next is the Followup and Treatment workgroup. Tracy Bishop, Luca Brunelli, J. Lawrence Merritt and Elna Saah and Marci Sontag were named to the Follow-up and Treatment workgroup. Okay. Now we've got the five lined up. Okay. There were go. Okay.

And then for Laboratory and Standards workgroup, we have Nathalie Lepage, Miriam Schachter, Stan Berberich, and George Dizikes.

So, I want to welcome all of you to the committee -- to the workgroups, and we look forward to your active participation in the activities of each of those important standing workgroups of our committee.

Next is new organizational representatives. I want to thank everyone who applied to their organization for a position as an organizational representative. We are finalizing those selections and plan to bring on approved new organizations and their representatives by the April meeting.

I have one more change to announce. My term as chair of this Committee ends after the next meeting and I just wanted to express how much it has meant to me to have been given this incredible opportunity to lead this committee and to work with so many extraordinary dedicated individuals. So, we'll talk more about that in April.

So, I'm pleased to announce that, following the April meeting, the new Chair of this Advisory Committee will be Dr. Cindy Powell. Dr. Powell has served with distinction on this Committee since 2017 and is an excellent choice to lead the work of this Committee going forward. Dr. Powell will also have more to share with us at the April meeting.

The next slide shows our future meeting dates. The next committee meeting will be held April 23rd and 24th. It's in person here in Rockville, and then you can see the meeting dates for the rest of meeting through 2019, August and November, and the meeting dates through 2023 can

be found on the committee's website, which is listed on this slide.

So, the next slide shows today's meeting topics. Today, we will hear updates from the Ad-hoc Workgroup on Risk Assessment and Interpretation of Newborn Screening Results, and we'll have an initial presentation on the Expert Advisory Panel Meeting, which was held in February, to review the committee's nomination, evidence review, and decision-making process.

Next slide. We'll also have an initial discussion on the project assessing the impact of adding conditions -- the recently added conditions to the RUSP. We will also have presentation of panel discussion on potential resources for facilitating rare disease research and data collection.

Next slide. Now, I'm going to turn the presentation over to Catharine Riley, who will go over the DFO slides. Catharine.

DR. RILEY: Thank you, Dr. Bocchini. Good morning to everyone who is joining us from

across the country. We know for those on the west coast, it's an early morning for you. So, welcome to everyone. The Advisory Committee's legislative authority is found in the Newborn Screening Saves Lives Reauthorization Act of 2014. This legislation established the committee and provides the duties and scope for the committee. However, all community activities are governed by the Federal Advisory Committee Act or FACA, which sets the standards for the establishment, utilization, and management of all Federal Advisory Committees.

As a committee member on a Federal Advisory Committee, you are subject to the rules and regulations for special government employees. So, I have some standard reminders for the committee that I want to go over.

I wanted to remind the committee members that as a committee, you are advisory to Secretary of Health and Human Services. 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 and I know prior to committing to an interview. I also must remind committee members that you must recuse yourself from participation in all particular matter likely to affect the financial interest 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 of interest, please notify me immediately.

So, according to FACA, all committee meetings are open to the public. If the public wish to participate in the discussion, the procedures for doing so are published in the Federal Register in the announcement at the end -- during the opening of the meeting. For this meeting, there were two requests to make oral comments received, and we did not receive any written statements ahead of time. Also, public

participants should be advised that committee members -- if we do receive written comments -- would be given copies of all written comments ahead of time. Any further public participation will be solely at the discretion of the Chair or myself as the DFO.

Before we proceed, I want to see if we have any questions from committee members. Okay. And then, I wanted to, as a webinar, just do a quick reminder just about the logistics about the webinar. For the members of the public, the audio will be coming through your computer speakers, so please make sure obviously you have your speakers turned on. There is also an option for calling in if you get disconnected so that you can hear the proceedings. For the committee members who are calling in, in your sound will be coming through your phone line. So, please make sure your computer speakers are turned off. This will help lessen the possible feedback.

Also, please speak clearly, and please remember to state your name first to ensure

proper recording for the committee transcripts and minutes. Since we're not in person, I don't have my fun sign that I put up for people. But, if you could remember to please state your name first, that would be very helpful.

For the committee members calling in if you have any issues with the phone line, you can press star zero (*0) and you will get the operator for assistance.

In order to better facilitate the discussion, during the discussion points of the agenda, please use the "raise hand" feature in Adobe Connect when wanting to make comments or ask questions. This is -- you can simply click on the person icon at the top of your screen -- it's in the middle section and choose "raise hand." This will allow us to put you in the cue. I will unselect your name once you are in the cue for making a comment, and Dr. Bocchini will announce the -- who is going to make the next comment or question. If you have any questions, please let us know at this time.

Okay, then I'm going to turn it back over to Dr. Bocchini. Thank you.

DR. BOCCHINI: Thank you, Catharine. So, we're ready for our first presentation for today, and it's on the Ad-hoc Workgroup update with the Assessment and Interpretation of Newborn Screening Results, and our presenter is Dr. Mei Baker. Mei is a committee member and serves as chair of this Ad-hoc Workgroup, which was formed at our last committee meeting to focus on two major charges. This Workgroup brings together expertise from the Laboratory Workgroup, Education Training Workgroup, and organizational representatives. We asked Dr. Baker to provide an update on the Workgroup's initial ideas for addressing the charges of the Committee. And so those charges, just real quick review, were to address opportunities and challenges related to interpretation of newborn screening results, and this would include communicating the strengths and limitations of newborn screening results and educating the different audiences, providers,

parents, and the public about what newborn screening results provide for their patients or their families.

The second charge is to consider options for the committee that could help states with risk assessment policies that would help them utilize more efficiently the resource document that was put together by APHL.

So, Mei, I'm going to turn the presentation over to you. Thank you.

AD-HOC WORKGROUP UPDATE: INTERPRETING NEWBORN SCREENING

DR. BAKER: Thank you, Dr. Bocchini. Good morning, everyone.

Next slide, please. So, here is our workgroup charges. As Dr. Bocchini stated, the people in this group have a variety of expertise. And in this group, we met over the phone on March 16, so I am going to record our discussion to the committee members.

Next one, please. As Dr. Bocchini stated, we have two charges, and the first charge,

we emphasize the newborn screening results interpretation. In that charge, we would emphasize risk assessment, and we also will discuss some terminology utilized in the newborn screening in the hope to clear up some confusion and also, we will try to interpret all types of categories. So, I think, historically, we emphasized screening positive, screening abnormal, but we feel at the time, we also want to address when screening is negative, when screening is normal, what that means. Also, we want to spend some time to really emphasize how we communicate the message, and this work will be based on the education. The subcommittee has already done so much, and we want to be based on that and see if we have any other avenue we can enhance.

For the charge two, the emphasis is recommendation regarding screening cutoff establishment and monitoring. As Dr. Bocchini said, the APHL committee has created very comprehensive documents and we want the working group to review them and look at the opportunity

to make some recommendations to the field. So, we emphasize thinking about the cutoff -- when you think of both sensitivity and specificity. And we also want to promote the idea for ongoing evaluation and make adjustments when necessary.

Next slide, please. So, how do we go about addressing workgroup charges? So, from now on, I will talk about the two charges separately so it will not cause any confusion.

For the charge one, the first we want to generate a report to the committee. Oh, sorry my screen went away. I'm trying to -- give me one second. And also, we hope to put impact when we have the report, we hope to base our report to generate to peer reviewed journal so we can more establish and also subject to the peer review and hope we can even reach more wide audience.

And third, based on the report -- based on the publication, we want to generate what's called a slide deck so we can become more convenient for the clinician to use, and even other tools.

For charge two, and our goal is to draft possible recommendation to the committee for the committee to the final decision how we do the recommendation.

Next slide, please. So, now I am going to present some general principles in terms of the work plan. When I say principles, because we still need to work on the details. And the work plan will have three parts. First is introduction. In the introduction, we want to address the rationale and targeted audience. So, as Dr. Bocchini states, the first target audience is family doctors and pediatricians. But, we know they are the people to communicate the results to the family. So, in the end, we want to be sure the messenger can be well understood and interpreted by the physician and the family receives the results.

And in terms of rationale, I think this group's members are very familiar in terms of newborn screening practice has been a long time and even certain things we do -- the perception of

the public is maybe not always exactly what we intend to do. So, I think it is time we're trying to find the large gap and meet all expectations so the key elements here are, you know, screening versus diagnosis, and also we will attempt to do some terminology harmonization so people will understand better.

The next part is besides the concept, also we want to gather more detail in terms of screening tests versus diagnosis tests, because the purpose of each is very different. So, to achieve this, we will go to the literature and find a reference, and actually we did some preliminary work. There's just not very much over there, and that also enhanced the importance of why we needed to do that. And certain things have been done by other groups. An example is called MOC4 from the Midwest Genetics Network. I think I'm very pleased we have two members of this group -- actually they were very engaged with the activities, and actually I believe they are leaders -- and they are bringing this back to us.

Also, I recently learned CLSI has developed some kind of document. So, we hope they will be in the public domain, and we can, you know, talk about their work.

I do believe APHL is doing similar work. We hope we can keep communicating with everybody.

Another thing we want to address is when it comes to newborn screening our emphasis on population. The decisions we make are based on the population. We need to be mindful and the public needs to know, sometimes individual -- the special circumstance could somewhat deviate from the general population, and we need to understand that.

Next one, please. The Work Plan, Part Two, is to describe a kind of practice where the emphasis is risk assessment. So, we can describe how practice is in the newborn setting, and I think the channel for us to communicate with the public and with the physician is through newborn screening report. So, the group will

describe the current in a given scenario how we report newborn screening. So, here is an example. The group member believes not in just a term, it's what the term entails, what is the action you need to be taking, I think is more important.

So, for the first one, it's really needed further action-taking. This action actually is action for confirmatory tests. People use different terms, screening positive, abnormal screening, out of range.

And another category with further action needed for recommendation is repeated newborn screening. So, people use the term borderline, possible screening positive, positive abnormal.

And the third category is no further action unless clinically indicated. So, this one, we will be very careful how we word them, and not cause anxiety, as sometimes people need to understand that when we say no risk, that doesn't mean zero risk in just about everything in the medical practice.

Another category we would address is -- we are now putting unsatisfactory is a different action. You really not have a decision because of other interference and situations. So, we will discuss this more. And a very interested local group actually talked about when you have two screening protocols in some state, and when you have the first one, you may not see it on the second one, so we kind of talk about how the terminology is used. And, for now, we put it as pending.

Next one, please. So, work plan, part three is Discussion and Recommendations. So, the goal is trying to make newborn screening assessment more transparent. We will utilize the language. For example, you can say, well, when this is the level potentially for certain disease, then we maybe just directly use risk. So, I think of this as a more real-time reminder, as a physician, when I read the report, and it also gives them a tool. So, then, they have this wording, then they interpret it to the family.

So, that's the kind of status we want to discuss more. And, as I stated earlier, so we will put some language -- recommend some language for normal newborn screening results.

At the end, we'll discuss about terminology, and we'll attempt to harmonize that. But, this is not small task. We recognize that. So, we can see how far we go on that.

And, the third one is the strategy for communication. As we said before, we can hope we can review what has already done and see if have more tools to provide to the physician when they're communicating the newborn screening to the family.

Next one, please. So, here is our timeline. As I stated before, so far, we have done quite a bit, even more emphasis on charge one. So, today, we will have discussion, and we are looking forward to the feedback from committee members, and we hope that at the next meeting in April, we will have outlines for the report and also start discussing some dissemination plan and

seeking feedback from the committee, and that by August, we hope that we have a draft of the report and that we'll have a more refined dissemination plan.

When we talk about this, something in our mind already is such as a professional conference so we can do something with the patient and also through our organization about how we may help to get our report and all white papers to be on the website, so to kind of have it accessible to their members, and that’s the kind of thing we are talking about. And then, we also want to start to draft recommendations for charge two.

So, by November, you can tell that's our plan, to have a final report and do some dissemination activities, and we hope by that time we're ready to prepare the manuscript.

And, for charge two, we want to have a draft of the recommendations and be seeking feedback from the committee. And next year, February, we hope we can finalize the recommendations and also have further reporting on

the dissemination activities, and by that time, can submit the manuscript.

So, I will end here, and thank you, everybody.

DR. BOCCHINI: Mei, thank you for a very nice update, and it's clear your workgroup has gotten a really good start.

So, let's -- we have about ten minutes for questions and comments for Mei. So, operator, if you'll please open the lines for committee members and organizational representatives. We're going to give committee members the opportunity to raise questions or give comments first, followed by organizational representatives.

As a reminder, please use the "raise hand" feature in Adobe Connect when wanting to make comments or asking questions. And, when speaking, please say your name each time to ensure proper recording of the -- of the conference. So, let's open this for questions and comments.

DR. RILEY: Dr. Bocchini, this is

Catharine, I'm not seeing any hands raised on the webinar at this time. Over the phone, if any of the committee members or reps have a question or comment, could you go ahead, since we can't see a hand raise?

DR. BOCCHINI: Okay. Your lines are open.

DR. RILEY: Oh, yeah. Chris Kus and Sue Berry.

DR. BOCCHINI: Okay. First, Sue Berry, and then Chris Kus. Sue?

DR. BERRY: Can you hear me?

DR. BOCCHINI: Yes. I can hear you now.

DR. BERRY: Okay. Thank you. I just had muted my phone because I didn't know where you were. So, I am happy because Mei mentioned our MOC4 project. If anybody has questions about that, I'd be happy to respond to them. But, I'm excited that we're moving forward with this. It's more comment than a question. Thanks.

DR. BOCCHINI: Thank you. Chris Kus?

DR. KUS: Yeah. My comment was that joined late and I'm here. Thanks.

DR. BOCCHINI: Okay. Thank you.

DR. FREEDENBERG: And this is Debbie Freedenberg, and I just have a question. A lot of the activities that are part of this workgroup are also being addressed by nurse organizations that have an interest in newborn screening, and is there any plan for harmonization or any plan to include those activities?

DR. BOCCHINI: Mei, do you want to take that?

DR. BAKER: Yeah. Well, I'm trying to understand the question a little bit better. If I'm understanding correctly, Debbie, you were asking because this kind of activity is also of interest to other organizations? So, how are we in cooperation with them? Could you repeat your question?

DR. FREEDENBERG: Well, that's pretty much it.

DR. BAKER: Oh, okay. Yeah, and as

of this stage as a member on the group, we haven't gotten that far yet, because we will discuss the dissemination plan, and now to me in my head right now, it's kind of a one-way street, because when I said that it means we have this and we want them to help us disseminate to the members, but I think you bring a very good point. Maybe we want their feedback too. So, let's talk a little bit more.

DR. FREEDENBERG: Okay, great.

Dr. RILEY: Dr. Bocchini, I'm not seeing any other hands raised via the webinar.

DR. BOCCHINI: Okay. We're going to give one last chance for additional questions or comments. All right. Seeing none, Mei, thank you, and thank the members of your workgroup. We look forward to the -- the timeline that you have put together and bringing the deliverables to -- to the committee for final decision. So, thank you very much for all that you're doing in this -- on this topic.

DR. BAKER: Thank you.

DR. BOCCHINI: So, next item on the

agenda is public comments. We have two requests for public comments that came in before the deadline for signing up for public comments, which was March 18th. So, we have two individuals who are going to make comments. The first public comment will be from Anne Kennedy, Senior Vice President for Parent Project Muscular Dystrophy. Operator, would you open Ms. Kenney's line?

MS. KENNEDY: Good morning.

DR. BOCCHINI: Ms. Kennedy, can you hear us?

MS. KENNEDY: Good morning. Can you hear me?

DR. BOCCHINI: Yes, go right ahead. Thank you.

MS. KENNEDY: Good morning. On behalf of Parent Project Muscular Dystrophy, I'd like to say thank you to the committee for providing me with the opportunity to address you this morning.

Over the last four years, PPMD has been leading a national effort to build a newborn

screening infrastructure for Duchenne in the US aimed at developed the evidence to support Duchenne newborn screening, building on the work led by Dr. Jerry Mendell in Ohio State in the Newborn Screening Pilot, which concluded in 2012. PPMD endeavored to learn from the best practices of that pilot and refine the systems further such that they could be replicated in a state with a high birth rate and eventually nationwide.

In Dr. Mendell's study, nearly 60,000 babies were screened throughout the state, and six children with Duchenne were positively identified, establishing evidence for a two-tier screen at birth for Duchenne within the U.S. Newborn Screening System.

Our Duchenne effort has convened experts and established the partnerships required to research, pilot, and implement nationwide newborn screening for Duchenne. PPMD's Duchenne newborn screening efforts have included the expertise and input of experts and leaders within NIH, HRSA, FDA, CDC, the American College of

Medical Genetics and Genomics, the broader newborn screening community, and the Duchenne community. Our efforts have also included an extensive collaboration with the world's leading scientific and technology developers to identify and refine the screening tests used in Duchenne newborn screening.

Based on the experience of the newborn screening programs throughout the world, our efforts have included a study to determine which approach to screening has appropriate analytical and clinical validity and utility for use by public health laboratories. These efforts were conducted in collaboration with the California Department of Health, PerkinElmer, UC Davis, UCLA, Stanford, and UC San Francisco. We are delighted that the yield from these efforts will now be applied to a pilot in a high birth rate state. We've also collaborated with the CDC and the American Academy of Pediatrics to develop diagnostic tools and resources for primary care providers and families.

As such, today, I am very proud to share that we have initiated a newborn screening pilot in New York State. The Duchenne newborn screening pilot program is designed to set up, validate, and conduct a consented pilot screen for infants born at select hospitals in New York State and to utilize tools, resources, and expertise at PPMD and the Newborn Screening Translational Network under the leadership of Dr. Mike Watson, Dr. Amy Brower, and Dr. Michelle Puryear and the New York State Department of Health under the leadership of Dr. Michelle Caggana and Dr. Tavacoli [phonetic.]

Our pilot is being funded through a unique model, in which PPMD has convened a pre-competitive consortium of biopharmaceutical industry partners with a commitment to early diagnosis and intervention in Duchenne. Consortia members include Sarepta Therapeutics, PTC Therapeutics, PerkinElmer, Solid Biosciences, Wave Life Sciences, and Pfizer. In addition, the pilot is being guided by a steering committee comprised

of representatives from federal agencies, provider groups, and representatives from key Duchenne stakeholder communities.

To prepare for this moment, PPMD is working -- has been working for nearly two decades on efforts aimed at readying the landscape for newborn screening efforts in Duchenne. These efforts have included leadership in the Newborn Screening Saves Lives Act, annual Duchenne-specific language within appropriations and report language to ensure that our federal partners are focused on Duchenne efforts, and leading the National Newborn Screening Initiative, which has included the development of published care standards for newborns, publications, and ethical considerations for Duchenne newborn screening, and the publication of A Roadmap to Newborn Screening for Duchenne.

Today, we're exceptionally grateful to the families, experts, and partners who have helped us to get this far and who have agreed to lean in even further as we move the resources

we've developed into this New York State pilot. With two recently approved therapies and a research pipeline filled with potential therapeutic interventions, newborn screening will provide optimal opportunities for care and treatment in Duchenne. The initiation of our Duchenne newborn screening pilot in New York State is an exciting and critical next step in improving outcomes for children with Duchenne. Thank you.

DR. BOCCHINI: Thank you for your presentation and all the work that you have done to bring this to this point, and we look forward to the additional data that will come from your new project. So, thank you.

Next, the second public comment will be from Brittany Hernandez, who is Director of Advocacy for the Muscular Dystrophy Association. Operator, would you open Ms. Hernandez's line, please.

MS. HERNANDEZ: Good morning, Dr. Bocchini. Can you hear me?

DR. BOCCHINI: Yes, I can. Please,

go right ahead.

MS. HERNANDEZ: Thank you very much. I'm obviously very happy to follow up on Anne's public comment. Thanks for the opportunity to provide comment today. My name is Brittany Hernandez. I serve as the Director of Advocacy for the Muscular Dystrophy Association.

As an umbrella organization representing more than 40 different neuromuscular disorders including two diseases that are currently on the RUSP, SMA and Pompe, MDA is committed to promoting early screening and diagnosis and is eagerly engaged in helping promote additional neuromuscular disorders to be added to the RUSP, including Duchenne.

We have been proud to work collaboratively with the clinician research and advocacy communities on screening efforts around Pompe and SMA, and we're pleased to see their addition to the RUSP in recent years. We hope that the community -- we hope that the community will continue its collaborative approach as we

collectively endeavor to add Duchenne to the RUSP as well.

MDA supports a robust network of more than 150 care centers nationwide that provide clinical care and access to support and services to families living with neuromuscular disease including Duchenne. It's this care center network that will play an important role in the Duchenne newborn screening continuum and is able and ready to provide the followup care and long-term support for the babies and families identified through the newborn screening process.

The care center network, which is led by some of the most respected thought leaders in neuromuscular disease, also serve for many of the clinical trials where potential therapies are investigated for Duchenne and other disorders. MDA also has the unique ability to gather comprehensive longitudinal clinical insight around the newborn screening population through the neuromuscular observational research hub called MOVR. The MOVR data hub gathers information on

multiple disorders, including Duchenne, in order to optimize clinical care and drug development, with specific emphasis on benchmarking the quality of care, safety and effectiveness of new treatment, natural history of disease, and correlation between genotype and phenotype.

Through these various efforts, MDA supports thousands of other individuals living with Duchenne every year. I encourage the committee to consider the strong followup and long-term care infrastructure that's in place to support the community when you consider our future RUSP nomination of Duchenne.

As MDA and other stake holders including TPND have shared with the committee, time is of the essence in implementing newborn screening for neuromuscular disease where early identification and treatment are really important. Together, our collective community of advocacy organizations, clinicians, researchers and newborn screening experts are working to ensure that these disorders are included into the newborn screening

public health program. We look forward to facilitating the addition of more neuromuscular diseases, including Duchenne, to the RUSP, as they are ready to meet the rigorous evidence-reviewed standards set out by this body. Thank you.

DR. BOCCHINI: Thank you, Ms. Hernandez. We are really thankful for the work that you've done, your advocacy, and again, we look forward to additional information as it becomes available in moving with this project. Thank you.

Next on the agenda is a discussion on the Evidence Review Process and Condition Nomination Project we started.

As I mentioned in November, we are conducting a formal review of the entire process from condition nomination to evidence review and the use of our decision matrix, while we're considering the development of the process also to reassess conditions which are on the RUSP, as well as a process and criteria for possible removal of conditions from the RUSP. Our aim is to determine

whether revisions need to be made to reflect the most up-to-date approaches for using evidence to successfully develop public health policies in particular for rare conditions.

We formed a steering committee of committee members and experts from the field to provide us with guidance for this process. We began with a two-day expert Advisory Panel meeting, which was held on February 5th and 6th. Dr. Alex Kemper, who leads the evidence-based reviews is helping to lead this effort. He co-chaired the Expert Advisory Panel meeting, and today he will present a summary of the meeting for us. I ask that the Committee members be thinking about these processes between now and April, and at the April meeting, a draft work plan will be presented for consideration by the Committee.

So, I would like to turn this over to Dr. Kemper, who will provide us with this overarching summary. So, Alex, are you online?

DR. KEMPER: I am and thank you for that introduction. I hope that you can hear me.

DR. BOCCHINI: We can. So, go right ahead.

DR. KEMPER: Fantastic. So, it was really an honor to be able to have this meeting last month, and as we are going to talk about, there were a lot of great suggestions about how to continually strengthen the evidence review process and make sure that it fits into the broader activities of the Advisory Committee.

So, my goal in this presentation is to really provide a 30,000-foot overview of the kinds of issues that were brought up in this meeting, and then in April -- in the April meeting and the subsequent couple of in-person meetings, there's going to be an opportunity for us to really dig in to the recommendations and to revise and continually strengthen the processes that we use to ultimately wind up with a recommendation for the Secretary around conditions considered for newborn screening. So, it was really -- one of the key messages that I want to deliver is that it was a great meeting with lots of fabulous

suggestions.

Next slide. Oh, actually now I have a little arrow.

DR. RILEY: I was going to say, Dr. Kemper, we did turn the slides over to you if you -- but, we're happy to advance, or you can advance as well.

DR. KEMPER: I just realized that. So, I can take over from here.

DR. RILEY: Okay, great. Thank you.

DR. KEMPER: The goals of this project, as I've listed here, was to gather information to learn how to improve the process related to each step that ultimately leads to recommendations. So, the nomination process, the evidence-review process, the decision-making process, and the new aspect that we've added in, as Dr. Bocchini mentioned, was reviewing those conditions that are currently on the RUSP. Okay.

So, I just want to give everyone a sense of the -- the timeline for this project that will ultimately lead to a final report in March of

2020. The real take-home message from this slide is that's there's going to be lots of opportunity for us in the in-person meetings to dig into things. Again, I would be remiss if I didn't thank the Expert Advisory Panel that helped put this together and that ultimately participated in the meeting, and I'm going to go over who that panel of experts included. It did include representatives from HRSA as well as other federal agencies within HHS, the Advisory Committee, our evidence-review group, state screening programs, and then a wide variety of other individuals that are involved with the broad range of newborn screening from the laboratory side of things to diagnosis and treatment, and also included experts in developing evidence-based recommendations. And here's a list of the leading participants, and I'm just going to leave this up here for a second so you could look at it. And I have to say, it was a really, really engaging meeting and included experts in newborn screening not only in the United States but from our neighbor to the north

in Canada. So, there were lots of lessons that we were able to get from the whole thing.

This slide presents topics that we discussed at the meeting beginning with an introduction to the committee process. We had a rich conversation around GRADE, which stands for the Grading of Recommendations Assessment, Development, and Evaluation. Dr. Holger Schünemann, who leads GRADE currently, was able to make a presentation, not only about how GRADE works, but how it could apply to rare diseases, which, as you all know, is a challenging issue. We talked about how to assess published and unpublished evidence, strategies related to the public health system impact assessment, determining -- it should actually say there values not just value from different perspectives. Again, I'm going to dig into that in a second. We discussed the decision matrix, how to reconsider conditions that are already on the RUSP, and ultimately areas that need further research and development.

I'm now just going to talk about some of the key suggestions that came from this meeting, and I'll talk about how I plan to bring these up at subsequent meetings.

So, in terms of the nomination process, there were recommendations around how to strengthen the nomination process before the evidence process begins. As I think most people know, there was this nine-month window to complete the process for the Advisory Committee, and there was a discussion around how to make it so that the nomination process could help better inform the work of the evidence review, but also at the same time making sure that things were transparent and that the nomination process itself didn't overly color what might happen with the evidence review process.

There was discussion around making sure that the nomination process clarified the primary and secondary targets of screening as well as the incidental finding, again, to make that more clear by the time the evidence review process

began.

And there was also discussion about the value of doing a scoping review, so not a systematic evidence review, but an assessment of what literature is out there before beginning the full evidence review process. Of course, that could be helpful in terms of figuring out what evidence is available and where the gaps might be, but work would need to be done in the future to figure out how that process would work.

Moving onto the evidence review, and it just suddenly occurred to me that with March madness going on, that it will be kind of fun to talk about net benefit here. But, in terms of the evidence review, again, there was discussion about making sure that critical outcomes are identified as soon as the process begins. Based on the GRADE, there was the recommendation that we even go so far as to predefine the list of core outcomes that we would investigate for all conditions as well as additional ones that might be added in as appropriate for that particular

condition.

There was a discussion about also the importance of considering outcomes from a wide range of different perspectives. And again, I'm going to dig into that again in a little bit.

One of the challenges that we faced in the past is around gathering unpublished data. In the fast-moving field, there were often times in the position of exploring, there's a lot of unpublished information out there, but it's challenging to both gather it as well as to assess the quality of the evidence or the potential risk of bias. And so, building off of the process that GRADE does, they have a formal written document that can be passed out or made available to individuals in the field who can then submit where unpublished evidence might be and the strengths and weaknesses of it. That is something that I think is going to be really important for us to adopt moving forward, and this is one of the central areas that I'd like to discuss in the April meeting.

There was broad agreement too around looking at issues of long-term followup during the evidence review process, because of the recognized challenges of long-term followup. So, that would include describing long-term followup plans during the review process and trying to assess the availability of long-term followup. Again, these are methods that will have to be developed in the future for our -- for the review process.

There was strong support about the need to assess values from different perspectives in addition to the usual clinical perspectives that we've been able to gather, looking at family's perspectives on various health outcomes and the potential benefits and harms of screening, as well as the public perspectives around the -- the potential benefits and harm of newborn screening.

Assessing values in a standardized way to be able to present in evidence review is challenging, and this is something that's going to require a lot of work for us to really be able to

put into the process, and in our in-person meeting in April, this is something that I think we really need to -- actually, I apologize. We're not going to dig into this values part in April meeting, because I want to allow our team to be able to do more methods work. And so, it will be the subsequent one. So, not the April meeting, not next month because I don't think they'll have enough information for people to inform the specific plan. So, it will be the meeting after the April one. So, sorry I misspoke there in the beginning.

The decision matrix will be the next big topic that we'll need to consider again. At the meeting, there was a lot of interest in figuring out how values and preferences could be explicitly incorporated into the decision matrix, and there was also strong support for considering resource implications for the states. There were also questions that were raised about whether moving into the future it still makes sense to consider a condition-by-condition approach versus

panels. So, for example, you can -- one participant brought up the issue of what if there is a panel for intellectual disability that could a wide range of conditions. Would it make sense to consider each of those conditions one by one versus a panel? And then, there was a discussion about whether or not it would be possible to have some sort of provisional or conditional recommendation for the RUSP. Again, that would be a future issue.

Finally, as Dr. Bocchini mentioned, there was interest in updating or reevaluating those conditions that had been added to the RUSP previously. So, future issues to tackle would include whether there should be a post-RUSP surveillance system to be able to assess what the impact was for adding a condition, including addressing things like epidemiology, net benefit, costs, and long-term followup effectiveness. And there was also support for routinely reassessing conditions on the RUSP instead of waiting for conditions on the RUSP to be nominated for

reevaluation. Again, all of these things are open for further discussion, obviously.

So, in terms of next steps, we need to refine the suggestions and related methods in partnership with members of the Advisory Committee and ultimately our goal is to use all this to develop a formalized manual of procedures.

So, with that, I will turn it back to Dr. Bocchini and see if there are any questions about this meeting or whether things are going.

DR. BOCCHINI: Alex, thank you for a very nice summary of -- of the meeting and the steps that you plan for going forward. So, let's open this up for questions and answers and committee discussion. Again, operator, would you please open the lines of the committee members and organizational representatives. Committee members will discuss first, and again, organizational representatives will follow. As a reminder again, please use the "raise hand" feature in Adobe Connect when wanting to make comments or asking questions, and when speaking, state your name so

that we can assure proper recording. So, let's open it.

So, we have first Scott Shone followed by Sue Berry. Scott.

DR. SHONE: Thank you, Dr. Bocchini. Can you hear me?

DR. BOCCHINI: Yes, go right ahead.

DR. SHONE: Great. Thanks, Alex, for the great summary. I have a bunch of questions, but I'm going -- I'll take one at a time and step back and then come back and raise my hand again. But, I guess the first question I would throw out there is on one of your slides about the nomination process, you had said to ask the nominators to identify critical outcomes. And I wonder if there was any discussion around even having the committee sort of have a discussion around what would be the critical outcomes for that, you know, and then that transition into the review period, because I feel like at least some of the recent debates and discussions on new disorders have suffered from us not agreeing on,

okay, what is the -- what is that definition of a critical to weigh the benefit on, you know, thinking about a recent discussion SMA, and Beth, in her summary, talked about, you know, if you're going to measure this on survival, there's one view, if you're going to measure this on improvement of motor function, that's another. And so, was there any discussion around -- around in general a definition of critical outcomes and how to measure?

DR. KEMPER: Yeah. So, Scott, thank you very much for that question. So, one of the recommendations that Dr. Schünemann made that came out of some of the GRADE work was that the process have a hierarchical list of important outcomes. So, you can imagine a list that would start with morbidity and then maybe have -- again, I'm just putting this out for examples -- quality of life, motor development, intellectual disability, those kinds of things, that would be a standard set of important outcomes that would be looked at for each condition, and again, there would be a

hierarchy of importance. And then before the review process began, that list in partnership with the Advisory Committee, could be realigned based on, you know, whatever the unique aspects of a particular condition are. So, there are a bunch of different ways of doing this from a process perspective, and I think that's something that we'll just have to dive into subsequent meetings. But, the point that you're making, which I think has universal agreement, was that the important outcomes need to be determined before the review process commences so that it can really stay focused and not tricked into something that may not ultimately be relevant for the decision-making process.

DR. SHONE: Thank you, Alex.

DR. BOCCHINI: Yeah, and I'll just add that I certainly agree with what Alex said, and, Scott, I think you brought up a really great point, and I think that if we do this as part of working with the Evidence Review Workgroup and setting what critical or important outcomes are,

then we could evaluate the strength of the evidence in terms of net benefit for each of those critical important outcomes, and I think that would help us standardize the approach as well as get the -- have those already settled before we start and make the discussion and the decision much easier when the evidence review is completed.

Scott, did you want to add additional questions at this point?

DR. SHONE: No, I'll set up for -- and let other committee members talk. I'm sure that many people have similar thoughts. I'll come back. I'll raise my hand again later.

DR. BOCCHINI: Okay, thanks. Sue Berry.

DR. BERRY: Hi, this is Sue Berry. Thank you, Alex and the group for developing this process and continuing to help us think about the right way to do this.

I'm going to take a whole step back and ask kind of two things that will help me to know better where you are going. The first one is

that the general principles that have been used to add conditions have typically sort of followed roughly the general assessment that you have a disorder for which you can have an impact in health, that has a good test, and an efficacious treatment. And I was wondering if the fundamental parameters that newborn screening has long been based on were at issue here, as in do an intellectual disability panel, and you might find a bunch of stuff.

And the second question is related but not quite as aggressive perhaps, is the temporal quality of intervention, which is because we have a public health mandate for newborn screening that every child receives as a neonate, what are we doing about considering what happens if temporal sequence of impact is not neonatal period? We've already kind of stumbled into that with things we're approved recently, and I think if we're going to do that on a regular basis, we need to have a much better plan for how we deal with the idea that we set this up as a newborn

screen because of immediate neonatal impact, and some of the things we may well wish to tackle are not going to be neonatal in onset.

So, with that, I'll leave it that the two questions are, have we changed our fundamental assumption and are we sticking to our let's do this in the newborn period rule?

DR. KEMPER: So, I'm going to -- again, thank you for those questions. I'm going to probably be able to answer that in a combined way. So, the easy answer to your first question is no. This is not a change in perspective. Ultimately, recommendations are based on whether newborn screening leads to meaningful impact on health outcomes for the individuals being screened. So, that fundamental approach is -- is not being challenged. The issue is how do we do better job of synthesizing the evidence to make that story.

In terms of your second question about what about screening for something may not have benefits until many years down the road, and

that's not really a question for us in terms of evidence review. But, what I will say is that in the evidence-review process, what we would look for is whether evidence that newborn screening led to better outcomes than case detection outside of newborn screening, however that might happen. So, the weight that the Advisory Committee might put on outcomes that might not accrue for many years is, you know, not within our purview. But, what is in our purview is that we will continue to look at whether or not newborn screening leads to better health outcomes than how things might happen with other usual care. Does that answer your question?

DR. BERRY: Sort of. But, I think we'll have a continuing discussion about this, because this has been, I think, on many -- this is Sue Berry again -- on many of our -- of our minds as we sort of ponder the decision, which is a very difficult one, about adding new disorders. So I -- it's going to be, I think, very careful -- we're going to have to use our resources that are

available to us very wisely and always consider the impact on the system as we -- as we make changes and add new things.

DR. KEMPER: Yeah, I agree.

DR. BOCCHINI: So, Sue, stay tuned. I think the first presentation after lunch will potentially address some of the questions that you raised related to some of the more recent conditions that we added to the RUSP that added different features, which included later onset -- later-onset disorders.

DR. BERRY: This is Sue, again. I think one of the other things that -- that hopefully that we'll discuss is one of the impacts we have when we -- when we sometimes just don’t know what we are adding, and we find out essentially afterward the impact of some of those decisions, particularly with regard to late-onset disorders. And so, I know there are other avenues that are also being discussed to try and thoughtfully manage not throwing the baby out with the bath water and being able to do a screen

that's impactful in a neonate but also may have longer-term consequences. So, we're just -- this is the right time for us to be discussing this, and I'm pleased we're doing so. Thank you.

DR. BOCCHINI: Great. Thank you, Sue. Next is Mei Baker.

DR. BAKER: Yes. I -- actually my question goes back to the first question. Besides Alex and Dr. Bocchini talked about why we are trying to do predetermined critical outcome. The one thing I want to add, if I recall, is we also want this to become more objective. So, before you already defined the impairment. I just want to add on this one.

DR. KEMPER: Yeah, thank you.

DR. BOCCHINI: Okay. We have Annamarie Saarinen apparently is in Mongolia and is listening in but cannot get online. So, she had a question. Has she been able to type it in?

DR. RILEY: No. So, Annamarie, if you can E-mail me your question, we're happy to read it in.

DR. BOCCHINI: All right.

UNIDENTIFIED FEMALE SPEAKER: So, can you guys hear me?

DR. BOCCHINI: Anybody else? Scott, do you want -- you can be up for the next question if you have additional questions.

DR. SHONE: Sure. So, hi. This is Scott Shone. My -- I guess my question -- well, first of all, I really appreciate Sue's comments and questions around sort of the science and the benefit of discussion. A lot of my -- at least my initial response to your presentation, Alex, is probably more around process at the moment while I digest it. So, you had -- you delve into, a little bit, the Decision Matrix, and I'm interested to hear the elaboration on the potential for adding resource implication and sort of this idea of provisionals is -- it was just a line in there, so I'm really eager to hear more about how that would even work or what that would look like. But, you know, I think about -- and I don’t want to say it's an addition to the decision

matrix -- but, it's sort of on the side of the public health system's impact. It doesn't necessarily have a role in overall the decision, but it sounds like maybe this resource implication where impact could get at that.

So, what I'm wondering is, you know, some of the -- some of the challenges recently and some of the feedback from the community and the system has been that disorders end up at different places on the matrix, but the outcome is always the same. And so, is there -- are there plans to look at instead of -- instead of putting a disorder or a view in a decision matrix bucket and then debating whether or not it goes forward, having some consensus or -- or an agreement on these position in the matrix are -- would generate this outcome, and focus our discussion on whether or not the review merits which bucket on the Decision Matrix, so that that process is now uniform going forward.

DR. KEMPER: Yeah, I mean, I was just thinking in terms of the March Madness analogy. I

appreciate you allowing me to make an extra point about that. Which, it's going to require a lot of additional conversation. So, there is this conversation about whether or not the decision matrix -- where -- where exactly you land up -- where you end up with direct -- is directly tied to a specific recommendation, or whether or not the decision matrix is a tool that's used to facilitate conversation but maybe is not necessarily directly linked to what the final recommendation is. And that's going to require a lot more conversation than what we could do at this for you. And then, there was a lot of conversation in terms of the resource issues that you brought up about considering what's required for long-term followup and whether or not long-term followup is even available, because if it's not, then, you know, the challenge to get the, you know, the -- the benefits -- to get out of newborn screening.

So, although this may be dissatisfying to you right now, we recognize all

the issues that you just brought up, and it's just going to require some facilitated discussion across the Advisory Committee about how -- how that -- how that decision-making process is going not work. And if somebody whose job it is to put forth the evidence, I also don't want to drive exactly how you all use that evidence to drive decisions. So, I think that that's just going to have to be an important topic of conversation.

DR. SHONE: Okay. Hi, this is Scott. So, no, I appreciate that, Alex, and I'm, I mean, I'm glad to hear that at least there is contemplation around that, because, I mean, you're right. I mean, that's -- and I don't know that I feel one way or the other, but I -- I agree it clearly requires more than a day or so of discussion around how to best land on -- on that process, and I -- and I completely appreciate having heard you present these evidence reviews many times over the last several years that you don't want to be -- you don't want what you're saying to be the -- to be the -- you're not

engaged in the assessment by providing the -- an overall review of what evidence is out there. So, I can appreciate the balance you're trying to strive and achieve, but the need for, I think, the committee to -- to realize what are we -- what and how are we to take all of that in and -- and then assess across each time a new disorder comes up. So, I appreciate your response.

DR. KEMPER: Thank you.

DR. BOCCHINI: Great. So, Alex, before you get too far into March Madness, I just wanted to let you know that LSU is in the same bracket as Duke. So, you can just leave it with that. So, next is Sue Berry.

DR. BERRY: Thanks. This is Sue Berry again. I want to just toss out there again since we're talking about this particularly with regard to the question about provisional approval. Part of the -- we're really talking about the evidence review, but you're also talking about process, and I think the time for conversation about the process by which we add conditions, I

think many of you have heard some of the conversation that we've been working on the Newborn Screening Translational Network to think about some strategies that might allow us to thread this needle a little more carefully by having some type of provisional approval that would allow us to study, understand, and make a better final decision regarding addition of a new disorder. I'm going to throw that into the mix as an added complicating but possibly helpful feature as something we can or may wish to consider as part of our improvements in process. I'm hoping that Mike is on and that he might to add a few more words, because there's a lot of good reasons why that might help us do a better and more responsible job in adding disorders.

DR. BOCCHINI: All right. Is Mike on the line?

DR. WATSON?: I am. I'm pondering which part -- which part did you want me to focus on, Sue?

DR. BERRY: I think you could be

willing to just talk a little bit about the process we're trying to go through about how we can facilitate the process and consider the possibility of a provisional approval or a pilot study format.

DR. WATSON: Yeah, I can touch on it briefly. I am supposed to talk about this at the April meeting, so I probably -- I won't go into great detail here. But, you know, fundamentally it's all about a rare disease problem where it's very hard at a population level to generate statistically robust data, you know, about -- about, you know, most anything. It takes just enormous populations when you have a highly variable disease, which many of these genetic diseases are. It really gets challenging to think about the statistics, but what we've at least begun to consider is something -- you actually have to couple together a number of different approaches to the problem. The Orphan Drug Act, for instance, is a mechanism whereby drugs for rare diseases are incentivized to manufacturers to

get them, you know, into the healthcare system, and basically, they get various kinds of tax incentives and things that incentivize them to develop these drugs. They get a seven- or eight-year monopoly on sale of the drug. But I think the unique thing about it is that it takes advantage of an FDA -- a broader FDA policy that allows for provisional approval of something, followed by what CMS would call coverage with evidence development or required sort of data sharing from the studies that are going on in the context of drugs and post-market surveillance. You know, in this context, it would probably be coverage with evidence development whereby you were assured of getting paid for services to asymptomatic people, while you're trying to figure out whether it's going to be added to newborn screening or not. There's lots of risk sharing models out there. I think Annie Kennedy referenced one when she spoke -- when she provided her public comment, which was a public private partnership in the pre-competitive space where

industry brought money generically to the problem. Although in that context, it's really around Duchenne. It's a much bigger problem with the pipeline of things coming. So, there's lots of different ways of thinking about expanding capacity and improving our ability to put things into newborn screening, capture the kind of data that really should drive the Advisory Committee's decision-making process, which, you know, if it was more robust, would certainly be for the better and would not be that model of, you know, that happens often with rare diseases, where it's just get me one positive and we'll -- we're good to go. I think that's good enough to go into a perspective process that's well organized and controlled of data collection. So, it's a -- there's a combination of things that one might think about, and we'll talk about them in more detail at the April meeting.

DR. BOCCHINI: All right. Thank you. Next, we do have an E-mail from Annamarie that Catherine has.

DR. RILEY: Sure. Hi, this is Catharine Riley. So, I am reading this on behalf of committee member, Annamarie Saarinen. She wanted to let us know she appreciate the question that Sue raised and was thinking that the answer that Sue was looking for was less about outcomes and more about how to find out if the matrix will account for things that can be picked up through newborn screening that may not have a clinical impact in the newborn period.

The second comment is that she is very happy to see there was some thought given to panels for emerging screening methods such as genetic or whole genome sequencing and things that would cover multiple diseases and disorders. So, I wanted to put those into the record, and if there's anyone who wants to respond.

DR. BOCCHINI: All right. Thank you. So, next is Cindy Powell.

DR. POWELL: Hi, this is Cindy Powell. Can you hear me? Yeah, hello?

DR. KEMPER: Yeah, we can hear you.

DR. POWELL: Hi. So, thank you, Alex. I just wanted to comment on Sue's prior comments about this idea of provisional approval. I think as a member of this panel, we spent quite a lot of time talking about that and, you know, as committee members, we know how difficult it is often to make a decision based on fairly, you know, short-term followup that's available on some of the outcomes that we're assessing. And, I think the idea of, you know, provisional approval versus having a method of putting something on the RUSP and, you know, reassessing it as more data comes in is, you know, was an important thing that we thought about and whether, you know, kind of one versus the other. I think that, you know, one of the dilemmas is that, you know, often you can't get that population data without doing population screening and having a state, you know, begin doing population screening for disorder unless it is on the RUSP. So, I definitely think that's going to be a challenge going forward and something that, you know, I look forward to

discussing more in the future. Thank you.

DR. BOCCHINI: Thank you, Cindy. Are there any additional questions or comments from committee members or org reps? None?

DR. TANKSLEY: Dr. Bocchini, can you hear me?

DR. BOCCHINI: Yeah.

DR. TANKSLEY: Hi, this is Susan Tanksley. Can you hear me?

DR. BOCCHINI: Yeah, Susan. We can hear you, go ahead.

DR. TANKSLEY: So, I was wondering if there was any word on the Newborn Screening Saves Lives Act and the possibility of the timeframe for the evidence review being removed from that. I mean, I know that that influences the quality of the evidence review itself and, you know, rushing through that process. So, I was just wondering if -- if anyone had heard anything about the potential change of that law, because I think that impacts this process as well.

DR. KEMPER: So, the committee

charter is up for review, but obviously we cannot participate in that discussion. So, we have not heard a thing.

DR. BOCCHINI: All right. Are there any other questions or comments? All right. Alex, thank you so much for putting this on track here, and I'll look forward to the next meetings where each of these items are going to be fleshed out in more detail with input from committee members and then ultimately to the final decisions on how to go forward. The whole process is really designed to really take a good look at what we're doing, and based on our experience, refining things in such a way that we're using the best approaches to evidence review and the best approaches to making our decisions going forward. So, I want to thank everybody for their participation to bring us to this point, and I know there's a lot of work going ahead, but I think the product is going to be really strong for the committee. So, thank you all very much.

So, with that, it's time to break for

lunch, or for those of you on the West Coast, a late breakfast, I guess. We have a half an hour, and we'll be back here straight up at noon, Eastern Time. So, thank you, all. We will be back shortly. Thank you.

[Lunch break from 11:30 am until 12:00 p.m.]

DR. BOCCHINI: All right. Good afternoon or late morning to everyone. We are ready to start the afternoon session of the Advisory Committee meeting. To begin, we will need to again take roll. So, we're going to start with committee members and then go to organizational representatives. So, Kamila Mistry? Mei Baker?

DR. BAKER: Here.

DR. BOCCHINI: Susan Berry

DR. BERRY: Here.

DR. BOCCHINI: Jeff Brosco?

DR. BROSCO: Here.

DR. BOCCHINI: Carla Cuthbert?

DR. CUTHBERT: I'm here.

DR. BOCCHINI: Kellie Kelm?

DR. KELM: Here.

DR. BOCCHINI: Joan Scott?

DR. SCOTT: Here.

DR. BOCCHINI: Cindy Powell?

DR. POWELL: Here. I was also here for the morning roll call and just having problems with my muting.

DR. BOCCHINI: All right, thank you. We gotcha. Melissa Parisi?

DR. PARISI: Here.

DR. BOCCHINI: And we'll wait to see whether we get another E-mail from Annamarie Saarinen since she can't get on the line from Mongolia. Scott Shone?

DR. SHONE: Here.

DR. BOCCHINI: Beth Tarini?

DR. TARINI: Here.

DR. BOCCHINI: And Catharine Riley?

DR. RILEY: Here.

DR. BOCCHINI: So, Robert Ostrander?

DR. OSTRANDER: Here.

DR. BOCCHINI: All right. Debra

Freedenberg? Michael Watson?

DR. WATSON: Here.

UNIDENTIFIED FEMALE SPEAKER: Debra Freedenberg is on.

DR. BOCCHINI: Okay. Debra is on. Okay. Jed Miller? Susan Tanksley?

UNIDENTIFIED FEMALE SPEAKER: Susan is on.

DR. BOCCHINI: Okay. So, Susan is on.

DR. TANKSLEY: I'm here.

DR. BOCCHINI: Okay. We thought you weren't going to talk to us. Chris Kus?

UNIDENTIFIED FEMALE SPEAKER: He's also on.

DR. BOCCHINI: Okay. Natasha Bonhomme?

MS. BONHOMME: Here.

DR. BOCCHINI: Rebecca Abbott?

Ms. ABBOTT: Here.

DR. BOCCHINI: Cate Walsh Vockley?

Ms. WALSH VOCKLEY: Here.

DR. BOCCHINI: And Shawn McCandless? Okay.

DR. RILEY: Dr. Bocchini, I just wanted to read into the record too that Chris Kus was on this morning, joined shortly after roll call.

DR. BOCCHINI: Okay. Thank you. All right. So, for our next presentation, it is entitled Analyzing the Impact of Adding Conditions to the RUSP: Drafting an Approach.

So, another task Dr. Kemper and his team have been assigned is completion of a retrospective analysis on how implementation of screening for new conditions in the last decade has gone, and what the impact on public health programs has been. For example, we have estimated time frames with implementation; have they been accurate? Have the barriers and challenges that we have expected been what was faced or whether there were different barriers that programs ran into, and whether there were findings or barriers that were not identified during our public health

impact assessment component of the evidence review. As mentioned earlier today, we have added some conditions with late onset, and we certainly want to have a better understanding of the impact that they had our public health systems.

So, our focus for this review is how each of the conditions added to the RUSP in the past decade has impacted the newborn screening system. So, today, Dr. Kemper will present an outline for this report, and we are looking for input from the Committee on the overall approach to the review and the contents of the report. So, Alex, are you on board?

DR. KEMPER: I'm on board. I hope you can hear me. There's a little bit of a bracket. I want to see that come across in transcription.

DR. BOCCHINI: Okay. All right. Go right ahead.

DR. KEMPER: So, with that, what I am going to present today is not the findings of the reports. So, if you were hoping for that, that's

not what's in this session. Instead, we're going to be talking about the outline for the reports around the conditions that have been added to the RUSP.

So, our charge is to review severe combined immunodeficiency, critical congenital heart disease, Pompe disease, mucopolysaccharidosis type I, and X-linked adrenal leukodystrophy. The reason these conditions were selected is because these were the conditions that were added to the RUSP between 2010 and 2017. But, in addition to learning the things that Dr. Bocchini talked about before I got on is the secondary goal. We really see this as an opportunity to think about things on the conditions that we're going to be looking at in the future related to implementation and outcomes. So, I think there's going to be a lot of lessons that we can learn from this review process.

One of the things that I want to highlight is that the review of SMA is a separate task order and will address a few additional

questions, and I'll describe that as we go through. And this is a special request that came from the Secretary at HHS in response to the recommendation from the Advisory Committee.

So, this is just a historical reminder of when the conditions came in, and I spoke a second ago about how SMA is a different -- somewhat different report, although many of the challenges are the same. So, SMA will be reviewed in a different report.

So, what I did want to do is just spend a few minutes just talking about where we are in terms of implementing of these conditions and some of these slides that I'm going to be showing you are courtesy of NewSTEPs. So, thank you for these, Team NewSTEPs. And you could see that all states now screen for SCID and states are still getting, you know, fewer states screening as you go to the newer conditions after CCHD. This is another way of looking at the trends in uptake of these new conditions. You can see all states screen for at least one or two of the new

condition, and then it falls off by time you get to six, and I've gone ahead and listed out the state newborn screening programs that screen for five or six of these, just in case you're interested.

This slide shouldn't be a surprise to people that the -- it takes time to add a condition to the RUSP. And so, the longer amount of time that's elapsed, the more likely that a condition has been added to the RUSP, and you can see that SMA is still in the early days.

So, in terms of the scope of the review, we are going to look at state implementation, public health implications, and clinical outcomes and impact, you know, of course where those data might exist. We have several guiding issues -- there are probably more than several as I look at all the bullet points -- that are going to -- that we're going to use during the review process. So, we're going to be interested -- and again, these are things that Dr. Bocchini highlighted. But, knowledge about the condition

and gaps in understanding when the condition is added to the RUSP. So, you know, what was known at the time. Status of newborn screening implementation and related long-term followup services over time. Again, the Advisory Committee has -- has repeatedly made the very important point about the need to understand long-term followup. We're going to look at, you know. Specific conditions related to the condition. Factors within newborn screening programs that impact the decision whether or not to add the condition to screening. Contextual factors that may be barriers or facilitators including things like what's going on with public health overall, the availability of grant support outside of the newborn screening program, advocacy, activities involvement of payers, clinicians, and others, availability and accessibility of healthcare services after the diagnosis. So, you know, again speaking to issues of long-term followup.

And then, one of the things that I think is going to be particularly interesting is

the changes in understanding of the condition that's evolved over time since newborn screening started because we're all well aware that once screening begins, our understanding of a condition rapidly expands.

So, I did mention before that there are going to be some additional key questions for spinal muscular atrophy, and again these were questions that were guided by the request from the Secretary. So, specifically focusing on what activity states are undertaking to implement screening, what's known about the clinical outcomes of infants who are treated early, and what's known about the potential harms for infants diagnosed with SMA. Again, these questions come directly from the decision letter.

So, we have a standard approach, and I'm just going to outline this from a high level. For spinal muscular atrophy, we are going to put together a technical expert panel who can help us understand where sources of data might be and important additional issues for us to consider.

Across all the conditions, we're going to be obviously looking at the previous report and outlining questions that the Advisory Committee had at the time that the decision was made. We'll be doing targeted interviews to understand issues of implementation. We're going to update the literature review, so going back from the time that the review was completed until the present, specifically looking at those key questions I talked about before. And then, of course, we will look for unpublished evidence that may inform our understanding about what happened after the condition was adopted. So, oops, I probably went too far out that way.

So, again, we're going to have a series of reports for each condition and SMA is going to be a little bit different simply because of the short period of time that has elapsed and the specific questions that came from the Secretary. Now I can move there to questions.

DR. BOCCHINI: All right. Thank you, Alex. This is now open for questions or comments.

Operator, please open the lines for the committee members and organizational representatives. We'll have committee members first, and then organizational representatives to follow. Again, a reminder to please use the "raise hand" feature on Adobe Connect when making comments or asking questions and when speaking, please state your name.

So, first is Mei Baker. Mei?

DR. BAKER: Thank you. This is Mei. Alex, I just want to ask a little bit, well comment or question. Can you present the slide that indicates how many states implement? I'm wondering, can you also include the one before this one?

DR. KEMPER: That one?

DR. BAKER: Yes. So, I think that would even have more information if you have another one to indicate how many babies are impacted.

DR. KEMPER: That's a good idea.

DR. BAKER: Right? Yeah. So, that's

what -- that's my comment.

DR. KEMPER: Yeah, to give a sense of the overall public health impact across the country?

DR. BAKER: Yes, the people -- like, you know, New York, California, they're much larger. Even, you know, so that's two ways to look at that.

DR. KEMPER: Okay. That's a good idea. We will talk to NewSTEPs about that.

DR. BOCCHINI: Next, we have Robert Ostrander. Robert?

DR. OSTRANDER: Yeah. Hi, Alex. I just wanted to bring up something that the Follow-up and Treatment Workgroup has been talking about at the last couple meetings that everybody knows, and that is the notion that we're trying to switch the work to longitudinal. The notion that there ought to be something in place for longitudinal followup, even if it's just an architectural draft at the time that a condition is added to the RUSP. And to that end, if retrospectively you could see

a place for longitudinal followup for these conditions and, you know, it would be real cool to know when that kick in did compared to when it was implemented. I think we would find it very useful and perhaps the committee would find it useful if they decide to implement some of our suggestions about making some infrastructure or at least again an architectural drawing, if you will, having that in place before addition to the RUSP as part of one of the conditions.

DR. KEMPER: Yeah, that's a good point. I really like your term sort of architectural layout for, and I'll adopt your words, longitudinal followup and thinking back to my earlier presentation, that's a notion that we should keep track of.

DR. BOCCHINI: All right. Next, we have Jeff Brosco.

DR. BROSCO: Thank you. Actually, Bob sort of asked my question. So, I'll have to use this opportunity to say you look very professional in your photograph, Alex.

DR. KEMPER: Well, thank you very much. That's my stand-in model.

DR. BROSCO: Yeah, exactly. Maybe broadening Bob's question a little bit, how do you see this work as fitting into, you know, you've been part of this for years, the long-term followup for newborn screening. Does this begin to answer it, or is it really, you know, you're very much focused on the outcome from being added to the RUSP? How do you see this fitting into the broader questions of states and others doing long-term followup?

DR. KEMPER: Yeah, I -- well, obviously they're complimentary, and the ability of us to find evidence of this report is going to hinge on what sort of long-term or longitudinal data are out there. But, in my mind, although I'm open to change things based on what you all think, is that this would help us better understand the impact of the decision-making process and how well the report anticipated the issues that were going to happen downstream. But, clearly, it's also

going to address the issues that I think you are pointing to and Mei was alluding to as well in terms of, you know, what was the impact of this on the health of the babies that were born during this time. Did that make sense? Did I answer your question, Jeff?

DR. BROSCO: Yes.

DR. KEMPER: Okay.

DR. BOCCHINI: Next, we have Scott Shone.

DR. SHONE: I'm good. I put my hand down. Alex mentioned the answer to my question in his response to Jeff.

DR. BOCCHINI: Okay. Sue Berry.

DR. BERRY: I'm really -- this is Sue Berry, and I'm very interested and again pleased by the sort of complements of the things that we're discussing here, because it's pretty clear that these all feed into each other in terms of ability to add new studies to and then decide whether we've done the job we needed to do. I think everyone -- I'm kind of a broken record on

this -- but everyone knows that we have not really fulfilled our responsibility to the kids to start with, not just SCID, CCHD, Pompe, and so on, but to all of the children without that longitudinal followup being part of what we plan. And so, I'm hoping that our work on the long-term followup committee will have some impact in terms of creating some infrastructure and planning for long-term followup or we won't be doing the whole job. And so, as we move forward in doing matrix decisions, rebuilding, and considering how we add new disorders, if this isn't a part of it, then we're not going to get anywhere.

A more editorial comment than a question, but one thing I would point out is that public commenters on DMD clearly took that responsibility head on without even being asked to, but know that it's necessary by telling us about what their plans are for long-term followup, and I'm hoping that we will continue to see that emerge as an expectation.

DR. BOCCHINI: That's a very good

point, Sue, and I think that that's why we wanted input from the committee, because the goal for this was not just to determine how many states and how long it took those to begin to screen, but to really have an impact on the state public health system as well as children being screened, and so that does include long-term followup. So, any specific thoughts about how to incorporate that into this review would certainly be helpful to Alex, and what other things the committee would like to see from this review, if it's possible to get it from states that would be really important. So, we can use this to help fill out some of the questions that we've all been asking.

So, next I have Natasha Bonhomme.

MS. BONHOMME: Hello. This is Natasha. On this slide, Alex, my question -- I guess I have two questions. One is, is there a definition of what pursuing implementation means? Does that mean there's legislation happening? Does that mean the state is pushing for that or advocates are pushing for that? Do you have any

idea what that means?

DR. KEMPER: Well, you know, I should probably -- because I don't have the definition in front me and I'm not sure if anyone from NewSTEPs is on the phone to answer that question directly. But, I think it's more than just -- and I should say just -- it's more than advocacy work. My understanding is it was either pursuing legislation or actually doing something within the lab. But, I could be wrong about that, so I don't know if Marci Sontag is on the line who could answer that.

MS. BONHOMME: And maybe we can get that answer later. I think that would be helpful to give some sense of what that really means in terms of how close or far things are in terms of whether it's in the legislator or in the lab or there are pilots or what that would look like.

DR. KEMPER: Yeah.

MS. BONHOMME: So, I think that would be helpful.

DR. KEMPER: And I promise in the

full report, we're going to have that like fully fleshed out.

MS. BONHOMME: Great, and then just to add onto a lot of the things have been said, I think that piece about followup is really important, and particularly -- again, I don't know if that would be under the purview of this work or other work -- you know, what is the loss to followup. So, not just what's happening for those kids that we have tracking of, but are we able to account for every single screen and every single identification? I think that would be helpful so that we can see, you know, how is this full system really -- really working as these conditions are added. So, that's my two cents on the followup side. So, thank you.

DR. KEMPER: Thank you.

DR. BOCCHINI: Let's see, is Marci Sontag available?

UNIDENTIFIED FEMALE SPEAKER: [inaudible]

DR. BOCCHINI: Oh. Okay. Let's see

if we can open his line.

UNIDENTIFIED FEMALE SPEAKER: He's open.

DR. BOCCHINI: Okay. Jelili? We can't hear you. Are you on mute? We've been told your line is open, but we cannot hear you. All right. Well, let's see if we can get that straightened out, but in the meantime, we have Sue Berry.

DR. BERRY: Hi. This is Sue Berry again. I am interested also in the yellow bars where things are not screened and some of the assessments are sort of general categories for why people are struggling. I know that in some cases, it means it's because they have to have legislation, and that's an onerous process. I know it's sometimes because they don't have the equipment, or wherewithal, or knowledge base to implement a specific screening strategy. I know that sometimes it's because the programs, even if they want to do, simply don't have the financial support or ability to add on an immediate basis.

So, a couple questions. One is, are we surveying some of the reasons for that? I'm pretty sure NewSTEPs has some of that kind of stuff.

DR. KEMPER: Yeah. No, that's -- that's definitely part of the, you know, the barriers of facilitators of screening that we're going to try to collect. And that's, you know, for our targeted interviews because it can sometimes be hard to get to those issues.

DR. BERRY: Yep, definitely. And then the other thing is, has any -- just throwing this out, and this is not necessarily the purview of this discussion -- but, one of the possible solutions for some of the strategies is to stretch our boundaries as far as what we consider to be state-supported screening and seeing if states can't come together when technology is an issue to help support some of those things, because, you know, we already have some precedent for that kind of activity in states that are small contracting to other laboratories. So, just thinking about some feasibility strategies, I'm hoping that's one

of the things the group will identify is mechanisms for overcoming some of those barriers.

DR. KEMPER: Excellent.

DR. BOCCHINI: All right. Next, Melissa Parisi.

DR. PARISI: Thank you. This is Melissa Parisi from NIH. A comment and a question. Alex, I'm hopeful that there will be some opportunities to utilize and at least explore some of the data that are in the long-term follow up aspect of the longitudinal pediatric data resource as part of the Newborn Screening Translational Research Network, because I think that may be helpful in terms of trying to discern some of the outcomes for these newer conditions, particularly for SMA and some of the others as well. But, I also was wondering if, in the course of your work, you might have an opportunity to explore some best practices for longitudinal followup, given that there are going to be different strategies employed in different states and different screening systems, and whether there

might be some lessons learned that might come out of this work.

DR. KEMPER: That's actually interesting. I hadn't thought about it in terms of not just long-term followup per condition, but what are the generalizable lessons across the various conditions. That's a really good -- is that what you meant, Melissa?

DR. PARISI: Yes, absolutely.

DR. KEMPER: Yeah. Yeah, that had not occurred to me before, that's a really good idea.

DR. BOCCHINI: Okay, we have an answer texted in from overseas.

DR. RILEY: Yes. Hi. This is Catharine Riley speaking on behalf of Marcy Sontag, who sent in an answer -- she's in listen-only mode -- that the activity by the public health program may be legislation or working with the Advisory Committee or seeking fee changes or getting new equipment, and that we'll be hearing in the future more from APHL on this at a future

meeting.

DR. KEMPER: Okay, great. So, even though I went to the rim of my knowledge, it turns out my answer was right.

DR. BOCCHINI: Well, some people are lucky, so that's good. Michael Warren.

DR. WARREN: Sure. So, this is a question that goes back to a little bit about what Dr. Berry was asking. I'm curious, as you all, Dr. Kemper, are approaching this, it's described as a review, whether there will also be some recommendations, and in particular I'm thinking about as you're looking at some of these contextual factors that are barriers for facilitators, states often rely on limited fund to be able to stand these services, and I think, for example, what they get from our [inaudible] grant and if there are efforts where there might be some autonomy of scale. If you see that as you're thinking about those barriers and facilitators, us knowing that would be helpful as we think about future funding opportunities or recommendations in

the event that we're ever asked about how we might structure funding opportunities. Looking for those might be helpful if you see those in your review.

DR. KEMPER: That's great advice and we will certainly make sure to explicitly look for that.

DR. BOCCHINI: All right. Now, we have a comment that was emailed in by Dr. Joe Schneider.

DR. RILEY: Hi, again. This is Catharine Riley on behalf of Joe Schneider, who is a workgroup member on the Followup and Treatment Workgroup. It's in response to Alex's presentation that CCHD may be implemented in all states, but the implementation is variable. In at least one state, there is no adequate public health reporting to understand whether it is being appropriately and adequately done. In essence, in this state, the legislature simply gave mandate to the hospitals to do CCHD screening but never funded the reporting mechanisms to ensure

compliance.

DR. KEMPER: Yeah, you know that's -- I completely agree with Joe's comment, and that's something that we'll need to explore, you know, that limitation around the data systems for CCHD and the fact that it's a point of care screening test really make these data collections challenging but important. So, that's something that we've already planned to look at.

DR. BOCCHINI: Okay. Are there any other additional comments or questions from committee members or org reps? Scott Shone. Scott?

DR. SHONE: Hey. Yeah. So, hi, It's Scott Shone. So, I just wanted to say that, Alex, I think, you know, your slide about guiding issues you have a bullet point, something to the effect of contextual factors that served as barriers or facilitators of adoption. You talked about public activities, grant support, advocacy, involvement of payers and involvement of clinicians. I would suggest that talking to states that haven't added

it to assess to have -- there aren't actual barriers, but just a fundamental disagreement with the addition of the condition to the RUSP and get a sense of the feeling within the state and their advisory committees, you know, around just a general feeling about the addition to the RUSP. So, some of this presupposes that everybody should add it because it's on the RUSP, but again, it's recommended not required uniform screening panels, so I just want sure that we capture that.

DR. KEMPER: That's a really, really good point. Thanks for adding that in. I'll make sure we do that.

DR. BOCCHINI: All right. Next is Mei Baker.

DR. BAKER: Yes, this is in followup to Scott Shone's comment. This is Mei. Actually, Wisconsin is in this category for two disorders, MPS1 and X-ALD. The committee evaluated and discussed it, and decision was made because benefit and risk and the potential problem, especially for X-ALD, the decision made not at

this time.

DR. KEMPER: Um-hum.

DR. BOCCHINI: Thank you, Mei. Who else?

DR. RILEY: I don't see anyone else at this time.

DR. BOCCINHI: Okay, no one else. Any additional questions or comments? Last chance. All right. Alex, thank you again for a nice presentation and a project that I think is going to add considerable information to inform subsequent decisions for us. So, I think this is going to be really helpful.

DR. KEMPER: Thank you. Thanks, everyone for their feedback. This is really very helpful.

DR. BOCCHINI: All right. Thank you. Good luck in your bracket.

DR. KEMPER: Who needs luck?

DR. BOCCHINI: All right. Next, we have a panel discussion. So, I'll give you a little background. During the past year, this

committee has had several discussions about what potential resources might be available for studying rare diseases and what data resources might be available to help inform the committee with regard to conditions nominated for the RUSP. We are also interested in knowing more about the data available to help us assess the impact of adding conditions to the RUSP and whether additional data sources are available to states to assess long-term followup and outcomes. It is also a timely topic for the committee as we embark on assessing the nomination evidence review process.

So, we put a panel together today entitled Resources for Facilitating Rare Disease Research. This panel will provide us with an overview of the resources available at a national level. This will start the conversation, which we plan to continue in April with an additional panel. As we hear from the panelists today, please be thinking about how the committee may be able to help perhaps by encouraging research on

rare diseases in the development of additional data resources, as well as identifying ways to have more synergy between the resources already available.

At the April meeting, we will hear from disorder-specific rare disease foundations and/or registries about their experiences in developing and implementing registries and the types of data generated that potentially could help inform the committees or states with long-term outcome data.

I'm going to introduce our three panelists now, and after each one has presented, we will then open up this for questions and discussion. First is James O'Leary. Mr. O'Leary was formally the Chief Innovation Officer at Genetic Alliance. He has worked with national public health systems, disease-specific organizations, and community groups to improve access to genetic services, engage consumers and national policy setting, and institute legislation that protects the public from discrimination.

Our next presenter will be Tiina Urv. Dr. Urv is the Program Director for the Rare Diseases Clinical Research Network, a multidisciplinary international program in the Office of Rare Disease Research. As the lead for the Rare Disease Clinical Research Network, she collaborates with ten NIH institutes to manage twenty-two consortia and a central data management coordinating center.

Lastly, Vanessa Boulanger. She is the Director of Research at the National Organization for Rare Disorder (NORD). In this role, Vanessa oversees the management of growth and implementation of NORD's research and scientific activities.

So, I'm going to start by turning this over to Mr. O'Leary. Operator, would you open Mr. O'Leary's phone.

DR. RILEY: Mr. O'Leary, this is Catharine. You have -- you are in presenter mode, so you should be able to advance your slides.

MR. O'LEARY: Oh, okay. Great. Can

you hear me?

DR. BOCCHINI: Yes, we can. Go right ahead.

MR. O'LEARY: Okay, perfect. Yeah. Thank you so much for having me here today. I really have been head-down writing lately, largely on what happens with patient data and healthcare systems. So, this is a good topic for me right now to speak about in a more global sense. I think everyone on this committee is pretty familiar with the need to accelerate rare disease research. But, even in the last ten years, I feel like the strategy has changed quite a bit. You know, more globally to attract attention and interest in this space, to rather the low-end barrier and promoting innovation in this space, which is frankly a very welcome change. And I think that's true in support, that's true in clinical care, it's true in drug development, and public health. And today, my task is to really give an overview, get everyone on the same page, kind of on the range of resources that are

available with a particular focus on registries and their diversity.

So, next slide. As field has progressed, I think the resources have progressed as well. But, like any space, maybe even more so in this space. The development is really decentralized and in the case of rare diseases, it's disease focused to these organizations or researchers focused on the specific disease, public health professionals focused on specific disease, or it's very institutionally separate. And that creates a lot of challenges to finding the time and resources to build broadly useful tools, and there are a lot of resources necessary because we're talking about a space with thousands of different diseases and with very different indications.

We have a figure from NCATS, and NCATS did a pretty comprehensive process of collecting and collaborating between many organizations of many of the different types of tools and resources, so I'm not going to go into

as many specific tools today, except in the registry phase. But, I will take a few minutes to talk about the types of resources that are available and the importance of them and really bringing them all together whenever you're thinking about engaging people in the space.

First, the one we always think of is information. That might be kind of guides online and maybe, you know, web resources, you know, how to guides, and that type of resource is valuable, but in many cases, it's lacking context. It can be incredibly challenging for people to use. What people need in combination with that is expertise. Whether that's internal expertise staff on hand or external expertise, people to guide them through the process. And, I think that's particularly the case, and we've seen that's the case around the RUSP, and helping people understand not only, you know, the importance of getting on it and the type of information that they'll need, but also really guiding them through the whole process of generating that, who to engage, how to engage, how

long it takes, what the resources look like, that type of thing.

I think tools and templates can also be incredibly helpful, things that are plug-and-play reduce the resources across many different types of conditions from contracts to validated instruments to outreach tools, and then going further, which is something I'll certainly touch on in the registry phase, platforms, whether that's open-source software, registry platforms, et cetera. But, they have to have sufficient capability and customization for the needs of the group in question, and they certainly take ongoing resources, which I think everyone in the newborn screening gets.

And then we can't forget about data. So, whether that's access to electronic medical record data, which is an ongoing problem for everyone, whether that's samples, et cetera, and then investment, which is resources, money, and certainly in time services and partnerships.

So, I'll go through all of this in a

little bit more detail in the registry space, but this is true across all of the resources for accelerating rare disease research.

The next slide is something I think sent this out ahead of time. It's called the Navigating the Ecosystem of Translational Science, and it's very much in the translational science space, it's in the drug development space. But, I wanted to put this up as an example. This is something that I worked on at Genetic Alliance, and I believe NCATS has a version of this, that they updated as well. And when we produced it, it was dispelled the myth of the drug development pipeline. You know, you hear that all the time that it's a pipeline, you know, one step at time to get to a drug, and that's just not real. In fact, it's this really interconnected process, with a lot of opportunities for problems but also a lot of opportunities for collaboration. And the complexity of developing this was not to scare people, but really to show off those opportunities for collaboration and the need for simultaneous

action. The same is true for screening and testing absolutely, and I don't know that I've seen a map like this in that space. The classic example is registry, which is if you wait to build a registry for when you need the data from that registry, you're going to be waiting a long time. And these things have to happen in parallel, and we need to be thinking ahead on not only how can we use data that's available, but how can we encourage those forces of data to collect the questions that are relevant to us. And I think that's certainly something that this committee is interested in.

So, let's drill down a little bit more on registry. You know, we have limited time today. So, feel free during the Q&A to ask me for more detail on this, because I'm really just going to give a high level to make sure that everyone is on the same page for the discussion.

There are many ways -- I think everyone is familiar with what a registry is -- but, there are many different ways to kind of

slice a registry. There are many, many, many thousands of registries out there in the world, and I like to think about them kind of in the who, what, why, and how. So, who is in the registry? Who are the participants? Is this a population registry? Is this a community registry? Is this a study specific registry?

What types of data and samples are being collected? You know, are there biological specimens? Is this patient-reported data, clinical-reported data? Is it data collected from apps or from tests or with insurance companies? You know, there's a lot of different data types that can be collected and useful.

The why of the registry, which is perhaps, you know, most important. Is it focused on natural history? Is it biomarker identification, trial recruitments, surveillance? Is it to promote a learning health system, identify clinical end points, public health checking, is it about coverage policy, et cetera? There is just a huge range of uses of registry.

And then the how. And this can be the most important, in fact, I would argue that this is most certainly the most important, which is both from how is the data collected from a data science perspective, but also how is outreach and engagement done, and how can you ensure trust and security to ensure the long-term viability of that process and data stream.

I have included some questions here that are the questions that I would ask anyone that was wanting to start a registry or to partner with one to, you know, better understand whether there's a fit, to better understand what the goals are, and ensure that there is a viable connection there.

So, the first item is what is the purpose of the registry. It seems obvious, but if the original purpose of lack thereof, which is a common problem is that people are interested in the registry because it's the thing to do, but if there's not that match between that original purpose and the data you need, there could be

limited utility for things other than exploratory purposes.

There's a lot of data creep issues with registry. So, it's really important to understand what that purpose is. And if that purpose is changing, to look back at all the aspects of everything from an engagement strategy to the data models, et cetera.

A lot of community-based registries, for example, or clinical registries, have the ability for ongoing connections to participants. That's one of the advantages of the registry. So, you can kind of pivot and change directions, but it should not be taken lightly.

The second question I would ask is about the types of data and samples to be collected and much of the same reason. You know, is it a match?

The third question is around who contributes the data from where that data is collected, as I mentioned earlier. All these data types, whether it's contributed by a clinician, is

it patient-reported, or other, have their value for different types of goals and different data types, and there have been a lot of studies on the accuracy of patient-reported data, for instance, or data collected from electronic medical records. So, how that is collected is very important, and certainly whether that data is representative.

Is that data longitudinal? In the research space, we are willing to accept a lot of bad kind of pre-screened data because there's less cost and it's easier to de-identify data. But, that is, you know, there's a lot more that you could do with ongoing connections between people and their data and registry can provide that.

National or international? It seems like a simple question. It is not a simple question in that there are a lot of kind of regulatory hurdles, funding hurdles in either collection, and challenges that occur when you move from a national to an international registry, but in the rare disease space, many times you do need to have an international focus. Similarly,

how the registry is governed is incredibly important. I would argue that these days, there's literally no excuse for a lack of community representation in the governance of the registry, and, in fact, broad representation, because that ensures the long-term viability, and it also ensures that the protocols that are being used are relevant.

Data ownership is incredibly important. Who owns the data? And there are a lot of instances where this is a very important question to delve down into because there is confusion in cases of research partnerships on how actually owns the data. Is it an institution, is it the government, is it the organization, the community, or the individuals themselves? And most of this is about control. Ownership is a term that people argue about a lot in this space, but control of the data is what it really comes down to. And then how the data will be used, and that needs to be clear if you're going to maintain trust in the registry.

The most important though and certainly for this committee and for the purposes here are how does the data get to where it's needed most, and this is a really important thing when you're looking at any registry or any partnership with a registry is to get this out of the way very early, because you don't want to get down the line -- six months or twelve months down the line in a partnership and then find out that there are data access issues, that the data can't actually be extracted in a useful way from a system. This is a problem that many, many people face when accessing electronic medical record data right now, and something that a lot of people are trying to create solutions around. But, this is something that frequently gets kind of ignored in the first conversations around this topic and then becomes the biggest hurdle later on.

So, I'll touch just a little bit on the reality of registry. This is something I could talk about all day. But, I included a cartoon here. I know everyone is ready the

cartoon first, so I'll talk about that first. It's not just to talk about data quality or, you know, the validity of the data instruments, but to also just say that we need to understand the context of participant's lives when we're looking at the data.

Registries can be very, very good at that, but also they can leave out important context, you know, who gets to ask the questions in a registry really matters. I always say there's so much power who gets to ask the questions. That's true of registries and it's true generally in life. It's not just what gets included but it's what's missing.

The reality of registries these days is there is just a massive amount of diversity. There are many, many thousands of registries. They're incredibly expensive to build and maintain. The costs of them balloon dramatically over time, and the way that registries have been funded is changing. A lot of registries -- your external registries or community-run registries

might have been funded through industry money in the past. Industry has been reticent to continue to fund registries because of the huge costs of maintaining them. So, because of issues around how useful the data is, the industry partner is staying out of the question generation process and how to maintain the neutrality of that registry but also to ensure that that data that comes out is useful to all parties.

There has been a move toward platforms to promote sustainability, to improve the technology, and to comply with international regulations, but also to provide all the tools and resources that go around creating a registry. So, you know, building a registry red cap is one thing, you know, you kind of serve out to red cap and kind of generate that research database yourself versus a more full-service registry, whether it's patient crossroads, which is owned by Invitae, NORD has a patient registry, Genetic Alliance has a platform called PEER, which they just announced a new partnership with LunaDNA.

Those types of more full-service [inaudible] platforms and in many cases participant-engagement platforms provide a different level of service to registries.

But, it's very clear that this space is rapidly evolving and that there's just a huge amount of quality data out there. But, it really takes looking with a closer eye at the registry what data they have collected over time, how old the registry is, how it's funded, and where they're pulling data from.

So, I think lastly and what's most relevant to this committee is, you know, what direction, and I think in the public health space in the screening and testing space, there is a huge need to identify what types of data are needed -- the who, what, why, and how are what groups are looking for.

I remember years ago -- I think it must have been five to ten years ago now -- we convened the conversation -- I convened the conversation with the advocacy organizations where

they were specifically asking how to dovetail their registry initiatives with their desire to have their condition be on the RUSP or USPSTF Grade B recommendation.

So, groups have been thinking about this for a while, but there was a complete lack of information available on how to just go about that -- about what types of validated questions to add to what types of requirements and baselines were needed to get there. And it's more than just providing a list of those data types. It's providing guidance on, you know, how to get from A to B, and doing so in a way that doesn't, you know, guarantee that that will happen in a short period of time, but also explaining that this is an ongoing process and that things need to happen in parallel so when we get to that place, you have all the data that's needed, and we can move faster.

I think it's also about creating a mutual space for collaboration just as I mentioned with industry, you know, it can be very confusing

on how to create a safe space for dialogue around what the appropriate question types are when you get down to disease-specific conversations, and so creating that space and an open dialogue around that is incredibly important.

And then just where possible, to clearly define those questions and data types to provide them in a way that, where possible, it can even be plug-and-play where things can be customized. It can be incredibly helpful, especially when some of the most valuable data sources might come from community-led registries, which can be from organizations that range from very small to certainly organizations that are international and have multi-million-dollar budgets. So, it's important to engage all those stakeholders, whether it's clinical registry, community-led registry, insurance, and industry to understand the full spectrum of data that's available or could be available.

And so, with that, I'm happy to delve down during the Q&A on any of these topics, and

certainly you can reach out to me with any other questions. Thank you for having me.

DR. BOCCHINI: Thank you for a great presentation to get us started, and I'm sure there are going to be some questions at the end. So, thank you.

Next, we have Tiina Urv. Could we get her slides up and open -- make sure her line is open. Tiina, can you hear us?

DR. URV: I can hear you and I'm here.

DR. BOCCHINI: Okay. We can hear you too, so we're in good shape.

DR. RILEY: Tiina, this is Catharine. Do you want me to make you presenter?

DR. URV: Yeah, that would be great. Sorry my zebras look a little dark on this slide.

DR. RILEY: Okay, just give us one minute.

DR. URV: All right.

DR. RILEY: All right. You should be all set.

DR. URV: Okay, great. Thank you so much. I am very happy to be back with my old newborn screening friends here today. And so, the title, which you can't see, or at least I can't see on my screen, is Rare Diseases Resources and Activities at NCATS, which is the National Center for Advancing Translational Science, and I work in the Office of Rare Disease Research, and this is all at NIH. So, disclaimer, disclosure, presentation reflects the views of presenter and does not represent NIH's views or policies, and I have no conflicts to disclose.

So, when we think about a disease that has a prevalence that is great than Alzheimer's disease, HIV, and all cancers, and almost equal to diabetes in this country, that would be all rare diseases combined, as they combine all cancers. So, that's 30 million people that have rare diseases, and they're making it to be about 7,000 rare diseases at this time, and we've been adding 230 a year for the last few years, so that 7,000 is very much a growing

number.

So, science has been advancing at breakneck speed and there are enormous opportunities that have been happening. There is the human genome project, we're curing cancer, and we're doing gene editing. So, with those opportunities comes the need to deliver on the promise of science for patients. And it's not just the promise of treating these patients, but it's really a responsibility for us to be treating these patients.

So, we face a lot of challenges in the rare disease world, and those are we have small numbers of patients, many disorders are poorly understood, genotypic diversity within a disease, patients are geographically dispersed, they have serious diseases, they're life threatening, there is little or no clinical trial precedence, and they affect many children.

So, where are we with treatments for these rare diseases? Only about 5 percent of rare diseases that have been identified have regulatory

approval treatment, 95 percent have no treatment. So, at the rate we're going right now at developing treatments, we're developing treatments for about three to five newly treatable diseases a year. So, as the rate is growing, it will take us about 1,000 years to have treatments for all the rare diseases. And this is a challenge for us.

So, one of the things [inaudible] and I did was we did this Ignite course through HHS, and we really talked to a lot of different people in the rare disease drug development field where we were looking at where some of the problems were and where some of the strengths were, and there are a lot of challenges that face us. And these are the same challenges that face the newborn screening field. So, we have natural history studies being done, but they're all done very separately. Everyone is on their own island, as we said, and there's not a lot of really good connections with the clinicians necessarily, and in developing the treatment, even at the NIH, there's not great linkage. And going over to

developing an IND, this can be very challenging because a lot of the investigators on say the left-hand side of the universe don't have a lot of experience in the drug-development side. And what we really need to do is develop pathways to link all of these things together. And if you think about it, what does this have to do with babies? What does this have to do with newborn screening? A lot of what we have to get done for clinical trials to happen and for a drug to be accepted are the same things that we have to do to have newborn screening put onto the panel. We have to have good understanding of the disease. We need to have a treatment. There needs to be good communication with families. So, a lot of the challenges are the same. So, I always think of it as there are multiple things that need to be happening at same time when you're developing a treatment for a rare disease. You also, in parallel, need to be developing a better understanding to get to a good screening tool that's been tested at same time, so you don't find

yourself with a treatment, but there's nothing that's been developed for newborn screening. So, I've always been a proponent that these activities need to be happening in parallel. We all need to get the trains to the station at the same time basically.

So, what's being done to address these many challenges? Today, I'm going to speak a little bit about some of the things that we're doing at the Office of Rare Disease Research at the NIH. So, at the Office of Rare Disease Research, our responsibility is to facilitate and coordinate between multiple stakeholders in the clinical rare disease community including scientists, clinicians, patients, and patient groups. And so, we've developed some tools, and we're also conducting some research. And I'm going to touch a little bit on both of these, but I'm always available to answer any questions you may have in these areas.

So, one of the programs we have is the Genetic and Rare Disease is our GARD program,

which was established in 2002, and GARD's mission is to really provide comprehensive plain language information on rare diseases that is freely accessible in the public arena. And so, if we look -- if we break it down and see who is looking for information on rare diseases, we find that 37 percent of the people that go to this website are family and friends, 30 percent are patients, and we have 10 percent, and 17 percent don't identify as to who they are.

So, one of the things that I think is really interesting is that if you look at who has been going to the GARD site to find information over time, this has been increasing, and if you look at this, this is the users by month. We have over a million users going to this website looking for information on rare diseases every month. So, there's a lot of interest. People are searching for information, and this is one place that they can go for it. It would be great if we linked some of the newborn screening information directly to our GARD, and that's something that just popped

into my head that we can make sure that there is newborn screening information in this resource as well.

So, we also have a new program, which is called RaDaR, which is Rare Diseases Registry. We like acronyms in the government, so we came up with RaDaR. Its mission is to develop an easy-to-use educational website that would enable the new patient advocacy groups to adopt good quality practices early in registry development. And how this really came about was everybody wants a registry. We can't afford to build a registry for everyone, but we can teach people what they should have in a registry. So, we can teach them to be good consumers if they're looking to work with a private organization, and we can teach them to be savvy builders when they're putting together their own. They're going to be able to ask the right questions to get what they need to have a registry that's not just a registry for the moment. We like the hockey analogy -- Wayne Gretzky's analogy of you need to be thinking of where the puck is

going not where puck is now. In newborn screening and rare disease drug development, we need to be thinking of where we want to be two years down the road, five years down the road, ten years down the road, rather than just in the moment of let's build a registry.

So, our vision is kind of a registry in a box, and another analogy for you is if you give a man a fish, he'll eat one meal; if you teach a man to fish, he will have fish, you know, he will eat for a lifetime. So, basically, we want people to build registries that will stand up rather than give them a one-time registry that can't be developed and doesn't grow.

So, the RaDaR website is online, and if you google in caps and RaDaR, this should pop up for you. What it does is it literally walks through how to setup a registry, how to manage a registry, and about RaDaR in general. So, if you walk through it -- and I'm not going to do it today, but you should definitely go and look at it -- how can you create your registry plan, you

know, how do you determine who should join, develop the right questions for what you need, and decide how to collect and store the data. So, if you look at the website, you'll see that, you know, one of the first things you need to do is set your goals, consider your constraints, plan for road blocks. It literally walks you through step by step of what you need to know to develop a registry. And you can go deeper and deeper into the technology as you want. You can keep clicking for more detailed information. So, if you want your informatics team to go into it, there will be information for them, or if you're just a parent looking to, you know, what should I know, what should I ask if I'm working with a company to develop a registry, you know, this will help you walk through it so you can be a strong consumer.

And so, again, you can see how detailed the information can be, setting short-term registry goals and long-term registry goals, and they have this for all the different steps that you need to go through as you're developing

your own registry, again, to have an informed public or an informed rare disease community.

Another thing that we have is the tool kit, and the RaDaR is part of our tool kit. And so, it really -- the tool kit was put together by patient groups to bring together the tools that they need to help advance medical research. The goal is really to ensure that patients are engaged as essential partners. So, it's really meaningful that you don't just bring them when it's time to go to FDA, but you bring them in early. You ask them questions early, and you involved them in a way that is meaningful throughout the drug development process and also in developing tools for newborn screening and understanding that.

So, there are tools for discovery, there's tools for prepping for clinical trials, and again, time is limited here today, so I'm not going to go through all of these, but again, I highly encourage you to go to these different websites to look at the detailed information that they gather, you know, clinical trials for FDA

review and after FDA approval, you know, what should you be doing. And this is a resource for family groups or researchers who might not be as familiar with this for them to use. And again, if you have any questions, feel free to contact me and I will get you to right person in the Office of Rare Disease Research.

Another thing that we're doing in the Office of Rare Disease is the Rare Disease Clinical Research Network, and this is something that we're part of the Public Law 107-280 to establish rare disease clinical research consortiums of excellence. In fact, in 2003, they funded seven consortia over time. Every five years, there is a new competition. In 2008, we funded nineteen. In 2013, we funded twenty-two. Over time, over thirty-one individual consortia have been established, two hundred and thirty-eight disorders have been looked at, and there have been over 40 thousand participants.

So, in 2018, where actually the applications came in in October of 2017, we had

our reviews in February, and we're right now in the process of deciding between eight different institutes who will be funded for the next cycle.

So, what these rare disease clinical consortiums -- what it's about is they are intended to advance the diagnosis, management, and treatment of rare disease with a focus on clinical trial readiness. And as I look at the definition of clinical trial readiness, to me, it's also newborn screening readiness. So, each RDC will promote highly collaborative, multi-site, patient-centric translational clinical research with the intent of addressing unmet clinical trial readiness needs.

So, how the network is set up, is we have multiple NIHICs that work together as partners. Each of these little honeycomb boxes is a consortium that exists right now, and a couple of these are looking at newborn screening. Jennifer Puck with the PID, the Primary Immune Deficiency Consortium, they're looking at newborn screening and one of the things that we have

written into the last RSA was to encourage people to follow up these babies who have been screened in newborn screening or work on developing something for newborn screening. Each one of these consortia consists of patient and advocacy groups and the patient advocacy groups have to be involved, as I say it, from soup to nuts in a meaningful manner. There are research and clinicians that are involved, and the NIH is involved. So, this is part of -- it's a U-54, so it's a cooperative agreement. So, everyone of the consortium has a science officer from the NIH assigned to it that helps oversee it, and it's a group of program officers from NIH that meets regularly and talks about these disorders.

The network is supported by a data coordinating center, and in the next round of the data coordinating center, what we're planning on doing is making the data that has been collected for the last fifteen years and will be collected in the future more readily available to public using appropriate safeguards for the data and for

the investigators and for the patients. We want to make this data that we're collecting more of a resource that's available for people to see and for scientists to use and have access to. So, that's one of our activities.

Another activity for drug development -- and this is something that, you know, is going on in parallel at the same time that you guys should be looking at developing new tests for newborn screening are our Therapeutics for Rare and Neglected Diseases and Bridging Interventional Development Gaps program, which really work on de-risking getting a clinical trial forward. So, you know, we have the Valley of Death, as we call it, to get from the basic investigator over to a startup company.

And so, the TRND Program works with groups who are trying to move from the lab to get to a clinical trial, and the Bridge Program does the same, and you will have the slides, and again, if you want any more information, the very last slide in this set has the contact people for this.

And, as you can see, or perhaps not see because the type is very small, it's partnering with these groups at various stages of the drug development, and then they pass off the studies to industry once industry is ready for it. And how that's done is the data that they are collecting is rigorous and strong and can be repeatable, and that's one of the things that we're really trying to focus on in the RDCRN to have strong data with strong data standards that will be attractive to move down the pipeline that will be useable if you need natural history studies for, you know, adding something to the RUSP. So, these are what these groups are doing. So, again, if you guys have any questions, I would be happy to answer them at the end. Thank you.

DR. BOCCHINI: Thank you very much, Tiina. We appreciate that, another great presentation. Now, we have Vanessa Boulanger. So, if operator, we could make sure her line is open, and let's see if we can get her slides up.

DR. RILEY: Hi, Dr. Boulanger. You

are on as a presenter, so you should be able to advance your slides.

MS. BOULANGER: Okay, perfect. Hi, everyone. Thank you very much. This is great. So, I'm the Director of Research and I oversee all the scientific and research work that NORD does, the National Organization for Rare Disorders, and I'm pleased to hop on the line today to share a bit about our registry program and our patient-centered research program. I think some slides are cut off a little bit. I'll start with a brief overview, introduction to NORD for those who are unfamiliar. I'll go through an overview of our registry program and some of the growth and impacts that we've seen since we launched. I'll talk through some of the registry partnerships that we've developed and our different models of engagement, and then I'll share with you some opportunities to engage in different research studies or data resources.

So, a brief introduction to NORD. NORD is an independent nonprofit that is leading

the fight to improve the lives of rare disease patients and families. So, 2019 marks NORD's 36th year as an organization dedicated to elevating the voice of the rare disease community. We're a truly independent 503(c)3 advocacy organization, so there is no industry on our board of directors or on any of our governance committees. We're fully funded by charitable donations, grants, philanthropy, membership dues, and by providing services.

Our overarching strategic priority areas that drive and align NORD's cross-cutting programs are innovation, development, and access, and this slide gives sense of where and how NORD's research work fits into the larger context of the organization. We have four programmatic areas: policy and advocacy, which works at both the federal and state level, relocation services program that we launched in 1987 that serves over 7,000 people annually, we have our education program, and part of their purview is that they put on our annual summit, which happens each

October in Washington, DC, and this year we have a new conference that we're putting on at the Patient and Family Conference, which is happening in June, so I'll share a little bit more about that later. And we also have our rare disease report database within the education department. And in the research department, we have three arms to the research that we do. We have research that we support, which is our registry program. We partner with folks to develop patient natural history studies. We have research that we help to fund through our research grants program, which this year is celebrating its 30th year, and we also have research that we conduct, which is original research and publications that NORD puts out.

So, to go a little bit more in depth about the IAMRARE Registry Program, this timeline shows the key milestones in the development of our program. So, after a multi-year, multi-stakeholder planning progress, we launched our first registry in 2014, and we've been fortunate

to have early and continued engagement with a committee of stakeholders, so folks from the NIH, FDA, community organizations, patients, researchers, and clinicians that really sort of formed the core committee that helped us design and develop our program to start, and then we've had continued engagement with those stakeholders throughout. And our intent was to build a platform -- a registry platform in a modular fashion -- to build a platform that was accessible to the rare disease -- the full rare disease community to keep the data ownership in the hands of the disease-specific communities, and then through partnership to build capacity and empower and support patient organizations become data stewards and data experts for their communities.

So, our platform is intended to collect data to understand the natural history of rare disease through patient-reported outcomes and patient experience data. We capture information on transitions in care, disease progression over time, heterogeneity of disease expression, and

really quality of life and lived experience.

So, the ultimate goal really is to collect data to advance discovery that saves lives, but our first goal is to collect high-quality in a way that's not burdensome to the patient. So, we really were intentional about how we developed our model so that it was easy to use and sort of reduced some of the research burden on the patient community.

So, as I mentioned, we launched in 2014 with five pilot groups. We launched and we tried and tested and refined our model, and then we were fortunate to receive a cooperative agreement from the FDA in 2015, which was really intended to help us scale up our model and to subsidize twenty new registry partners. Since then, we've seen steady growth and expansion, which I'll talk a bit more about, and I just want to note that this year, 2019, marks the five-year anniversary of the launch of our program.

So, for those who are less familiar with NORD's natural history study platform and

rare disease research program, I'll just give sort of a high-level overview. NORD provides the registry platform. It's a common infrastructure for longitudinal data collection. We have a core set of surveys to support cross-disease analysis so there is a common core set of surveys that are common and the same across the different registries that we host in our platform. And then we also allow for the flexibility to support custom disease-specific surveys. So, for those more nuance questions that are truly related to each condition, we also have the capacity to support those surveys as well. So, it's a tool to capture survey-based, patient-reported, and patient-experienced data in disease-specific registries across distinct rare disease communities. And then, NORD provides the programmatic support around the registry. So, we provide training, user guides, instruction guides, best practices, recommendations, guidelines. As I mentioned, we have a core question repository, a core survey set that we provide, we have templates

for consent and marketing. Also for the IRB, we have protocol templates, and then we have an IRB partnership with an independent IRB. And then, for our community, we really are focused on a rare disease registry community, so we have a portal through our registry system for the registry leaders to communicate with each other and share resources. We bring our leaders together one time a year in person so that, again, it's a nice like networking opportunity and a chance for resource sharing, and then throughout the year, we host webinars and educational videos, and we put out an end-of-the-year newsletter as well.

For those interested in learning more, I am happy to answer questions at the end of this presentation or, you know, through followup. But, we also do offer monthly demonstrations of our platform on the third Thursday of each month. So, if anyone is interested in seeing how the platform actually functions, I'm happy to help get you connected with a demonstration.

And I should say, NORD, as I

mentioned, provides the common infrastructure, the core surveys, and then the data elements for those core surveys are pulled from the GRDR, the Global Rare Disease Registry Repository, the promise standards, BRFSS. So, they are validated measures for capturing quality of life and other topic areas.

So, just a high-level overview of some of the partners that we have on our registry platform. So, we are up to thirty-four registry partnerships, and they are all in various stages of actively collecting data or development. And this is just an example set of questions. So, for example, for the TKU registry, the different sort of question sets that are captured within the registry are represented on this slide. So, about the participants, your sort of standard demographic data, we collect diagnosis information for the date and type of diagnosis, treatment information, you know, age at PKU diet, diet start and stop, medical food, adherence to diet, we collect medical histories, so, you know

vaccinations, physical function, activities, serious illness. We collect insurance information, so a better understanding who is on insurance, what type of insurance, and the medical costs associated with managing the condition. Education -- so whether or not educational assistance or services were needed, and then family history. Mood -- so the hospital anxiety and depression scale is captured in our registry, and then a maternal history, so pregnancy history and birth history and assessment.

And then for community, so we have our 2019 stats. So, from 2014 when we launched through the end of 2018, we've grown to 34 registry partnerships, we have over 8,500 users, and we've collected over 45,000 survey submissions. At this point, we have a nice mix of registries that are maturing that have 2-5 years' worth of data in addition to newer partnerships. So, there's a lot of cross-learning that happens in that sense as well for the more advanced registry clients that are kind of advising through

a peer/mentor type network of the registry clients that in the earlier phases of development.

So, these are just some of our early community successes that demonstrate the application and impact of the registry data. In November of this past year, 2018, a new mechanism was identified for SYNGAP-1 that was informed by the registry data collected by the Bridge the Gap Foundation. There was a paper published in *Nature* and it reflects the link between patient-reported registry data and lab-based research. So, there were reports in the registry of children not feeling pain. For example, a child broken finger for multiple days who wasn't complaining about it or a child that kept putting their hand in the dog's mouth with very little reaction or response. And so, that patient-reported experience data really led to new pathways for exploration in mouse models, which then led to the identification of a new mechanism for SYNGAP-1.

In our Fibrous Dysplasia Foundation, they held a competitive application process for

researcher projects who work with the FDF registry data, so they ended up receiving six proposals and the institutions we selected, you know, Boston Children's Hospital, University of California in San Francisco, and Harvard Medical School among others. And then our registry community members are getting invited to different meetings and forums to present as experts on the registry data. So, Platelet Disorder Support Association was specifically asked by FDA to present on their registry experience and the registry data at a public workshop on key ways to effectively engage with patient communities. So, organizations are starting to seek out our registry partners as resources and experts in this space.

So, I'll just chat through a few of our new partnership models. As I mentioned, we really started out with our model -- our original model for the registry was when NORD partnered with Patient Advocacy Organization. It was a two-way partnership and really again, the intent was to help develop the capacity of the Patient

Advocacy Organization to run and manage their registry, you know, owner data, be good stewards of the data, and then NORD was the platform provider, but also an educational resource for the community. And so, just in this last year, we've actually expanded our model to a few additional types of partnerships. So, one new model is that we now can include registries for communities that do not have a formalized 501(c)3 foundation, so NORD can sort of set up the registry sponsor, the program manager, and the idea over time will be to transition ownership of the registry back to patient community once there is a formalized organization. But, as an initial step, we decided to sort of put this out as a model toward reducing barriers to registry development and participation and as a way for NORD to help elevate communities that don't yet have an organization to advocate on their behalf.

Another model that we recently put out in the second half of last year was the ability to run a substudy, so where there's a

primary registry on our platform, a third-party researcher or industry partner can partner with NORD and the Patient Advocacy Organization to develop sort of like a nested study. So, it's particularly important, as we're all well aware, with small patient population, is to keep the communities together, to reduce redundant and duplicative registry efforts and data silos, and this is really toward preserving the power of the data, but also for communication purposes and reducing confusion and research burden in the community, which ultimately leads to reducing delays in scientific progress.

So, this substudy feature allows a third-party researcher to come in, run a nested study on the IAMRARE platform. The study can be time bound or funding bound. It doesn't have to be an enduring resource like the primary registry is. And so, it sort of pathways for partnership. And I still have to say the substudy feature can have its own eligibility criteria and its own consent mechanism as well. So, it's sort of a

separate study that is related to the primary registry.

And then, our final model of partnership this year that we recently launched is that we're piloting a partnership with Treo Health as our analytics partner with the intent really to liberate the data from our registry. So, we are working with our registry community to develop posters for presentation at conferences, manuscripts for peer review, publications, and we're putting together a rare disease book, which will speak to some of the patient's stories, as well as share some of the aggregated data from a subset of our registry clients. So, really just kind of getting the data out there and the findings out there so that it's usable and actionable and liberating the data from the registry.

So, a few opportunities to engage. We are always open to exploring different registry partnerships. We have a collaboration with all of our registry partners, so if there is any interest

in accessing the data on any of the registries that we host on our platform, we'd be happy to make that connection with the community organizations and to help facilitate those conversations. And then as research project collaborators, so either on sort of original research projects or on disease-specific projects, we can also help to facilitate those connections as well. We are also always looking for high-quality speakers at NORD events, so if you have any interest in that, I'm open to passing your information along. We will be recruiting for additional members of NORD Scientific and Medical Advisory Committee in the next few months. So, if anyone is interested in that, please do reach out to me. And then, we're always looking for experts to review or write rare disease reports for our database.

NORD and the FDA have an MOU to facilitate patient listening sessions. The FDA just in the last two weeks put out their Request to Connect portal, it's live. So, this portal is

an opportunity for patients and caregivers to submit a question or to request a meeting with the FDA, but it's also a way for rare disease communities to request a listening session that are co-hosted and co-facilitated by NORD and the FDA.

And then, as I mentioned early on in the presentation, we do have two events this year. So, we have our new Living Rare, Living Stronger Patient and Family conference in June in Houston, which will be followed by our Rare Impact Awards and then we also have our annual Rare Summit, which is in October in Washington, DC. So, it would be wonderful to see folks there.

And then, if you have questions, I'm always available. I'm happy to chat further about the specifics of our program or our research work in general or just, you know, connect you with the right folks at NORD if the research department is not the right party. Thank you so much for your time today and allowing me to contribute to the conversation.

DR. BOCCHINI: All right. Thank you very much. I think we've had three great presentations, and now we are ready for Q&A and committee discussion. So, once again, I am asking the operator to open the lines of committee members and organizations representatives. Committee members again will go first, and then organizational representatives will follow. Just a reminder, please use the "raise hand" feature in Adobe Connect when wanting to make comments or asking questions. And when speaking, please state your name so that we have proper recording.

So, let's go ahead. I guess Tiina -- a lot of people are cueing up. In addition to the website that you have that provides advise to advocacy groups for setting up a registry, do you also have individuals who help support them if they run into difficulties or have questions?

DR. URV: You can always contact the Office of Rare Disease, and we will hook you up with whoever needs to be contacted. So, we're happy to help anytime.

DR. BOCCHINI: Okay. Perfect.

Next, we have Cindy Powell.

DR. POWELL: Hi. This is Cindy Powell. Thank you very much for your presentations. I think there is so much valuable information that we can get from patient-entered or caregiver-entered data. However, I worry sometimes that less economically advantaged patients and families will be able to participate in things like that. So, I'm just wondering if anyone has any thoughts about how that limitation might be overcome.

MR. O'LEARY: So, this is James O'Leary. I think, yeah. That is a huge problem, and it's definitely a problem across, you know, community-led registries, you know, registries in academic institutions, and also in, you know, incredibly well-funded industry trials. So, this is kind of an across-the-board problem. You know, one of the big things that I've seen that has been effective, especially with community-led registries, is partnerships with organizations

that are able to be more on the ground. And that includes some technology fixes like having iPads with registry surveys available in waiting rooms at clinics. But, it's more of a kind of on-the-ground, you know, people-based approach, which is making sure that you're partnering with Medicare navigators or community liaisons or, you know, promotore models, and that is expensive, and so a lot of people do cut corners on that, and one of the -- we need better solutions in that space.

DR. POWELL: Yeah, I agree with that. We need to -- that is one area we really need to reach out and work in.

MS. BOULANGER: Yeah, this is Vanessa from NORD. Again, I do echo James' comment, and it is certainly something that we need to be very intentional about so that we are ensuring that our samples are representative, because, of course, diversity in research and representative sampling defines the science but also better medicine for everyone.

In our model, as I mentioned, the

registries really sit with the Patient Advocacy Organization, so there is a lot of sort of one-to-one outreach with the communities, and what we are finding is that we're actually undergoing an assessment across our registries now, because some of the patient population are quite skewed in terms of racial distribution and also socioeconomic status. So, we're doing sort of an assessment now to see who on our platform has actually done well at recruiting a representative sample and what we can learn kind of as best practices from across our communities.

But, what we are finding is that folks who are really on the ground, like, who host community events or host like a conference or, you know, exactly what James said, can sort of bring the registry to the community, that seems to be working well, which is, of course, a big lift in terms of resources, you know, human and time resources and also financial.

DR. BOCCHINI: Sue Berry is next.

DR. BERRY: Hi. Can you hear me?

DR. BOCCHINI: Yes, we can, we can.

DR. BERRY: Thanks. I just have to make sure I turned my mute off. So, this is -- all these -- this is a very exciting group of presentations and really speaks to some of the long-term needs we have. But, a couple things I just wanted to bring up and ask a little bit more about. One of them is the focus totally understandable on patient-centered and patient-centered outcomes, but there is an equally important and necessary contribution that has to come from clinicians and other knowledgeable people and that has been a very difficult task to accomplish. All of these registries are really compromised in the long term by degrees of sustainability and by the feasibility of data entry, and I'm wondering if people could comment a little bit more on things like AI and other strategies for data mining and electronic records, for example, which has been sort of kind of a pipe dream, that we really haven't gotten far with.

And then, sort of mismatch of

resources, it seems like that have been appropriated for other conditions as opposed to rare diseases. Someone, I think it was Tiina, that highlighted the commonality to how often rare diseases are seen as health impacts, but we spend a bazillion dollars on cancer and not very much on this collective group. I'm just thinking a fantastic presentation I saw by one of our oncologists for a whole clinical trials network that they have set up for first time in people on trials for children with cancer, and I'm so happy that have that, but we've got nothing like that.

So, I guess what I'd say is feasibility, sustainability, engagement of clinicians, and resources. Those are the questions that I see as needing to be able to address as we talk about all of this. So, I leave that for comments from the committee -- from the panel. Thank you. And thank you for the presentation. It was very good to hear all of this at once.

DR. URV: This is Tiina. One of the

things that we are trying to focus on in the Office of Rare Disease Research is that make people aware that rare diseases as a whole are not so rare and really emphasize that, and that's a message we're really trying to get out, and I think the more we get that message out, the more people might start thinking about it as a whole like cancer as opposed to individual group. And I think sometimes that it might be important that the individual with rare disease group think about working together instead of having 7,000 registries, you know, working together even partnering to build a platform to have their own -- - to have the individual registries there together -- their own individual instance, but, you know, the base that they can all pitch in together and work on. I way that might be a way to go, and I think that's a little bit what we're doing with some of the clinical research in the RDCRN in that, you know, let's work together, let's build a common platform that can be shared, and let's leverage that. And I think until we start doing

that, you know, we're never going to be able to fund anything, because we're going one by one by one, and I think that's a very challenging way to approach research.

MR. O'LEARY: This is James. On the clinical data front, things are challenging. It's -- if you look at things like [inaudible] as examples, you know, where there is investment and learning healthcare system models, you know, really at the healthcare system level, you know, how to implement platforms on top of their electronic medical records and internal processes for making that data available, things are progressing, albeit slowly. But, you know, on the artificial intelligence front and data mining, it's just incredibly challenging because even though we are consolidating the EMR vendors, for example, the majority of health systems might be on EPIC, but they're on 300 different versions of epic. And so, it's incredibly hard to build anything that can do this consistently across structured and non-structured data.

I think that we are getting there. But, more often what you see from examples, like I mentioned earlier, is that you just need to build a whole 'nother system on top of what is already there to make it happen.

Disease groups that have partnered with health systems to do this in collaboration, I think are also very interesting examples. So, like Parent Project Muscular Dystrophy is a great example. You know, they really wanted to do their patient-reported data that that worked very well with the system, but they wanted to collect clinical data. A lot of those groups, though, lined up essentially funding clinical sites and then putting requirements on for entering of structured data and then coordinating those two data sources together, which is not -- everybody can't do that obviously. It's very expensive.

MS. BOULANGER: This is Vanessa. I just -- I won't pretend to be a technology or AI expert, but I do just want to sort of put a thought out there that if we are mining skewed

samples or nonrepresentative samples, I wonder if we need to be cautious about who the models for AI will be developed around or off of.

DR. BOCCHINI: Other comments from the panel? We have Sue Berry.

DR. BERRY: Thanks so much. I wanted to comment on behalf of SIMD and Shawn can't be on today because he's on another -- has another webinar responsibility. So, I wanted to throw in a pitch for that organization, which is Shawn is spearheading an effort on the part of the SIMD to try and bring together the clinicians that represent the metabolic disease care community to try and think about how we can do a more comprehensive sharing of information and gathering of data across metabolic conditions using the SIMD as a point of origin and with the idea that clinicians may be able to help facilitate some of this conversation. The same challenges will still apply for SIMD as it has for other groups, but just a commitment on the part of the metabolic disease clinician and research community, that we

want to make that happen and are going to try and contribute to the process by having an organizational effort on that part.

DR. URV: So, Sue, this is Tiina. Some of the NIH Institutes and FDA also have natural history initiatives that are out on the street over the past few years -- I think NICHD did as well -- to really help groups come together and start collecting natural history data.

DR. BERRY: This is Sue. Tiina, that's fantastic, and I think we all kind of keep our ear to the ground about those options. I think we all do suffer to some degree from the one-off, you know, if you do it with one group, then you do another group, and finding some more concerted ways to bring the rare disease community together more generally so that we can leverage some of that people power -- it's going to be really necessary, without losing the need for each individual condition to be able to define its own history and so on. So, you know, if we're going to develop a children's oncology group for rare

diseases, we could go a long way.

DR. URV: That would be cool

DR. BOCCHINI: All right. Now, I have Cindy Powell.

DR. POWELL: This is Cindy Powell again. One of the challenges is, you know, because of the rarity of most of these diseases, if you have a very enthusiastic family, they are likely to sign up, you know, into more than one registry if there is one or participate in various tests, and I think, Vanessa, you may have mentioned this on one of your slides, but any thoughts about how to preserve patient confidentiality and yet make sure there's not duplicate cases of patients who are in more than one registry?

DR. BOULANGER: Yeah, this is Vanessa. That's a great question. And in terms of interoperability, it's a challenge. On our platform, we can track, you know, each participant is given a unique participant ID, so we can track across our registries, but it's a fairly limited

tool. So, it's certainly something that we think about because we would like, of course, our data to be more easily interoperable with other systems or shareable with other systems per the terms of consent as folks are contributing their data. But, I don't know if that answers your question, but it's certainly something that we're thinking about internally, and we've really only addressed it within our community.

DR. POWELL: Yeah, thank you. This is Cindy again. So, you know, I certainly would advocate for the need for a GUID for many different reasons, you know, for just basic needs in newborn screening where, you know, children are often given the same name when they're born on the same day in the same hospital, and it's really a challenge, and it may just be part of our healthcare system with the difficulty in this and a lot of pushback over the years in, you know, people worrying about loss of confidentiality and the government having information. But, I do think that's an area that needs to be explored

further. Thank you.

DR. BOCCHINI: All right. We have an internet comment from Joe Schneider that Catharine will read.

DR. RILEY: Okay. Thank you. This is Catharine Riley, and I'm reading in a comment from Joe Schneider, who is a member of the Followup and Treatment Workgroup in response to the discussion on registries. He said in his experience as a Chief Medical Officer in a large healthcare system, there was no way they could financially support electronic connections to all of the multiple registries in addition to many of the other registries that other large organizations require. So, it's true for both the hospitals and physician practices that he has worked in. Clinicians who dealt with these registries were frustrated that they had to do everything manually. So, the many-to-many connection model that we currently use for registries is inefficient if there is a desire to populate these rare diseases and newborn screening

registries with clinical data from hospital, physician offices and other clinical organizations, then there needs to be single place to which these organizations can report and the single place then can send the information into the dual registry. The American Academy of Pediatrics is in the initial phases of considering this "report once, distribute to many" model. I strongly encourage discussions to find a way to get closer to this approach regardless of who is the single receiving group. Thank you.

DR. BOCCHINI: All right. So, we have nobody else requesting to speak. Nope, we do? Oh, Melissa Parisi. We're going to give you the last question or comment.

DR. PARISI: Hi. This is Melissa Parisi. It's an awfully big burden to be the last speaker, but I wanted to make a couple comments. We -- we're just -- there was a Muscular Dystrophy Coordinating Committee meeting, also a FACA Committee that met on Wednesday, and I know there is some overlap with some of you who are on this

call. But, I mean, a lot of the same themes were emerging because there was a special emphasis in discussing registries. And I quickly want to thank our three presenters for what they had to say.

I would like to echo some of the comments that have been made, and the importance of really trying to have some sort of global unique identifier that can link data on the same individual from disparate sources, because the redundancy that can sometimes exist for enthusiastic families who may want to participate in more than one registry can be very challenging.

Sue, I also like your idea of trying to have a more concerted effort for natural history studies. At NICHD, we do have a program announcement with specified review that is for specifically newborn screening conditions and natural history studies. But, you know, those individual studies, when they do get funded, we don't necessarily have a good way to coordinate all the data in a useful manner, aside from some

of the other resources that have been created, such as the Newborn Screening Translational Research Network.

And then, finally, with regard to Dr. Schneider's last comment, you know, I think that's the Holy Grail, really, is being able to combine data resources, not only patient-reported data, but clinical data through the EHRs and additional data that may be collected through advocacy groups and other mechanisms. And, I was really intrigued at the Muscular Dystrophy Coordinating Committee Meeting on Wednesday by the presentation by Parent Project MD, trying to really develop a model -- a template for combining these data sources in a HIPAA-compliant and most useful way. So, you know, it's early days, and it's something we've been talking, it seems, for at least five years. But, I'm optimistic and hopeful that we will have tackled some of these issues that are largely kind of IT-related and administrative in just a coordination effort, which is really overwhelming, but it's really essential for the field to move

forward.

DR. BOCCHINI: All right. Thank you for those comments. I think that this has really begun an important discussion for us, and I certainly want to keep in touch with our three presenters today and their organizations. I think has been a really excellent panel and excellent comments. So, I think we can move this along and I really look forward to April when we begin to look at some individual registries and perhaps help bring these all together in some form of recommendations or ways that we, as our committee with the work that we do, could potentially utilize the information that might be available through these registries as well as maybe states can for long-term followup. So, again I want to thank our panelists. I think this has been a great discussion. Thank you.

So, the next item is New Topics. This is open to committee members and org reps. Are there any new topics that have come to mind that you wish the committee to be considering at

the present time? Bob Ostrander.

DR. OSTRANDER: Bob Ostrander: Yeah, hi. I don't know if this is in your purview or not, but I kind of think that it is. And that is, whether we should be talking about or thinking about the direct-to-consumer screening that's being done outside of the RUSP process and the state panels. The whole direct-to-consumer issue has obviously become a big concern for everybody and, you know, at least one of the companies, the SEM 4 or whatnot that [inaudible] will do a newborn screening panel with the doctor's order provided by someone that they contract with or have without actually even conferring with the parent at all. You know, you just basically, you send for the kit, they send you a questionnaire, you swab your baby, and then a doctor reviews the questionnaire and enters the order to comply with the FDA. And again, I'm not sure how that all fits, but I think it's got the potential to cause harm and muddy the waters and open up Pandora's box. You know, it is a heritable disease issue of

newborns and children, and it may be something that we should talk about its implications and potential policy pieces. I've been working with this both in the adult and newborn and children's side with the AAFP about developing a policy statement about what the sort of minimum requirements should be for these sort of tests to be done in terms of, you know, just run of the mill standard basic ethics, informed consent, interactive pre-test counseling, interactive post-test counseling, and so on. But, you know, it's happening out there kind of around us, and I guess I kind of think that we should at least -- it should be on our radar and we should have thought about it and talk about it.

DR. BOCCHINI: All right. Thank you, Bob. That is something that we should really begin to think about and see whether there would be a potential role for us. Mei Baker

DR. BAKER: Yeah, hi. This is Mei. The one thing that comes to my mind is the carrier screening. When I say that, it's not just saying

well, in newborn sometimes we aren't intending to identify some carrier. My talking is actually intentionally to do in adults, like, if we talk about newborn screening as a system, can we have a more connection with OB/GYN groups, you know, so we have better understanding. If it just applies to newborn screening, is it justified to encourage to do the carrier screening for this group of disorders, because, you know, when we talk about whole genome and this today, the timing still -- it takes a long time to decide other issues, and I was thinking is we have newborn screening, we have followup, we have a clinician involved. On the downstream, [inaudible] is it time we start thinking of upstream and link so you could talk about [inaudible] medicine, things that are kind of into this, because then we'll be more targeted and I think partially will help be of value because you have this genetic information. I think it's something I would be interested in seeing this happen.

DR. BOCCHINI: Thank you. Mei. We'll

keep that on the books as well. Thank you.

DR. FREEDENBERG: Hi, this is Debbie Freedenberg, and I just wanted to echo the previous concern about DTC or direct-to-consumer testing around newborn screening, because it is becoming a larger concern in which some of its being marketed as supplemental screening, but some of it is being marketed as replacing state-based newborn screening. And so, I think it is something that should be on our radar as well.

DR. BOCCHINI: Thank you. Okay. I see no other hands up. So, I want to thank everybody for their participation in this meeting. As you know, this is a truncated meeting, which had to be rescheduled because of the issues surrounding the government shutdown. But, I do I think it also puts us closer to the next meeting, which is going to make everybody at HRSA work harder. But, I think that in spite of that, this has really been a good meeting, well organized, and I think we got a lot of information, and it's clear that we are making progress with a number of

the projects that we have begun, and so I really look forward to the next few meetings to see how these all work out.

Remember, the next meeting is going to be April 23rd and April 24th. This is an in-person meeting at the HRSA headquarters, and it will be available by webcast as well.

So, again, thanks to HRSA, thanks for everybody who worked to organize this, and thank all of the speakers and participants. We'll look to seeing you again at the next meeting. So, thank you. We appreciate your time and your efforts for newborn screening. That will conclude the meeting. Thank you.

[Whereupon the webinar was concluded.]

[Off the record at 2:09 pm]