The Advisory Committee on Heritable Disorders in Newborns and Children

HRSA Meeting

Washington, D.C.

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P R O C E E D I N G S

DR. JOSEPH BOCCHINI: All right. Good morning, everyone. I'd like to welcome you to the Advisory Committee on Heritable Disorders in

Newborns and Children, our May 2017 meeting.

The first order of business for our meeting is for us to take roll call, so I will go in alphabetical order. Don Bailey?

DR. DON BAILEY: Here.

DR. JOSEPH BOCCHINI: Mei Baker?

(No audible response)

DR. JOSEPH BOCCHINI: I'm here. Carla Cuthbert?

DR. CARLA CUTHBERT: Here.

DR. JOSEPH BOCCHINI: Jeff Brasco -- Brosco?

DR. JEFFREY BROSCO: Here.

DR. JOSEPH BOCCHINI: Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH BOCCHINI: Fred Lorey, who is here by webcast?

DR. FRED LOREY: I'm here.

DR. JOSEPH BOCCHINI: Thank you. Michael Lu?

DR. MICHAEL LU: Here.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETRICH MATERN: Here.

DR. JOSEPH BOCCHINI: Stephen McDonough, who is also here by webcast?

DR. STEPHEN MCDONOUGH: Here.

DR. JOSEPH BOCCHINI: Kamila Mistry?

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH BOCCHINI: And Melissa Parisi, who is taking place for Dr. Diana Bianchi, who will be here later this morning?

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Beth Tarini?

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: Cathy Wicklund?

MS. CATHERINE WICKLUND: Here.

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

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: For organizational representatives in attendance, American Academy of Family Physicians, Robert Ostrander?

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: American Academy of Pediatrics, Robert Saul, who is here by webcast?

DR. ROBERT SAUL: Here.

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

DR. MICHAEL WATSON: Here.

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

(No audible response)

DR. JOSEPH BOCCHINI: Association of Maternal and Child Health Programs, Kate Tullis?

DR. KATE TULLIS: Here.

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

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Association of State and Territorial Health Officials, Chris Kus, who's here by webcast?

DR. CHRISTOPHER KUS: Here.

DR. JOSEPH BOCCHINI: Department of

Defense, Adam Kanis?

DR. ADAM KANIS: Here.

DR. JOSEPH BOCCHINI: Genetic Alliance, Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. JOSEPH BOCCHINI: March of Dime -- March of Dimes, Siobhan Dolan?

DR. SIOBHAN DOLAN: Here.

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

MS. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: And Society of Inherited Metabolic Disorders, Carol Greene?

(No audible response)

DR. JOSEPH BOCCHINI: Oh, Mei Baker is here now on the phone. Mei?

(No audible response)

(Off-mic speaking)

DR. JOSEPH BOCCHINI: Oh, she's -- Oh, okay. She just called in. She's on her way. Okay. All right. All right.

(Laughter)

(Off-mic speaking)

FEMALE SPEAKER: Virtual waiting room.

DR. JOSEPH BOCCHINI: Virtual waiting room, okay. All right.

So, at this -- I'd like to introduce two organizational representatives in more detail. For March of Dimes, Siobhan Dolan is joining us in person today. Dr. Dolan is Professor and Vice Chair for Research in the Department of Obstetrics and Gynecology and Women's Health at Albert Einstein College of Medicine at Montefiore Medical Center in the Bronx.

Trained as an obstetrician/gynecologist and clinical geneticist, Dr. Dolan maintains her clinical practice in the Division of Reproductive and Medical Genetics. She also serves as a medical advisor to March of Dimes, where she works to improve the health of babies by preventing birth defects, pre-term birth, and infant mortality. Dr. Dolan's research interests focus on the integration of genetics into maternal/child health.

And our new ACOG representative is Dr. Britton Rink. She is joining us by webcast. Dr. Rink is Director of Perinatal Genetics at the Mount Carmel Health System in Columbus, Ohio. She is dual board certified in maternal-fetal medicine and genetics and maintains a practice in both specialties.

Dr. Rink is the incoming chair to the ACOG Committee on Genetics after serving on the Committee for several years and most recently as its vice chair. She has particular interest in prenatal diagnosis, advanced fetal imaging, fetal therapy, and recurrent pregnancy loss. Dr. Rink has authored several books and chapters and publications on genetic testing and screening and pregnancy.

We'd like to welcome both of these two representatives to the organizational representative group. So, thank you for being -- joining us.

The next item on the agenda is a vote on the February minutes. The minutes have been

distributed in the agenda book. We've received some typographical changes from Dr. Matern and a couple of questions for clarification. Are there any other corrections or changes that the Committee would like to bring forward related to the minutes?

(No audible response)

DR. JOSEPH BOCCHINI: If not, then I need a motion to accept them, as submitted, with the changes suggested by Dr. Matern.

DR. DON BAILEY: So moved.

DR. JOSEPH BOCCHINI: Thank you, Dr. Bailey. A second?

FEMALE SPEAKER: Second.

DR. JOSEPH BOCCHINI: All right. So, now we need a formal vote to accept the minutes. So, vote either "yes," "no," or "abstain." Don Bailey?

DR. DON BAILEY: Yes.

DR. JOSEPH BOCCHINI: Let's see, Mei is still in the virtual room? Okay. I vote "yes." Carla Cuthbert?

DR. CARLA CUTHBERT: Yes.

DR. JOSEPH BOCCHINI: Jeff Brosco?

DR. JEFFREY BROSCO: Yes.

DR. JOSEPH BOCCHINI: Kellie Kelm?

DR. KELLIE KELM: Yes.

DR. JOSEPH BOCCHINI: Fred Lorey?

(No audible response)

DR. JOSEPH BOCCHINI: Fred, are you on mute?

DR. FRED LOREY: Yes. Can you hear me?

DR. JOSEPH BOCCHINI: Yeah, we can hear you now. Okay. Michael Lu?

DR. MICHAEL LU: Yes.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETRICH MATERN: Yes.

DR. JOSEPH BOCCHINI: Steve McDonough?

DR. STEPHEN MCDONOUGH: Yes.

DR. JOSEPH BOCCHINI: Kamila Mistry?

DR. KAMILA MISTRY: Yes.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Yes.

DR. JOSEPH BOCCHINI: Melissa Parisi?

DR. MELISSA PARISI: Yes.

DR. JOSEPH BOCCHINI: Beth Tarini?

DR. BETH TARINI: Yes.

DR. JOSEPH BOCCHINI: And Cathy Wicklund?

MS. CATHERINE WICKLUND: Yes.

DR. JOSEPH BOCCHINI: Okay. The minutes are approved.

So, next slide. So, just to give you an overview of today's agenda: The -- Oh, the next meetings are listed here -- thank you -- the next meeting, August 03rd and 04th, and then the final meeting of the year, November 08th and 09th. But as you know, the meeting dates have been set all the way through 2020 so that you could put the meetings on your calendar, and they're available on the Committee's website.

Next slide. So, for today, the -- we're going to begin with further discussion related to laboratory result ranges and cutoffs. We're going to have a presentation on interactive web-based tools, the R4S and CLIR programs. We're going to have a presentation on the CDC's Quality

Assurance and Quality Control program, and we're going to hear some examples from states on how cutoffs are established --

(Audio interference)

(Off-mic speaking)

DR. JOSEPH BOCCHINI: -- how cutoffs are established, updated, and how out-of-range and borderline results are communicated.

Next slide. We will then take up the spinal muscular atrophy condition nomination. The Nomination Prioritization Workgroup has evaluated the nomination packet and will be presenting information related to that, and the Committee will discuss that and make a decision about whether to move the nomination to the Evidence-Based Review Committee.

We will also have a final report on the medical -- medical foods for inborn errors of metabolism, with the Committee's vote to accept that report.

Next slide. On Friday, we will have some discussion and presentations on implementation of

the Critical Congenital Heart Disease Screening program, and we'll have condition review updates on the consumer-friendly summaries of previous evidence reviews -- evidence-based review process, and an update on methods to assess costs for -- of newborn screening.

And then, this afternoon, our workgroups -- our three workgroups will be meeting, and we'll have reports from those three workgroups tomorrow, towards the end of the meeting, and -- and hear what the progress is on the -- on what they are working on.

Next slide. Now I'm going to turn this over to our acting designated federal official, Catharine Riley, but as you've noticed, we're missing our -- our federal -- designated federal official, Debi Sarkar, and it's because she's on maternity leave. She has a healthy baby boy, and mom and baby are doing well, and we expect her back in August.

So, Dr. Catharine Riley is standing in for her today. She is the lead for Newborn

Screening in the Genetic Services Branch at HRSA, and she will be serving as the designated federal official for our committee meeting today and tomorrow. So, Catharine?

DR. CATHARINE RILEY: Good morning. As Dr. Bocchini said, my name is Catharine Riley. I'll be serving as the designated federal official. On behalf of HRSA, I would like to welcome the Committee members, organizational representatives, our presenters today, and members of the public who have joined us, both here in person and on the webcast. Welcome and good morning.

The Advisory Committee on Heritable Disorders in Newborns and Children provides advice and recommendations to the Secretary of Health and Human Services, and the Committee's legislative authority is found in the Newborn Screening Saves Lives Reauthorization Act. This legislation established the Committee and provides the duties and scope of work for the Committee. However, all Committee activities are

governed by the Federal Advisory Committee Act, or FACA, which sets the standards for establishment, utilization, and management of all federal advisory committees. As such, I'd like to remind the Committee members: You are subject to the rules and regulations for special government employees.

Next slide, please. So, I'd like to go over just a few standard reminders for the Committee. I want to remind the Committee members that as a Committee member, we are advisory to the Secretary of Health and Human Services, not the Congress. For anyone associated with the Committee or due to your membership on the Committee, if you receive inquiries about the Committee, please let Dr. Bocchini and myself know prior to committing to any interviews or discussions.

I also must remind Committee members that you must recuse yourself from participation in all particular matters likely to affect the financial interests of any organization in 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.

Next slide, please. 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 have been published in the Federal Register or announced in the meeting today. For this meeting, in the Federal Register notice, we indicated there would be public comment period, and that will happen today, from 11:30 to 12:00 p.m. We also welcome written statements. Committee members are given copies of all written statements that are submitted.

Any further public participation will be solely at the discretion of the chair and myself,

as the designated federal official. Public participants may ask questions of Committee members, presenters, or other participants only when prior approval of the chair or the DFO is received.

At this point, do any of the Committee members or organizational representatives have any questions?

(No audible response)

DR. CATHARINE RILEY: Any questions from those on the phone?

(No audible response)

DR. CATHARINE RILEY: Okay. Next slide, please. So, this is just some housekeeping for those who are here in person with us at HRSA headquarters. So, visitors only have access to the fifth floor of the building, which is the floor that we're currently on. We're in the pavilion. The cafeteria is just across the way here. Restrooms are in the corners there, across -- across the pavilion, and then the meeting rooms, where the workers will be meeting this

afternoon. All other areas of the facility are restricted and require an escort by a HRSA staff member. There's no exceptions to this.

If you need to leave and reenter, you will be required to go through security screening again and will require an escort to meet you at the security checkpoint, like you -- like you did this morning. For your convenience, after the lunch break, we will have escorts there. If people need to leave for lunch and come back, we'll have escorts from 12:45 to 1:00. If you need reentry for other reasons, please notify one of the HRSA staff members or those at the registration table so we can assist you.

Just a reminder for Committee and organizational representatives: If you have a question or comment, please raise your hand. Dr. Bocchini will call on members in order. Dr. Bocchini will call on Committee members first during the discussion and then organizational representatives. Please state your name before your question or comment so that attendees, both

in person and on the webcast, can know who is speaking, and also so we can accurately record who is speaking. You might see me raise this little thing here in case -- if people forget.

So, for Committee members and organizational reps, please speak into your microphones. As you can see, when the red light's on, the microphone is active, and when you're not speaking, please deactivate the microphone. For the Committee members and organizational representatives on the phone with us today, please keep your lines on mute until you'd like to provide a comment or ask a question.

For our presenters today: We -- we do have a full agenda today and look forward to hearing from all of you, so please keep your presentations to the time allotted, so we can get through all of the agenda items.

For those joining us via the webcast today, welcome. If you experience any technical difficulties, there is a help desk number at the bottom of your screen to call.

So, I'm looking forward to a productive meeting, and with that, I will turn it back over to the chair, Dr. Bocchini.

DR. JOSEPH BOCCHINI: Thank you, Catharine. So, we're going to begin now with a discussion related to cutoffs and setting the -- for -- and laboratory testing, and for this first presentation, Dr. Dieter Matern will recuse himself from -- from this portion of the -- the meeting.

As you know, we began, at our last meeting, discussing cutoffs and how laboratories set ranges and update those ranges, and we had three excellent presentations. Led to a discussion from the Committee about what the Committee felt was needed to be heard related to this as we begin to make decisions about how to approach potential issues related to setting cutoffs, ranges, and, very importantly, how families and providers are given information related to laboratory results that are near the cutoff range -- end of the cutoff range. And so,

we based the -- the presentations today on the feedback from -- from the Committee and -- and what came from the discussion.

So, the second set of presentations today will be the second part of the -- of the -- of the presentations. Further work will be done, and then we'll have a third set of presentations and, perhaps, some recommendations for one or more of our standing workgroups to help discuss and determine next steps.

So, in addition to the -- the discussion related to what the Committee wanted to hear, there also was a discussion about the development of a survey to determine what states might be doing at the present time related to these -- these issues. And the Association of Public Health Laboratories is putting together a survey for states, collecting information from their programs regarding their practices on establishing and evaluating and updating cutoffs, as well as the utility of case definitions for each condition. So, we will be hearing from APHL

when that survey is completed, and -- and the likelihood is that that may be available to us in -- in August. We appreciate the APHL working in this area.

So, the first of our presentations this morning is from Dr. Piero Rinaldo. Dr. Rinaldo is traveling, but he's made himself available by -- by phone to give this presentation this morning. We really appreciate that.

Dr. Rinaldo is a pediatrician, MD, PhD, and Professor of Laboratory Medicine at the Mayo Clinic. He currently serves as Chair of the Division of -- of Laboratory Genetics and Director of the Biochemical Genetics Laboratory in the Department of Laboratory Medicine and Pathology at the Mayo Clinic. Dr. Rinaldo has focused his research on clinical, biochemical, and molecular characterizations of newly discovered metabolic disorders, as well as clinical applications of tandem mass spectrometry.

So, Piero, are you on the --

DR. PIERO RINALDO: Yep.

DR. JOSEPH BOCCHINI: -- line and ready to go?

DR. PIERO RINALDO: I am, and --

DR. JOSEPH BOCCHINI: All right.

DR. PIERO RINALDO: -- I hope -- I hope you can hear me well. So --

DR. JOSEPH BOCCHINI: We can. We can hear you, and so go right ahead. Thank you.

DR. PIERO RINALDO: Okay. I just want to clarify that, actually, the chair of the division is Dr. Matern, who is my boss, basically. Anyway.

Okay, I was asked to give you -- First of all, thank you for the opportunity to give you an -- an update on the work we have been doing now for the last several years. And some of you may have heard, and probably many times, these two acronym, R4S and CLIR, but some may have not, and so we'll try to give you a little bit of perspective.

So, if I can have the next slide? We -- I received specific guidance from the Committee

about the things that you would like to hear about, and as you can see, at least in here, it -- - what they are, what they are used for, and also, increasingly, people ask about what the differences are between these two system. There was also a question about who can access these web-based systems and how they do that, and, finally, how they can be used in the context of setting cutoffs or establishing algorithms. And I have to warn you that you may found my answer or my response a bit unexpected.

This is, again -- Next slide, please -- is an outline -- again, the background of the two system, and then I go a little bit in details about what are the differences with a comparison between R4S and CLIR in term of differences, access, utilization, and examples of performance.

If I can have the next slide. This slide was title about R4S. It's a slide I've been using now for quite some -- few years. In fact, this all started in 2004, and we are certainly -- I am very fond and grateful for the opportunity given

by HRSA. When they founded the Regional Genetics Collaborative Programs, this was recognized as one of the priority projects, and, really, the concept was: How can we make different programs, different states, work together?

As you can see on top, we started with seven states, and that has grown quite a bit. The R4S was funded by HRSA for two cycles, from between 2004 and 2012, and at the end of the second cycle, there was a transition, and R4S database and tools became part of NBSTRN, or the Newborn Screening Translational Research Network, which is funded -- still funded by the National Institute of Child Health and Newborn Development.

Next slide. What is R4S used for? Well, R4S, at this point, is used exclusively for newborn screening by tandem mass spectrometry, and with a very important limitation: It's limited to the first pass. We know there are quite dramatic changes that happen, probably around 7-, 10 days of age, in term of normal

level of most of the markers we measure, and so actually has been one of the defining characteristics, first specimen only, no repeats.

And if you look at the numbers, R4S certainly has grown quite a bit. We have 258 labs in 68 countries. We have 1,227 -- actually, that's already outdated -- users with an active password. That's the good news.

The bad news is that in term of active utilization, it is somewhat a different story. In 2016, on average, 72 different people logged in on any given day. Per month, there was 335. So, it's about a third of all the people that could access it. And you can also see that those who do log in have been using it quite extensively. The key is utilization of these post-analytical tools, and those were used 88 million times for 17 million newborns.

We tried to start other applications -- for SCID, for biotinidase, for repeat sample, and those really didn't take off, for a number of reasons. We -- we did ask -- I asked a number of

people to be, sort of, what we call the curators, or content experts, but they somewhat lost interest or -- or -- or just because it was -- as I experienced on my own scheme, very difficult to be a hunter and chase people and try to convince them. And I use, deliberately, that word, hunters, because -- I will come back to this concept later. So, personally, I think, for a number of reasons, R4S is probably not a good environment for future pilot study.

Next slide, please. CLIR -- CLIR is more of the same. It is the second generation of the software we developed. It's a multivariate data recognition software. It went live at the beginning of 2005, and you see it's being actively modified. In fact, just last month, for us, was a major milestone because we're able to achieve the delivery of what we said from the beginning to say was our main goal.

If anybody goes to that webpage and click "About Us" -- If you go to the next slide, there is a small blurb that I will elaborate a little

bit more. The point I want to make over this slide is, really, this is a collaboration between three major entities: my institution -- the Mayo Clinic, both the Department of Laboratory Medicine Pathology and the Department of Information Technology -- our collaborators at Oslo University, and our collaborators at the California Department of Health.

Next slide, please. This is, really, like, the elevator pitch about what CLIR does. Well, very ambitiously, I must say, you know, we want to change everything. We want to replace conventional reference ranges. We want to replace, and actually eliminate, analyte cutoff values. We want to enhance the clinical utility of the things we measure by, as you can see, calculating ratios. And also, we want to eliminate sequential algorithms. We want it said, "Well, if you do this, and you find this, then you do this." We want everything done in parallel mode.

Next slide. This is a slide that repeats

what I just show you in the previous slide to really highlight the two fundamental differences. In R4S, we can now create or use covariate-adjusted percentiles, and the fact is, there is no place, no space, in CLIR for cutoff values.

Why is that? Well, because if you go to the next slide, this is the slide that shows you the reference range for 17-hydroxyprogesterone, one of the markers, you know, measure as a part of newborn screening by an amino acid. You can see, when you take more than 1.6 million data points, and you simultaneously provide for age and birth weight, and you see the differences between the left and right, between female and male, it's simply not possible to draw a line, a line in the sand or saying: This value above is normal, abnormal, or vice versa. It's just not possible. So, it's really a different concept, about creating a different system to really facilitate the clinical decision of what is normal and what is not.

The next slide. Again, CLIR is used for

the same thing R4S is being used for: newborn screening by MS/MS. One important change is that we can look now, because of this system, up to 1 year of age. So, any repeat sample is fair game. But participation is smaller -- it's being used only 13 U.S. states -- and we have 275 users with an active password. As I will explain later, it's a completely different approach.

But newborn screening is just a small portion of what we do here. We pretty much are on a path and well advanced to put everything test that we do in our particular field, biochemical genetics, but also in laboratory management.

So, I'll show you another -- another in the next slide, please. For those of us middle-age or older, next time you have a lipid panel done, and you know that the magic number is 200, I hope you will remember this figure to show the massive differences in reference ranges, by the way, obtained from CDC data, from names, of just a sample of that between male and female, and yet, this is not captured in any way in clinical

practice, and we intend to change that.

If you go to the next slide. For that reason, and what I'm going to show you in the next slide, I believe that CLIR could be, very well, an ideal environment for pilot study. Why is that? If you go to the next slide, again, the main differences: code, comparison, data, team, and tools. Starting with the next slide, the differences in code.

Then, important -- two important thing here: From a regulatory compliance perspective, CLIR really has been tested as a clinical product. You can see that thousands of testing scenarios have been documented, with thousands of hours of system quality assurance that have been performed before going live with any release.

But the fundamental issue here is that we do not have the bandwidth or the -- the -- really, the manpower to do any upgrade to the code. So, that means that how long R4S will remain around is really a Microsoft decision, because whenever they decide to stop older

versions or supporting or creating patches for older versions of .net, that is the time that, probably, it will not make sense to use it. On the other hand, CLIR is, really, up to the latest possible version.

Next slide. Again, this -- this slide's probably redundant. For the sake of time -- again, just another reminder that cutoff values don't have a place in CLIR.

Next slide, the data. This is actually an important slide, because we really have transitioned from gathering, in a fairly cumbersome and time-consuming way, cumulative percentiles, so data already processed and manipulated. Now, everything in CLIR happens with raw data, raw data that can be very easily uploaded. This data also quarantined, something that doesn't happen in R4S. In other words, any new addition has to be verified by a curator. And finally, what I think is a very important thing in -- in really -- to really show how this system work: The users, the peripheral users, having

full control over the data, they can delete them whenever they want.

The next slide is just a picture of the people involved, with some names. The newborn screeners in the room probably will easily recognize people like Bob Currier or Joe Rocini from New York, or Tricia Hull from -- from Georgia. But we really have professional IT people that are involved in managing, supervising, testing, and that really makes a big difference.

Next slide. Again, there are differences in tools. There are many more tools in CLIR, and we keep listening to our user, finding ways to improve it. The other fundamental difference: Now we can create site-specific panels. We can customize a CLIR application just exactly the way a state wants it.

Next slide, access. In R4S, about 70% of access is given after people contact us directly. The other 30% is through the registration process on the website of NBSTRN. That is shown at the

bottom.

So, this is an example of an email -- next slide, please -- just, an email that came 2 days ago -- for you, it's Monday. And -- and this is actually an important find to make, because we are really seeing, certainly, a steady interest in people who want to consult the system, not really people that want to use it. The people -- well, it's, like, becoming an e-book -- and say, "Oh, that would really help me to work on my case."

If you go the next slide, the eligibility, pretty much anybody with a natural or indirect affiliation with a newborn screening program can request. We have tons of residents, fellows in training. We have, again, patient advocates. Some organization, of course, AMG, government agencies, people at NIH, others at CDC and, I believe, also, FDA who have access, and some commercial entity.

Now, this is the most important slide on my presentation, so the next one that says 6-

month moving average of R4S users. What you see, you see two very different trends. I can say with confidence that R4S has been quite a strong success internationally. Some things, though, at the national level, the domestic field -- things are just going down, and as you can see, just as evidence, international participation grew 22% in 2016. National U.S. participation dropped by almost 10%. And that's the way it is. You know, certainly, the -- there are -- there might be a reason why people don't want to use it, but it is a fact that it's being used less and less.

The next slide, actually, is a summary of the last year, from May 2016 to April 2017, and it's a map -- a heat map generated by Google Map, and I can -- you can see that there are four U.S. states that really are using it, and also using it the way it's supposed to be used, by using our way to process large amounts of data. Connecticut, Georgia, Kentucky, and Maryland are the only U.S. states that will basically rank among the top 20 countries worldwide. So,

international participation is growing; domestic participation is declining.

Next slide shows you the access to CLIR is completely different. So, we occasionally receive some requests via email, but the 95%, vast majority, use our registration process on the CLIR homepage.

If you go the next slide, very basic thing asking people who you are, what's your email, where you are from. We also ask information about what kind of institution or entity, and also, what kind of professional field. When people click "Send Request," this will appear on our, sort of, support inbox.

Next slide. This is probably the second most important slide of -- of this presentation. As I believe I mentioned, it's -- CLIR is free, as R4S is freely available, but we have really changed things in a dramatic -- quite dramatic way. Now we expect people to contribute data, and if you contribute data up front, you basically are given access.

If you go to the next slide -- again, my reference to hunting. In R4S, we were hunting, and we were not very good at it, because, really, we didn't catch too many people, and we are losing some of those we caught. So, in CLIR, we're fishing. We are basically there. We welcome everybody with open arms, but we are certainly not trying to convince anybody to join us.

As a final slide, I just want to show you an example. Well, we don't use cutoffs, and these are three example of performance. For R4S, the last time we -- the last year we did the state of Minnesota, we had a false positive rate of 0.024%. For the first 14 months of screening, using CLIR, for the state of Kentucky for three lysosomal disorders, our false positive rate is 0.0015.

And finally, we also started testing babies born within the Mayo system for the three condition added to the panel: MPS-I, Pompe, and ALD. And so far, it is a small number, but we certainly didn't have any false positives. We

believe that the near-zero false positive rate is achievable, and, basically, this is the evidence we have.

And if you go to the final slide, it's just to tell you, this is process still evolving, and we keep adding new functionalities. And, again, everybody's welcome if they're willing to contribute data, and ideas are certainly welcome if we can come up with ways to make it better and better. I'll be happy to answer any question you have.

DR. JOSEPH BOCCHINI: Piero, thank you for that excellent presentation. This presentation's now open for questions and comments.

DR. STEPHEN MCDONOUGH: This is McDonough, can you hear me?

DR. JOSEPH BOCCHINI: Yes, go right ahead.

DR. STEPHEN MCDONOUGH: Thank you for your expert presentation. What recommendation would you -- or what dots do you have (audio

interference) --

DR. PIERO RINALDO: I -- I could not hear the question. Can you please repeat it for me?

DR. JOSEPH BOCCHINI: Steve, did you hear that? Could you please repeat the question? None of us really got the full question.

DR. STEPHEN MCDONOUGH: Can you hear me?

DR. JOSEPH BOCCHINI: Now we can. Go ahead. If you'll repeat the question?

DR. STEPHEN MCDONOUGH: Yep. The -- the question was, to Piero -- and thank you for the presentation, and what recommendations would you have to our committee as -- as to what we could do to reduce false positives in newborn screening across the country?

DR. JOSEPH BOCCHINI: So, the -- Piero, what -- what recommendations or suggestions can you make to -- to the Committee related to reducing false positive results?

DR. PIERO RINALDO: And again, I was -- I was told to be careful not to, quote/unquote, promote anything, but I said use it. Use the

systems. And they are tested, validated, and available to everybody. And so, I think, eventually, when you look at the consequences of high false positives -- high -- high false positive rate and also false negative results, I -- I really don't think I've heard a valid reason not to. But then again, I kind of -- after trying for 13 years, I feel I somewhat -- I've paid my dues, and I don't have to chase people and try to convince them anymore.

DR. JOSEPH BOCCHINI: The next is -- Okay.

MALE SPEAKER: Yes.

DR. JOSEPH BOCCHINI: He answered. Okay. All right, Cathy?

MS. CATHERINE WICKLUND: Yeah, thank you for that presentation. This is Cathy. I'm supposed to say my name, right? Okay.

DR. JOSEPH BOCCHINI: Mm-hmm.

MS. CATHERINE WICKLUND: I was wondering -- So, this is completely open access, especially the R4S, and has there ever been a time that

you've actually had to deny access to anybody?

DR. PIERO RINALDO: Well, yes. We have denied access to -- for a number of reason. We also have terminated access when people have used the -- the tools inappropriately. There are examples that I can provide, if requested, of pieces of R4S being published without my knowledge, often misrepresented, or just plain completely wrong. And so, I think, in those cases, people -- their access should be revoked. There are other situations where I made a decision that some people may not have access. And I don't think it's really something to discuss here.

MS. CATHERINE WICKLUND: Okay.

DR. JOSEPH BOCCHINI: Beth?

DR. BETH TARINI: Is this a publicly funded source because R4S was funded with federal funds?

DR. PIERO RINALDO: R4S was publicly funded, and CLIR is entirely funded by the Mayo Clinic.

DR. BETH TARINI: Perhaps this is something to discuss at a later event, but when I write grants and I publish, I have to make my data available to everyone on Pub Med. So, I'm not clear how -- how the data cannot be publicly available if created with public funds.

DR. PIERO RINALDO: Well, the data collected -- First of all, you really have to find the reasonable compromise between the strong request by people who contribute data that their data are protected and nobody else can see it. So, everybody who enters CLIR can see cumulative data -- or R4S or CLIR, but only if you have read and write access you can see individual cases from a site. And -- and all -- this is all published.

DR. MEI BAKER: This is Mei Baker. Can I ask a question?

DR. JOSEPH BOCCHINI: Yes, go ahead, Mei.

DR. MEI BAKER: Okay. Yep. Piero, I understand that when each individual site, and you don't use a cutoff -- I was wondering, when

you build in this program behind the scene, did you have some kind of threshold? And I -- theoretically, I do believe it be fine to take the -- you know, the -- the tests that you also -- I mean, the tests and result that you also use, like, gender and gestation age, or birth weight, and theoretically, it should be more comprehensive. But I think maybe I'm just -- well, you know, somehow, when you build in this, behind the scene, you still have some threshold, or not?

DR. PIERO RINALDO: Well, it depends on what application. The one thing has worked best for lysosomal disorders, like something that is pretty -- you're very interested in, is actually that we are simply saying: Any case that has anything that is just above or below normal, that will actually move to the next step, which, as you know, is the other tool that we call the dual scatter plot.

DR. MEI BAKER: Mm-hmm.

DR. PIERO RINALDO: So, they -- I should

have mentioned that, really, one of the most important things we do, we actually start using, as a resource, false positive cases. So, we can actually tell the difference between true positive and false positives when we look at fairly complex profiles. They're integrated for -- the results are integrated for the covariate.

So, there is no cutoff. You can say that if anything greater than zero, in term of a integrated score, will move to the next level of evaluation, which we found that we eliminate 98, 99% of the results. The remaining is really evaluated through second-tier tests. I haven't talk about it, but it's really not about -- So, all of this work is to really come down to the smallest possible number of cases that require additional testing, and again, based on the same specimens already available. We use a definition of false positive that is far more conservative what many programs would like to entertain before -- as any case where there is additional patient contact constitute a false positive. That include

if you -- even if you ask a repeat blood spot.

DR. MEI BAKER: Well, thank you. I think, actually, you kind of answer my second question is -- things that is very comprehensive. Then, my second question is, is the second tier something like -- that's not what you -- totally replace second-tier testing, right?

DR. PIERO RINALDO: Not at all. The second-tier tests are really the ones that are used when really indicated, that our goal, as everybody else, is to maximize specificity but also sensitivity. So, we basically have three level of evaluation, and I didn't elaborate on that, but we have initial, single-condition tool -- the one that answer the question "yes" or "no," and possible "yes" is anything that has even a single marker slightly outside of the covariate-adjusted reference range. The second is the tool that makes the differential diagnosis between true positive and false positive. The third is the -- the second-tier test. And we're working hard to have a second-tier test for every

condition that we test for.

DR. MEI BAKER: Thank you.

DR. JOSEPH BOCCHINI: Next, Jeff.

DR. JEFFREY BROSCO: Hey, Piero, it's Jeff Brosco. So, I just want to clarify, because I've heard you present before, and it maybe didn't come out as clearly as it could in -- So, for a state newborn screening program that enters data into CLIR, there's -- would be no charge, so it's a free access from that point of view, if they enter data, and you believe that this would reduce both false positives and false negatives overall. So, it would seem to be a real benefit for state newborn screening programs. Is that correct?

DR. PIERO RINALDO: Absolutely. And -- and I just want to be clear on one thing: Nobody gets charged anything. This is a freely available product. As we evolve, transitioning from R4S to CLIR, we actually ask people to contribute in kind with data. I strongly believe that data from many sources are always better than anything that

any program could or would do in isolation. The first letter of CLIR is "C," collaborate -- not charge, collaborate.

DR. JOSEPH BOCCHINI: So, I give Carol Greene the last question, then we're going to move on to the -- Oh, we've got -- Before that, Carla Cuthbert.

DR. CARLA CUTHBERT: Carla Cuthbert here. Hi, Piero. I have one quick question. Do you envision any point in time when CLIR might be made available, perhaps, to federal agencies?

DR. PIERO RINALDO: Again, I -- I'm fishing, Carla. Come and talk to me. And you will -- you and your colleagues at CDC have access -- had access to R4S for years and years. But if you'll remember, at one point, I told you I was not really -- I was surprised when you start stopping using R4S ranges in your UDOC (phonetic) program. So, you had access for 10 years.

DR. CARLA CUTHBERT: I'm speaking about CLIR, because CLIR has a very different approach to it, and I'm thinking about the design of

quality assurance materials. That's it.

DR. PIERO RINALDO: I --

DR. CARLA CUTHBERT: We can talk about this offline, Piero.

DR. PIERO RINALDO: Yeah, we had this conversation before, because, you know, once you adjust for covariate, if those are made up, it will give a -- a -- an abnormal or a incorrect result. But I'd be happy to talk, of course.

DR. JOSEPH BOCCHINI: All right. We're going to -- Okay. So, Carol, we're going to give you the last question then move on to the next speaker.

DR. CAROL GREENE: Carol Greene, SIMD. Hi, Piero, and thank you. The -- You didn't mention anything about data dictionary or criteria. I -- I think we're going to be hearing about case definitions, but how do you handle case definitions since the accuracy will depend on whether you were, in fact, correctly told that a case was a true positive or a false positive? How do you -- Do you have ways of verifying that,

or do you have a shared data dictionary or case definitions? How do you handle that in both R4S and in CLIR?

DR. PIERO RINALDO: Well, it -- it really -- it's a different answer based on the kind of condition. So, for example, now, where we have a strong focus on lysosomal disorders, has to be a known and verified pathogenic genotype to even be considered to be included as a true positive case.

For the others, that goes back to my slide when I was talking about the need of curators. There are 20,000 true positive cases in R4S, and believe me, I have reviewed every single one of them as they come in, because in R4S, they go straight into the tools. I'm really -- and certainly, we had horror stories about people putting crazy stuff in. So, if there is any doubt, if the biochemical phenotype is not consistent with what has been the definition up to that point, those cases are questioned, and if no adequate answer from the submitter is

received, those cases are removed.

Again, we have to rely on local protocols. We cannot -- and certainly, it's not our job to try to say you have to meet this criteria. If somebody calls a patient an MCAD, and the biochemical phenotype looks like MCAD, I'm not going to ask any other question.

DR. JOSEPH BOCCHINI: All right. Thank you, Piero. I understand you'll be able to stay on for a while to --

DR. PIERO RINALDO: Yep.

DR. JOSEPH BOCCHINI: -- listen to the others, and then potentially participate in the discussion at the end. So, thank you, again.

Next, we are going to hear from Dr. Carla Cuthbert, Branch Chief of the Newborn Screening Molecular Biology Branch at the Centers for Disease Control and Prevention. She's going to discuss CDC's Newborn Screening QA/QC program. Carla?

DR. CARLA CUTHBERT: Thank you. I'll just wait for the slides to come up. Is someone going

to do that?

(Off-mic speaking)

DR. CARLA CUTHBERT: Oh, I see. I see Paris slides, Stan.

(Off-mic speaking)

DR. CARLA CUTHBERT: Oh, I see.

MALE SPEAKER: Here, it --

DR. CARLA CUTHBERT: Okay. I get it.

(Off-mic speaking)

DR. CARLA CUTHBERT: That's correct. Great. Thank you. So, my name is Carla Cuthbert, and I'm here representing the Newborn Screening and Molecular Biology Branch at the CDC, and I just wanted to give you an update to just sort of give you a high-level picture about what we do in helping and working with state programs to assure high levels of quality in their measurements. And, again, in distinction to the post-analytical tools that -- that we were talking about with Piero in -- in that first session, what we do is provide support in the methods itself, in the measurements, and in being able to get the -- the

best kinds of results.

So, we get, pretty much, our marching orders from the Newborn Screening Saves Lives Reauthorization Act of 2014, and you can see here, it specifically says that the Secretary, acting through the CDC, and that's targeted specifically to our branch, that we should provide quality assurance for laboratories, which would include quality assurance in newborn screening tests, performance evaluation services, technical assistance in technology transfer to newborn screening laboratories. So, we're very, very hands on in terms of our applications and in terms of what we do.

Our branch is organized into five different teams, and each of the teams are -- are specialized to do various kinds of activities. We number about 40 to 50 or so scientists and other technical people who provide services for -- for the programs. Again, many of you will have the slides. I'm not going to go through that in much detail. But, again, the overriding goal is to

assure early and accurate laboratory detection of newborn conditions using blood spot testing.

So, I came -- I joined the -- the branch about -- a little over 7 years ago, and once I got there, I -- I created these priorities to outline a lot of what was already being done and to make sure that we had a very clear focus in terms of where we were actually going. And everything that we do in terms of visioning, in terms of how we spend our resources, which includes time, funds, and any kinds of effort, fall into these four priorities.

The first is really based on the fact that this program has been in operation for over 30 or 35 years, is really to take a look and highlight what we do, make sure that we continue to do what we do well, well, and anything that needs to be improved, we focus on improvement.

Secondly, we look at what is coming down the pike. So, there are recent additions and -- and anticipated conditions for newborn screening, and we spend a lot of time actually focusing on

making sure that we're ready for that, and we're not the bottleneck in terms of making sure that states are ready for implementation of these new conditions.

We pulled out molecular testing because that requires special kinds of handling and -- and a special focus. It -- it is -- it requires a lot of effort, and it requires a lot of technical expertise and oversight.

So, that is our third priority, and the fourth priority, while it's a little wordy, really what it means is that we really want to work well, outside of the lab, with everyone in our community who is -- who is interested in newborn screening, and that includes within CDC, our federal partners, and any of the newborn screening stakeholders.

So, again, CDC is very unique, in that we are the -- we -- we provide very comprehensive quality assurance materials. We are -- we do this not just for the United States but for the world. And this covers proficiency testing, quality

assurance materials. We do an extensive amount of method development that's not on this list, but we spend a lot of time doing that. We also do an extensive amount of training and consultation based on the expertise and the -- the technical experience that we have, and -- and we do some filter paper evaluation.

The quality control materials that we keep talking about, really, are materials that the states can actually use that mimic the conditions of -- of -- that are on the RUSP and that -- that they're actually testing for, and it provides them an opportunity to really monitor method performance of their test so that they can identify problems and take corrective action appropriately. Usually, if you have a kit, kit will come with its own QC, and so you use that on a regular basis, and you're required to do a certain amount of QC testing with each run. And so, that's put on -- usually put on every plate.

We provide state programs with external QC and their supplemental materials that they can

use. It's generally not for everyday use, but they ask, we give. So, really, they can -- they can use it; they just need to request it from us. So, again, if there are big changes in lot numbers and so on, they want to make sure that there's an opportunity to make sure that there's not big fluctuations in their testing from day to day, from year to year, and decade to decade for the most part.

Proficiency testing is a little different. It monitors laboratory performance, again, but it is -- they're samples that are treated like patient samples, or as close as we can get to it. So, there's a lot of innovation and a -- a lot of -- a lot of work that we actually have to do to make sure that the samples look a lot like baby samples, and when we do get that, we make large batches of it, as you'll see in the next couple of slides.

Just to -- just so that you know, it's -- it's a requirement -- proficiency testing is required for all screening laboratories, all

diagnostic laboratories, as well, and we have -- 100% of our state programs are covered with the materials that we -- that we create. They all participate in our program. They get three challenges of five-blind coded specimens every year, and generally, you need an 80% consensus for a specimen to be graded.

We have an online reporting system, and we're actively updating and -- and upgrading what we're doing. Much of this, right now, is blinded to most of our participants, but we do have a lot of quality improvement work that we're doing on the back end that we've been involved in for the last few years. The -- the results are posted. It's really paperless, and the web location is known by all of our participants.

There is active follow-up of -- of cases if you don't get what we expect. Each of the subject matter experts will track you down and have a chat. Often, it could just be transcription errors, but if there are errors in -- in -- in techniques or anything like that, our

subject matter experts and scientists will work with each of the programs to ensure that -- to ensure that they are -- get right -- back on the right path. Additional challenges are available to states as they need, as -- if they actually need to -- to do some further development with their methods.

Technical assistance and technology transfer is something that we take very seriously. I think one of the really good advantages of being able to have a proficiency testing program is that we get to know each of our state programs very, very intimately, and we really understand what -- what they do, and it gives us a lot of input in terms of how we can design resources, how we -- It helps me focus on how to determine how we can help. And we have a lot of partners. APHL, the Association -- Association for Public Health Laboratories, works with us very, very closely to be able to help address a lot of these issues, as well.

This just gives a list of the -- of the

conditions that we have quality assurance material programs for, and that really just lists all of the conditions on the RUSP. We are approaching about one million dried blood spots produced every year. These are produced in-house. We don't contract out any of our work, so we prepare, we certify. If it doesn't meet what our criteria is, we ditch it and start again, and only when we have properly certified material do we distribute that to each of the programs.

So, it's a very involved process, and again, all of the newborn screening tests are arranged in different programs. Over 650, actually, laboratories participated last year, about 78 countries in 2006 -- 2016, and that tends to grow. And as I said, over 800,000, 900,000, approaching one million blood spots are being created every year.

As a result of the program that we -- that we have for the domestic newborn screening programs, we have been able to leverage some of the materials that we create to provide materials

for the international newborn screening community, and we are sensitive to their needs. They do help us, and, you know, the numbers, well, helps us to make better products, essentially. And as those programs grow, we do encourage them to develop their own quality assurance programs and to create materials themselves, internally.

This is just a slide that shows the 78 countries that participated in some form of program in -- in NSQAP in 2016.

We also do a certain amount of filter paper quality assurance, and, again, this is just to make sure that -- that we can monitor performance of new -- new commercial lots. This is not a requirement. The vendors send their materials to us; we evaluate and -- and send them a report.

Now, the second priority really focuses on whatever is coming down the pike, so, really, we encourage you, if you're thinking about nominating a condition, make sure you get in

touch with CDC to make sure that we have methods and quality assurance materials ready for you. So, what we have done in this area is provide -- and we continue to provide some funding for state programs to implement newborn screening, and we've done that since 2008, with SCID, and we're continuing to do that right now. We have a lot of in-house method development.

So, our scientists are very much looking at -- at -- at what is being anticipated, so we have methods for LSDs and X-ALD, of course, for guanidinoacetate methyltransferase deficiency, or GAMT deficiency. We have methods that we have published for spinal muscular atrophy. We've published a method, and we're improving that method, as well. So, we're ready to -- to work with -- with any state that is interested in bringing on these conditions. And, of course, DMD, the biochemical assay, is ready to go, and we have -- we have some work being done on the molecular approach.

So, again, quality assurance materials:

We -- this is something that -- that we need to do. Whoever is in charge of that particular new program needs to make sure that we have a sustainable source. And as I've indicated before, you know, if you just have to buy a reagent and add it to blood, that's one thing. If you're dealing with enzymes and different kinds of markers, molecular markers and so on, that -- that requires a certain amount of strategy and -- and development.

So, we're looking at that, and we're also looking at expanding what we're doing to create other materials that would be appropriate and helpful for states as they do development and validation, which would include things like linearity pools and so on, that would help them for new conditions.

Training, as I said, is very, very important. Just last week, we had the mass spec group come by for training, and that, again, is something that we do in -- in collaboration with APHL. Everything that you see starred here is --

is done together with APHL. As a federal entity, we tend to be a little limited in terms of how we can get things to happen, and APHL has this miraculous little way of just doing and doing and doing. So, national meetings, site visits, laboratory-based training are -- and website resources are things that -- that they help with. We do have SMEs, like I said, who will provide one-to-one consultation and actual data review as you're bringing on a test, so that you can actually walk through the data and -- and get help in that regard.

That's just a picture of newborn -- mass spec training that we had some time ago, and generally, that helps to support 10 trainees, and we have about 5 laboratory instructors helping.

One of the things that came out when -- you know, in -- in doing all of this -- these training applications: We had 30 applicants for that mass spec course. And we can't touch everyone, all at the same time, so, one thing that we've thought about doing was coming up with

some kind of online module that could be used for training. And we contracted with the Society for Inherited Metabolic Diseases to create 15 modules that will be due sometime soon to address and to -- to target to newborn screening professionals. That's something that is ongoing, and we're really excited about that possibility, as well. So, people can sit back during lunch, have a sandwich, and learn all about newborn screening of the disease of interest.

The third priority -- and I'll go quickly here -- really deals with molecular detection. We have a number of different approaches. Again, methods -- very, very important, being able to create methods that are -- are -- are applicable to the high throughput arena of newborn screening public health labs.

We have as a focus to identify gaps and to work collaboratively with the states to come up with useful solutions. We've developed a molecular assessment program, which is a -- a non-regulatory -- CDC's not a regulatory agency,

so it's -- it's a group of -- of peers that go into a molecular -- into the laboratories to give an assessment of how they're doing, and they come up with a report, and we have a number of different hands-on and web-based educational tools, as well. So, the -- the molecular resource website is on the APHL website and provides a number of different resource applications for state programs. Sorry about that.

We have a -- a training course that happened a little earlier this year, where we -- that's been ongoing for -- for 5 years, and we train about 14 participants in different kinds of molecular activities and molecular assays. And of course, the molecular assessment program has been going on for some while, and we're now considering applications to support sequencing implementation.

Molecular repositories -- Again, the target here is molecular -- just molecular targets, and being able to get patients with unique specimens for -- for -- for detection is -

- is always a challenge, and we have three different programs and -- and universities that we're working with to be able to assist us with that. We're also looking at ways to develop and validate DNA sequencing and large deletion reference methods, as well. And more recently, we've -- we have a cooperative agreement with New York State for the development of sequencing technologies for genes associated with SCID.

And, lastly, working with other people -- We are so glad that we don't have to carry this burden entirely on our own. While we spend a lot of our time in the laboratories and so on, there's much that we do sitting in -- in the company of -- of colleagues. And so, we do have a number of federal partners that's listed here that we've had some kind of engagement with over the last couple of years.

And again, our biggest partner in being able to accomplish a lot of these tasks is APHL, who, through the Newborn Screening and Genetics and Public Health Committee and its -- its -- its

subcommittees, the QA/QC and the Newborn Screening Molecular Subcommittee, really help us to address issues that are more national and so on, and helps us to become informed about how to address and help with -- with issues that are a little bit more pervasive.

So, and that's it. I'd be happy to take anymore -- any questions.

DR. JOSEPH BOCCHINI: Carla, thank you for that excellent overview, a very comprehensive program. So, that's -- that's wonderful for states and for implementation and -- and then quality control. So, let's open this for questions or comments from the Committee.

(No audible response)

DR. JOSEPH BOCCHINI: How about organizational representatives? Mike first, and then Natasha.

DR. MICHAEL WATSON: Morning, Mike Watson.

DR. CARLA CUTHBERT: Mm-hmm.

DR. MICHAEL WATSON: So, I'm curious how

you're going to -- Where -- where's this balance going to come? You know, right now, we have -- Molecular testing has -- has been well understood, targeted variance within the newborn screening lab environment, but a lot of what we're doing in the current disorders is variant interpretation that's associated with clinical phenotypes that often happens in a diagnostic sector, where there are certain requirements for training and licensing and other things for the lab directors.

So, we certainly have a workforce deficiency on the diagnostic side, and as more states begin to move into this place where they're getting into a pseudo diagnostic role with sequencing, I'm wondering how you're looking at it -- sort of how it fits in with the, sort of, diagnostic side? Because some states do the sequencing, others pass it to the diagnostic sector to do it, so it's not uniform across the country at all.

DR. CARLA CUTHBERT: That -- that's a

very, very good question, and actually, we -- we have been thinking about that for some time, and earlier this year -- I think it was in February -- we had a sequencing -- a newborn screening sequencing meeting, and this is where -- with APHL, and -- and this was really led by the Newborn Screening Molecular Subcommittee. They brought people together to discuss the impact of -- of sequencing in newborn screening, and many of those things that you brought up were discussed.

And -- and, again, we're going to hear a little -- I think this is going to be discussed in the molecular -- the -- the -- the -- the -- the breakout session this afternoon, but those are issues that -- that states are considering. There are some states that are going to be a little bit more advanced in terms of doing sequencing and having the appropriate molecular geneticists involved to be able to help interpretation, and others who do not. I don't have an easy answer to this. We've identified

this as being an issue, so.

MS. NATASHA BONHOMME: This is Natasha. Great presentation, and it's really been wonderful to see all the work that this division has been able to do under your leadership, particularly for the component of the work where you're creating all those blood spots and working with so many countries and states. It -- What is the -- Just how many people do you have working on that? I mean, it just seems like so much, and I think it's important not only just to see all the output but what it really takes to -- to do that and to really be able to be supporting newborn screening around the world.

DR. CARLA CUTHBERT: So, right now, we have about -- between 40 and 50 scientists. I -- I say that there's a range because, generally, we have students and guest researchers and so on coming on, and so that's how many we have. And of course, I know that one or two of them might actually be listening to me right now, so they know that every time I say, "I have a -- a great

idea," each one sort of slinks down and goes, "Oh, my gosh, what does this mean for me?"

So, they -- they're -- they're fantastic people, and one of the things that we're trying to do is actually look at ways to -- to get better efficiencies. We are looking at updating our -- our database systems and -- so that much more of their time would be used in just thinking and doing the work. So, I might be stuck with that level. We keep asking for more FTEs. We get laughed at by our supervisors and so on in this environment, but -- but we have a lot of great ideas about what we can actually do.

Mike just brought up a really fantastic question about, how do you even get into thinking about molecular sequencing, when, you know, you've got an entire college devoted to being able to interpret those -- those -- the data that come out. So -- so, they -- they work very, very hard, and if they're not listening to me right now, they're actually working. Well, they always work, but -- Sorry, guys.

DR. JOSEPH BOCCHINI: We'll give Don the last question or comment.

DR. DON BAILEY: Hi, Carla, Don Bailey. Thanks, again, for all the great work that you and your team are doing.

There are probably hundreds of disorders that would fit -- that would meet the RUSP criteria if there was a laboratory test that could cheaply and accurately identify them, so how does your group work in terms of prioritizing things? Do you wait until investigators out in -- around the world, you know, get to a certain point, and then you move forward, or do you start -- You know, how do you -- how do you kind of look -- And -- and it relates a little bit to Mike's question about molecular, but it's -- it's broader than that. And so, how do you decide what conditions that you start to develop new tests for in an anticipatory fashion?

DR. CARLA CUTHBERT: That is an excellent question, and if I -- I don't actually have a formula, but I do keep my ears open. So, for GAMT

deficiency, I was at an ACMG meeting and -- and understood that -- that this was something that -- - that -- that was probably going to be nominated. I try to look at things that are probably mature enough to be approaching a nomination package, and I'm -- I also look at the kind of expertise I have in-house, as well.

So, things that would be a little bit more amenable for tandem mass spectrometry, I -- I send off to that particular group. If it's a molecular target, like it is with SCID or SOV (phonetic) -- You know, in some cases, different groups may approach different ones of my scientists, and we can actually get moving with -- - with that.

So, it's -- it's more of an art rather than anything else. We're trying to keep our ears open, and so we do really want people to tell us when -- when the -- when the programs that they're thinking about is -- is getting to a mature place.

DR. MEI BAKER: This is Mei Baker. I want

to make a comment, actually, of something with Mike Watson talk about, how the molecular get into newborn field, and how you, bottom line, determine diagnosis. So, you -- to me, I see the utinity (phonetic), how the molecular compound is, and Mike (audio interference) wasn't limited in the mutations and all variants. You have a very good curation already, knowing the function. And instead of getting into trying to interpretate (phonetic) the variances, we don't have a good understanding yet.

DR. JOSEPH BOCCHINI: Thank you. Thank you for the comments, and, Carla, again, thank you for sharing the -- what's being done at CDC and the work that you've created.

Next, we have presentations from three experts in the field, and -- and I'm going to just introduce each of them, and then they can come up sequentially to make their presentations. They're going to provide overview on identifying and following up out-of-range and borderline results from three different state programs.

First is Michele Caggana, who is Director of Newborn Screening Program, New York State Department of Health, be followed by Scott Shone, who is the Research Scientist/Program Manager for New Jersey Department of Health Newborn Screening, and then Amy Gaviglio, who is Follow-up Supervisor/Genetic Counselor, Minnesota Department of Health Newborn Screening program. So, invite Michele first.

DR. MICHELE CAGGANA: Okay. Okay. Good morning. I want to thank the Committee and Dr. Bocchini and the audience for listening to me this morning and for the invitation. I was given a pretty broad topic to cover in a very short period of time, so I'll do my best. But my task was to basically follow-up on a talk in February that I gave on the webinar and to illustrate the points I brought up with some examples.

So, the first topic I was given is to cover SCID screening and validation and -- and cutoffs and that sort of thing, and it was interesting that that question came up earlier.

When you think of SCID screening, you can think of many different types of SCID. So, you can have this severe combined immunodeficiency disorder, and there's three different kinds of that. You can also have low white cells, and that could be T-cell lymphopenia due to unknown reasons, and in addition, there are syndromes that have immunodeficiency as a component of them, so that's sort of another form, and then you can have other secondary forms. And so, the question of case definitions is one that we're cognizant of all the time as we go through.

So, just quickly to go over timing of SCID: We had -- we're developing the assay, and we took about 9 months and used about 6,400 specimens to do that. We have to submit an audition package to our regulatory program in New York, and that's sort of New York specific, and we had a drop-dead date for funding to be able to get funding to do this by the end of September, which is the federal fiscal year. Our emergency reg was approved on the 27th, so right in time --

and we started screening on my 20th wedding anniversary, so this is near and dear to my heart -- and this is -- Our first true baby was found about 3 months later.

We -- I'm going to go through, sort of, the evolution of SCID screening in New York because, since 2010 -- it's been almost 7 years, and we've changed our algorithm several times to accommodate changes that we've picked up along the way. So, this is a complicated slide that I'm not really going to go into, but just appreciate that this is what an algorithm looks like. When we're screening, we're actually screening for a risk assessment, so we're not diagnostic at this point. So, the idea is, we cast a wide net, and we assess risk, and then we do this without any clinical information about the babies that come in the door.

So, you can have low TRECs for many causes, and so we want to start off conservatively, and that's what we did. Our providers wanted us to refer every baby in our

assay that had less than 200 TRECs -- T-cell receptor excision circles -- and that's the little piece of DNA that floats around in blood during -- after thymic or during thymic rearrangement. At that time, we had no PP -- we call it a PP category. It's also called a borderline result. All babies less than 200 were referred. And the immunologists were swamped; they had about two referrals per day across the state, and they said, "Wait, we have to make a change."

And so, we went back and looked at our data, and we said: We can, okay, conservatively now, cut off at the -- at 150. We also look at a control amplicon to make sure we don't have low TRECs due to a failed amplification, because it's a DNA-based test.

So, we made that change in January, and our number of babies that went to flow dropped down. And we looked at it again, and we decided we could actually edge that down just a little further and go down to 125. And so, we did that

for about 3 years. And we were in the process of moving to a new laboratory, so when we wanted to move to a new laboratory, we were able to change our assay, and we had to make sure our cutoffs remained the same. This is an example of what we call a fixed cutoff: 125 TRECs and the baby gets referred. It's different than the floating cutoff that I'll talk about in a -- in another moment.

The other thing is, we validated this using only about 6,400 samples, which is a little over a week in our program. There was already expertise in the field about SCID screening. We had other states that were screening already.

And so, when we -- we were planning on our move and thinking about how we were going to do things in the new building, we also had a baby who had zero TRECs multiple times but kept getting a normal flow result, and we realized that one of our primers actually had a base change under them and that we had to revamp the assay. And at the same time we did that, after we sequenced and figured out what was going on, we -

- we went through a series of steps up here that allowed us to cut the extraction time. We changed our boxes that we do the QPCR in, and overall, the number of referrals and borderlines decreased with these various changes.

And so, right now, this is what we're doing, and the referrals are in the -- in the ballpark of what our providers are happy with. Again, when we do these cutoffs, we're interested in reducing as many false positives as possible, all at the cost of not missing an infant. And so, this just shows you the change in referral rates, and the assay has been steady since we moved to the new building and made those changes.

So, the emphasis on how we go about making these alterations is the idea of continuous quality improvement, and so the changes we made here are -- are summarized, and also where we're going. So, the borderline category allowed us to reduce the number of infants that got referred by almost 90%. Our PPV for SCID exclusively went up to 5%, and we also

institute what we called a zero TREC rule for premature babies.

So, babies can be premature, and they can have SCID. Babies can be premature and have low white cells. And we want to make sure any baby who is going to have SCID certainly gets identified as early as possible, and so now any infant who has no TRECS in triplicate on our assay, regardless of gestational age, gets referred.

The primer redesign I talked about and also other issues that come up while you're screening and things that you find out once the baby gets worked up clinically, such as maternal engraftment -- You -- you'd run a -- a different marker to pick that up on the flow panel.

As Dr. Cuthbert alluded to, we also are working on a molecular test, and that's really to cut down the time to diagnosis. Other things that are being talked about in the field is whether you say a baby is positive, you give a quantitative TREC number, or do you use the value

off of the machine, the CQ. And Dr. Berberich, Dr. Baker, and others are looking at percentiles and multiple to mean instead giving a -- a TREC value to normalize the data across the country.

So, I'm going to shift gears and talk about Krabbe disease. It's a deficiency in the lysosomal enzyme and causes demyelination effects and causes damage to the central and peripheral nervous system. And there are at least two forms: There's an infantile form, which is very severe, has a very quick onset and death by 1- to 2 years of age.

And as you probably know, this was added in New York State during the governor's State of the State Address. So, this was, essentially, a mandate.

Unlike SCID, no one was screening for Krabbe disease, and so we were unclear as to how the assay would behave and that it could be ramped up to -- to be done on all the infants in New York. And so, we actually screened about- three quarters -- two-thirds to three-quarters of

the year, 157,000 samples, before we went live. So, we did this by anonymous screening, and we went live on August 08, 2006, and we looked at the various cutoffs -- the various levels of referrals at various cutoffs.

Now, for this, we're doing a floating-type cutoff. It's not strict enzyme activity. And the reason is shown on this slide, where you can see that there is some seasonal fluctuation in the activities. When you looked across the validation data and continuing through testing, we had about 4.4 micromol per liter per hour was the mean activities in those -- in that validation set.

The other thing that you have to have, obviously, to do a -- an assay is positive controls, and up here, the very light blue is one baby -- cord blood from a single child that was tested multiple times, and then the green diamonds, I think they are, they were -- that same child, a blood sample prior to transplant, tested multiple times. The pink are carriers, and

then the blue are other Krabbe patients, and these are older Krabbe patients, not newborn babies.

And so, what we did was, over that time, tested these multiple times, as we were doing the anonymous study on all infants coming in the door, and we were pretty comfortable that at a 10% cutoff here that we would catch the Krabbe kids, with the exception of this one test. This was the same -- same person tested multiple times. We would be pretty good with that -- starting off as that percentile cutoff. We also knew that was -- it was all the same person, same child.

We also knew that there were mutations that attenuate activity, and so we thought, at the time, it would be important to rule these out, because there are non-disease-causing polymorphisms, and that would help cut down on the referral rate. So, we instituted testing for those and sequencing of the entire gene, and we ended up with a algorithm that's shown here, with

a cutoff of 10% of the daily mean. Anything less than that goes to DNA, and anything with one or more mutations gets referred.

This has been upgraded now from 10% to 12%, and the reason are these two infants, who were referred on the same day, and this child here was our first transplanted baby and came in with a value of 9.9%. And so, that made us nervous, and so we bumped up the cutoff to 12%.

We also implemented other changes to the algorithm, so now we're also screening for Pompe disease, and so we look at both of those tests and set those up. Any baby less than 12 is screen negative. We assess the GAA and GALC activities, and we -- we come up with an in-house, borderline-type result, and then we send that and do a 6-plex evaluation for that.

So, we are doing a pilot study, funded by NIH, to Dr. Melissa Wasserstein at Montefiore. Because we're doing that testing, we can look at all six enzymes, and we normalize based on the highest activity in that segment, and then we

changed the referral scheme that any child less than 10%, after this analysis, then goes to DNA. And we're also working on another biomarker, which I'll talk about in a -- in a second. After that, the kids go through the same DNA-type testing algorithm, so the bottom of the -- the bottom of the algorithm remains the same.

So, I'll talk a little bit about psychosine in a sec, and then we're looking at some other biomarkers. Dr. Rosini (phonetic) is working with Dr. Matern and Dr. Rinaldo at Mayo to look at some other markers to be used, and also the CLIR tool.

This was the -- the proof of principle study showing that psychosine actually was a good biomarker for Krabbe disease. If you look in the first group, that's patients. These are Krabbe patients. Psychosine is the substrate for the enzyme, and you can see that there's an elevation of psychosine in those patients. When we looked at our early onset confirmed Krabbe babies that were detected by newborn screening in New York,

you can see that the psychosine is quite elevated, and then as you look across all the other newborn categories that we have -- these are kids that are asymptomatic -- all of their psychosine levels are basically similar to babies who are screened negative. And so, this looks like a really good biomarker to use after the enzyme test.

This work was done, originally, by Dr. Rosini in -- in New York and folks at Genzyme. We -- we turned this assay over to Dr. Matern at the Mayo clinic, and he's using it, as you may have heard, on -- for screening in Kentucky for Krabbe disease. We're in the process of bringing this in-house, also, because we have mass specs that are highly sensitive and can do this test.

Looking really quickly at Pompe, we had a similar -- a similar approach here. We used about 6,000 tests. It was part of the pilot study originally given from NICHD to Dr. Wasserstein as a consented pilot, and we also got some specimens from the Missouri program, from Patrick Hopkins.

There were positives, negatives, mixes, carriers, et cetera, and we got concordance, and 12% was the highest result on that panel. And so, we bumped our cutoff to 15% to be conservative.

So, we pilot tested for Pompe beginning in 2013 and then went universal in October of 2014, and that was because we actually got more funding from NIH to be able to do it on a universal -- all the New York babies, so that pulled out of the pilot and was made universal.

There was a lot of discussion on case definitions for Pompe disease, because there is an early infantile form, where babies die pretty young and suffer heart damage pretty early on, and then there's also these later-onset-type conditions. And this isn't unique to Pompe. It's -- it's part and parcel for a lot of the lysosomal storage diseases.

And so, it really makes us think about, what is newborn screening. Do we -- We definitely want to detect that baby with cardiomyopathy and -- that will die without treatment, but do we

want to detect somebody in their 40s and 50s, when they experience muscle weakness or gait abnormalities? And so, not only are we worried about case definitions but, really, the -- the creep of newborn screening.

This is -- I'm not going to pretend to be an expert on this. You've heard some of this from Dr. Rinaldo, and this is work that was done by Monica Martin in our lab and Dr. Rosini. What we do is export our data to the CLIR tool, and it runs through a 3-plex, single-condition tool and turns out a score. The scores then are used to assess whether a baby has a positive or a negative screen. If the baby has an -- a score greater than zero, it goes back through. We retest for all six. We export the data back -- back to the CLIR database, and then we have this -- a 7-plex, which takes into account birthweight and also gestational age. Again, it turns out a score, and we use this in our assessment, as well, and then babies who are indeterminate go on to second-tier testing in New York.

And so, we've been doing this prospectively, and we also did a retrospective study, and this is just an example of a -- of a result from -- This is a screen grab that Monica gave me, and this is from the 3-plex tool, and you can see here, there's a baby who may be positive, but when it goes into the 7-plex tool, it gets bumped into the false positive range. And so, that baby would have been excluded from additional follow-up.

So, the preliminary data we have from the retrospective study -- We had about 4 months' worth of data that we uploaded at that time. In that population, there were 33 babies who required second-tier DNA analysis. Twenty of those were for Krabbe, and fifteen were for Pompe.

We did second-tier testing, which enhances DNA testing. Twenty-one infants were referred for follow-up diagnostic testing. Eight were for Krabbe and thirteen for Pompe, and then all of the eight infants that we referred for

Krabbe were negative, and nine of the thirteen cases were false positive -- or -- Yeah, they were negative for disease, so they were false positives. Using the CLIR tools, 10 of those would have required DNA instead of the original 21 on the second bullet there, and the CLIR tool was able to detect all the possible Pompe cases that we put in retrospectively.

So, we're using this in tandem, and the plan is to start using this in our assessment at the -- in the fourth quarter of this year. We're going to continue with our prospective work.

So, I just want to, kind of, conclude with some thoughts based on both of the talks that I've given to the Committee thus far, and these came up in -- in some of the work that Dr. Rinaldo talked about.

When we change kits and reagents and assays, we have to go back and revalidate, and so the training set, a lot of the data that's in CLIR -- We -- we -- we submitted our data to CLIR to be able to help train the data, and when you

have any changes -- and I'll talk about one in a sec -- the changes to the tool -- the tool has to be revalidated, as well as the cutoffs and the laboratory piece. So, we need more prospective- and retrospective-type studies in real-time, in practice. Dr. Rinaldo described the lock-down in the software and the version control that he's implemented, and these are really important, because we need to make sure, if we're running a test today, that we get the same answer at -- at another time.

One thing that we've run into -- and this isn't a CLIR issue, or an R4S issue; it's a -- it's a lab-based issue -- is, any kind of training set that we use for cutoff determination or that we use to set up our algorithms, we really should have those positive controls be sustainable. And when you're using newborn specimens, our real estate on the blood spot is fairly limited, and so it's really hard to keep that set of controls to do -- to retest every time there's a change.

And the examples I show here are for Krabbe. We had -- For a very long time, our mean activity was about 4.4, as I described. That was -- we were getting reagents from Genzyme and the CDC. When we changed to a different reagent set, our mean went up to six. And if you're using a straight cutoff value, that would severely impact your -- your screen positives. Pompe, we saw the similar change when we went from one set of reagent to the other, and we also see differences, even, in how we extract DNA in our SCID test.

And so, as we think about how to deal with this going forward, we just need to keep these types of things in mind, so that when we develop new ways to look at the data and new ways to analyze and process it, we have to make sure that all those things still hold true.

And so, thanks for your attention. I know I went fast, but Dr. Rosini -- Well, it went off. Dr. Rosini gave me, you know, a review of the presentation, as did Dr. Rinaldo, my co-

presenters, Amy and Scott -- and sorry, April helped me pull some data together for SCID, and Monica's our -- our CLIR expert in New York state. So, thank y'all. Going to answer questions now or at the end?

DR. JOSEPH BOCCHINI: I think we're going to have all three presentations and then --

DR. MICHELE CAGGANA: Okay.

DR. JOSEPH BOCCHINI: -- bring you back up to answer questions. So, thank you very much, Michele.

Next is Scott.

DR. SCOTT SHONE: All right. I want to thank the Committee for inviting me to speak. I also want to thank my co-presenters, and I want to especially thank not only Michele, but also John Thompson and Carol Johnson, who gave presentations back in -- to this committee earlier this year, sort of set the foundation, the ground work, for what we're talking about today.

My goal today is, like Michele said, to

address a quite complex topic, with a lot of data, in a very short period of time. And so, I'll do my best to -- to keep everybody on the same page, but please feel free to slow my Jersey talk down if I'm going a little too fast for everybody and -- and -- and glossing over some things. But I took a little bit of a different tact than -- than Michele. I have a -- more of a broader view. I'm also going to be looking at tandem mass spectrometry before the acylcarnitine immuno acid disorders, so -- So, some of this might be a little bit repetitive, but I want to talk about -- I'm sort of going to try to tell a story and go through the process of setting and then reevaluating cutoffs.

And so, three terms are often used interchangeably: cutoffs, reference ranges, reference intervals. They're not exactly the same thing. Obviously, reference ranges and reference intervals tend to refer to the normal range for patients, where -- where a normal value's going to fall. Cutoff is that point above which a value

would be considered abnormal, or below which, depending upon the disorder that we're talking about.

But, regardless, these reference ranges and intervals are required, from a regulatory standpoint, to be established, no matter what type of testing we're doing. This isn't newborn-screening specific; this is clinical lab issue. And obviously, there are issues between screening and diagnostics outside the scope of this discussion, but -- but clearly, there are many points to consider. When we're talking about a screening test, it has to balance false positives, as been discussed multiple times this morning, at the expense of not having any false negatives.

But regardless of what type of laboratory test, there are certain factors that influence the decision-making on establishing reference ranges. There are endogenous factors, which are out of the control of -- of the laboratory or any individual, such as age of the -- the specimen --

age of the patient, rather. With respect to newborn screening, birthweight is another example of an endogenous factor. You have exogenous factors that can be controlled, such as feeding status: Did the baby receive hyperalimentation prior to obtaining a sample? That could affect amino acid.

Clearly, genetics and the ethnicity of the population are going to drive what -- what a laboratory sees, sort of indicative of why a state needs to establish their reference range based on their own population. Clearly, that's what they're going to see on a routine basis, so the reference range should be established on patients they're going to see routinely.

From a laboratory's perspective, there are preanalytical, analytical, and postanalytical factors: what time the specimen might have been collected, how was it collected, was it exposed to environmental factors, how long did it take to get to the laboratory, how was it handled in the laboratory can affect the results and,

ultimately, a reference range. And then, finally, statistical approaches. We've heard a variety of different methods today. Michele mentioned a couple additional ones. Are we using mean, standard deviation, median percentiles, interquartile ranges, multiples of the mean, multiples of the median?

And so, I'd like to suggest that it -- it doesn't necessarily matter, as long as you're consistent and you can back up, you know, what you've calculated, though I think we're learning more -- and -- and Dr. Rinaldo presented this morning about more complex covariate analyses that can clearly benefit in some -- some respects.

And ultimately, the evaluation population is key. Population that you use to establish your reference ranges must be heterogeneic enough to ensure that you see enough variability in the population to establish the reference range for that group and -- and consist of the appropriate populations.

And Michele mentioned size. I mean, she can have over 3,000 specimens in a week. That's not an option for all programs.

So, the time to establish a reference range can vary greatly depending upon your program. It provides an opportunity to collaborate and -- and work between states, but, again, you're then balancing out the populations you're ultimately going to be screening when you go forward.

So, I think I can capture a lot of these with a story about establishing cutoffs for tandem mass spectrometry that really began 9 years ago. So, in the spring of 2008, program acquired two new Waters Quattro tandem mass spectrometers -- Quattro micro, that is -- and was using the FDA-cleared PerkinElmer NeoGram Kit. So, new instrument required a performance -- a regulatory-required performance validation to ensure that it's performing well, and I'm not going to go into all the aspects of that performance validation and verification, but I'm

going to focus, obviously, on the cutoffs and reference range aspect of it.

And the -- the materials utilized for that aspect of the validation and verification were routine patient specimens, kit control material. Carla mentioned the CDC provided controls, as well as proficiency testing that helps establish those ranges, and then finally, and most critically, the confirmed positive and negative patient samples. I'll mention them in a minute in terms of the challenges, especially nowadays, with obtaining those samples and using them in terms of crossing that kind of lines.

So, a few years ago, Sue Berry presented to this group, and she presented a slide that looked like this and said, "I present this to you not so that you can read it, but that you can be impressed," and so I sort of share the same thing here. There is lots and lots of data. This is clearly a mass spec, so for every specimen -- and there were thousands of specimens run as part of the verification -- there were dozens of analytes

to review, and this is an Excel spreadsheet that is -- doesn't even encompass all the data for this -- for this -- for this run.

And at the time, there really were no specific tools available. I know R4S was available, and I'm going to talk a little bit about that in a minute -- I think back then, it was still called Stork, but the program didn't have any specific tools outside of Excel to analyze this data. And so, even if this was a single analyte review, there are still a lot of data, and it's a monumental lift for programs to analyze and interpret the data.

But the good news is, everything's normally distributed in our population, and all the babies fall neatly under this curve. That is so not true. So, this is a histogram from that validation of propionylcarnitine -- C3 -- about the first 3,400 babies that were run, and the actual data on the slide is irrelevant for the purposes of what I'm trying to explain to you, but rather, the methods that were utilized to try

to interpret and -- and identify break points for potential cutoffs. On this slide, we have the average identified three standard deviations. The current cutoff that was utilized prior to initiating a new method of verification. We also showed interquartile ranges.

And then, finally, what I'd like to point out on the, sort of, middle right of the slide is, if we didn't do any of this, if we just said, okay, we'll use the same cutoff -- all right? -- we're -- we're just screening for propionylcarnitine -- Setting the same cutoff would have resulted in double the number of referrals, just as a result of a change in instrumentation. And Michele talked about this at the end of her talk, with changing reagents but also instrumentation.

So, this is not only regulatory required, but the data support the need to -- to continually do this and monitor this. And I'm going to talk about continuous quality monitoring as I go forward.

But the -- setting the preliminary cutoffs is -- is really based on not only statistics but also collaboration. So, I showed the histogram and the establishment of -- of the -- the appropriate descriptive statistics. I show here, on the slide, Region 4. So, we accessed the -- at the time, the -- the Region 4 database, and -- and looked at peer cutoffs for -- again, this is propionylcarnitine; it's just an example that I -- I decided to use for today's talk -- the current cutoffs that were in use, and then a variety of different proposals based on interpreting the data and calculating the data different ways.

One thing that I want to be clear about is that the challenge with collaborating with other states is, again, different instrumentation, different -- some aren't using the same FDA-cleared kit, and so they're all guides. All this is just a tool to better inform the process that the program is undertaking. And -- and at least in New Jersey, the relationship

with the specialist for each disorder -- in this case, the metabolic geneticist -- is strong. And we rely on them to help, from a clinical -- clinical perspective, adjust and -- and review our cutoffs to say, should we identify this case? This is a case that should be caught by newborn screening and identified early.

The challenges remain -- and I mentioned them before -- population size. We clearly had enough population size. We're about -- New Jersey's about 100,000 births each year, so getting to 3,000 samples shouldn't take terribly long. The subpopulations, different methods in instrumentation, as I mentioned, obtaining specimens. So, clearly, getting specimens of confirmed positives or, actually, negatives can be a challenge.

And more importantly, finding false positives and -- and false negatives to add into the -- the group. I mean, I think the good thing is that there are not that great a number of false negatives, so that's clearly a -- a -- a

support for the system. It actually works pretty well, screening 4 million babies each year, but they do exist, and so trying to identify them can be a challenge.

But bigger than that is, trying to identify all the potential biological variants and the -- the differences you're going to see within a disorder. You could still be called a classic form, but there are mild classic forms of a disorder. And -- and so, when you're establishing a cutoff, and you're basing it on 3,400, or 5,000, or even 10,000 specimens, it doesn't guarantee that you're going to see the variance, when you only have that disorder 1 in every 50- or 60,000 babies.

So, there are inherent challenges, especially with setting cutoffs initially. And I think the -- the message is that cutoffs, reference ranges, remain an eternal work in progress. We are constantly reviewing and changing.

And so, before I get to that -- that

continuous quality review, I -- I'll say that those preliminary cutoffs that were set, that I mentioned here, are then -- I'll use the word validated, probably not the right term for it -- but then by running as many confirmed cases as we could garner, both within our program, as well as working with colleagues around the country -- And you can see the sample on the top left -- Or you -- I -- I'd like you to see the samples on the top left of the -- of the one plate that was run on a given day, where we substituted in MCADs and 3-MCCs and propionic acidemias and whole host of known disorders. And then, on the bottom left are the interpretations.

These were easy. You have an -- a -- an MCAD case with a C8 of 12.1. If a program can't find that, then there's bigger problems that just establishing your reference ranges. But we have to begin somewhere, right? So, it goes back to my discussion of, there are MCAD babies who have a C8 that's 1, all right? And so, the challenge is trying to figure out how to incorporate them in,

and that comes with time. Right?

So -- so, that leads me to a discussion of continuous quality monitoring. So, now we have -- now we have cutoffs that are established with data, data that drives all. It's -- it's not simply just common sense and where does something go. It's based on data.

And so, with the spectrum of continuous quality monitoring, a routine review of assay performance is essential, critical, and required. Beyond that, continuous monitoring of the process ensures that as the number of specimens increase, you're going to naturally see an increase in the variation of the population. So, you're going to see those babies that tend to be at the edges of the limits. People often ask, "Why do you have a borderline category?" Well, it's -- You're trying to ensure that, at some level, you're going to capture those, so that if you do identify them -- I have examples later of a borderline that we reviewed to say, "Hey, should this have been called out earlier?" -- is found.

And CLIR requires, as a corrective action, that adjustments to your reference ranges be made if the laboratory determines that the interval is inappropriate. All right? So -- so, if a -- if a newborn is not identified on the screen, it is not simply a knee-jerk reaction of the program to adjust the cutoff because it wasn't identified; it's a -- it's a requirement, and it's a documented requirement, and not only why was it not identified, but what is the corrective action to move forward.

And so, why would -- why would programs make adjustments and changes to -- to the program? So, now, flash ahead several years. The program has acquired a -- a more improved statistical tool. I don't have Excel spreadsheets anymore. We have this fancy tool. You upload your data, and then you can select percentiles and -- and/or fixed cutoffs and see where they'll fall. So, this is -- it doesn't say on the slide; I apologize -- C16, palmitoylcarnitine, where the initial cutoff was set at 7. It was about the

99.95 percentile, flying anywhere between 40 and 50 babies a year, but over time, over about 6 or 7 years, we began to see, as the instrument aged, a little drift, population variability. And so, this ended up falling to about the 99.9 percentile, and then we were flagging unnecessarily over a hundred babies a year.

So, we looked at, well, if we wanted to reestablish a percentile cutoff, what would it be? And that would be 7.5, and we'd get back to the same number of referrals that we had historically. And this is an ongoing process. At least in Jersey, this is done every 6 months, because we meet with those consultants every 6 months to review and bring back to them any potential changes we'd want to propose.

And, again, we went back to the R4S tool to look at where the peer percentiles, and on the top, you have the 7, on the bottom you have the 7.5, and it still falls around in that middle target range of what, at the time that this was calculated, R4S suggested. Now, this doesn't

necessarily mean that a cutoff is warranted. It still requires review of cases, or to confirm this case, CPT II or CCT disorders fall, but at least it gives us a starting point or an idea of -- of where a change might be warranted before a problem occurs.

The example I show here is actually working more efficiently and working smarter, not harder, in trying to eliminate false positives. This is an -- looking at: Oh, a case was not identified, or a case was really close to the cutoff, and we need to make an adjustment.

And I mentioned R4S, and the next few slides I want to talk about is using that as a potential tool for programs to help hone it. And -- and I know Dr. Rinaldo presented this morning that R4S is sort of, I'm going to say, dying a slow death, but it's really unto the -- up to the -- the world of Microsoft to support the infrastructure behind it, and I don't have any clear discussion, because we don't actually use -- I haven't had experience with CLIR yet.

But there are many examples -- and I'm not going to show them all -- where the laboratory algorithm that's established, the cutoff-based algorithm, matches what the R4S tools show, and that's fantastic. R4S says it's likely, the algorithm says it's a referral, a referred baby gets identified.

But there are also times when interpretations agree, but it's a false positive. So, in this case, this was a VLCAD. Both the R4S tool and the lab -- the -- the laboratory values on the bottom left indicated that the baby likely had or was at higher risk for VLCAD, and the baby was referred and ultimately cleared by diagnostic testing. And that's fine. I mean, false positives happen. We've talked about it. We try to minimize them, but they do occur, and in this case, both -- both tools agreed.

But then, the tools can disagree. And in one instance, the program might need to adjust the range. In this case, the laboratory's citrulline cutoff was 100 micromoles per liter,

did not flag an individual for referral, and the baby was ultimately diagnosed with argininosuccinic aciduria. Looking at -- And -- and ultimately, the program adjusted the cutoff. But looking at the data over the history of the program, no diagnosed case ever approached the cutoff that might have warranted adjustment, and working with the consultants, there was never a suggestion, as we did case reviews, of, you might want to drop that cutoff below what it is.

And then, we had a citrulline baby one. All right? So, a retrospective review, through the R4S tool, said this was very likely, so we packaged all the review together, our -- our statistics -- which didn't necessarily show any kind of shift that would warrant a change, but we did now have a case that was slightly below the cutoff -- and the data out of the R4S tool suggested lowering the cutoff. So, the cutoff was lowered to ensure that that -- that lower value would have been captured going forward.

And likewise, there are times when the

laboratory algorithm is correct, and the R4S tool doesn't -- doesn't agree. And this is a case where an initial C5OH was flagged as borderline. That's the .78 you see on the screen; flagged in yellow is borderline. The previous slides had red. That was presumptive and an immediate referral. I should have pointed that out before. The repeat came and -- and was again flagged as borderline, so the baby was referred -- through borderlines is a referral in our algorithm -- and the baby was ultimately diagnosed with 3HMG. All right?

So, we wanted to look at, should this child have been identified as a presumptive and -- and sent off on -- based on the initial? And we looked at all our tools, looked at, where do our cutoffs fall with peers, but also run the all conditions tool and the case score, and it came up with that it was not informative for this case.

So, it is quite possible that the tools don't agree, and -- and that's -- and that, I

think, stresses the importance of, there's not one tool that solves all the problems and all the challenges that we have here with this. And I would say, you know, that would be something to look at as we go forward with any new tools that are developed and used, like CLIR, where we have to be cognizant that, really, the idea here is to work as a system.

We have talked about this -- I won't say ad nauseam, because it's actually one of the most fun parts of what I like talking about, is, thinking about what we do, not as a laboratory anymore but as a system -- all right? -- that follow-up and -- and our discussions with follow-up and these integral meetings, where follow-up brings back cases, cases that were identified -- and that's good -- cases where it was called out as a presumptive and -- and what you would describe as a screaming hot presumptive, and the baby was ultimately diagnosed as -- as -- or cleared for the case. Well, why does that happen?

So, these constant discussions are

essential for the continuous quality improvement of the program, and then I stressed earlier, but consultation with the subspecialists -- I mean, they see these babies. They understand the workload that's put on them and trying to balance out and help the program balance out where we go, and then, finally, technical assistance in collaboration with colleagues.

So, I think, going forward, I mean, there needs to be an understanding that setting and monitoring cutoffs has multiple challenges. Right? Laboratory diversity, instrumentation used, methodologies used, the volumes of data that it takes to -- to analyze -- or the volumes of data that is required to be analyzed has a cost. All right? There -- it might not have a monetary cost, but there's opportunity costs.

And so, entering data into a repository requires time, and there's a cost to that. And the person who might be entering that data might not enter data into another repository, such as the NewSTEPs Quality Indicator Repository, or

might not be working on the hospital report cards that we all found are necessary for timeliness. All right? I don't -- I mean, I think everybody's aware that newborn screening program staffs are not blowing out the seams, so we're -- we are literally doing a lot more with less at the moment.

So -- so, there are challenges. I'm not saying that they can't be addressed, but there are challenges. Biological variability is -- is a challenge. I mention that over and over again, and then I'm not going to rehash case definitions, but I think it's a crucial part when you're -- when you're -- At least when -- when we look at our own data with in a program, we know what the consultants define as a case, because we meet routinely. But I don't know, necessarily, what New York or Colorado or Minnesota defines as a case, and if I'm going to base decisions off their data, I need to understand that better.

I -- I'll say it again: There is no one tool or methodology that covers all the

regulatory requirements, addresses all the good laboratory practices of which we are aware, or tackles all the above challenges for establishing reference ranges and cutoffs. And -- and like every other challenge we have faced and continue to face and will eventually face in the system, it must -- it necessitates a multidisciplinary and a collaborative approach to identify those newborns at risk.

So, again, I want to thank my co-presenters and my team at New Jersey, and I'll be available for questions after.

DR. JOSEPH BOCCHINI: Scott, thank you very much. A great presentation. Amy?

(Off-mic speaking)

MS. AMY GAVIGLIO: There we go. Thank you, Dr. Bocchini and the Committee, for inviting me here today, as well as my previous two presenters, Michele and Scott, for setting me up so nicely, because my task today is to really look at addressing and interpreting cutoffs in the realm of the postanalytical space, or follow-

up space.

So, to start, I will do a quick overview and recap of some of the points that were made by Dr. John Thompson and Carol Johnson at the previous meeting, first of which is to really define the role of follow-up. So, for states who have follow-up, those staff are charged with overseeing that the family is connected appropriately to the health system and that we ultimately get an outcome after an out-of-range newborn screening result. And that outcome can be that the child is actually found to be unaffected, so a false positive, or that the child is, indeed, affected, so a so-called true positive. And this is typically accomplished by the program contacting either the primary care provider and/or making connection to the appropriate subspecialist, and in terms of communication strategy for this, there's a multitude of modalities that may be used: phone, fax, secure email, et cetera.

The other point that I think was made and

that I really want to reiterate is the importance of that ongoing communication between the laboratory and follow-up in order to be able to facilitate the appropriate review of the cutoffs and testing algorithms. And I know Scott said he didn't want to rehash case definitions, but I'm going to, multiple times, because I think they're really important in ensuring that the lab understands, if I close out a case as a true positive -- that they're really understanding what that means and that it is comparable to other cases that I deem a true positive.

And my final point is that population health screening, especially in the world of rare diseases, requires a balance, both between what we know about the disorder in terms of natural history or how we expect it to present, as well as the unknowns, which, in many cases, there are -- there are unknowns with these disorders. I mean, certainly, the balance between false positives and false negatives, but in the space of follow-up, I want to touch on the fact that

the balance between false positives and false negatives really extends past the laboratory metrics of sensitivity and specificity, but understanding that if we lower a cutoff to a point in order to try to avoid missing anyone, and we increase our false positives, that that has a very real downstream effect to the medical system and has the potential to bog down an already overburdened subspecialty system, which, ultimately, can have consequences for individuals who are affected and need to be seen by these individuals.

So, for the remaining of -- remainder of my section, I'm going to be focusing on one of our endocrine conditions that we screen for, congenital hypothyroidism, in hopes that it will illustrate a few queue -- key points.

So, briefly, congenital hypothyroidism -- and I'll abbreviate it CH so I don't have to keep saying it -- is actually one of our more common conditions, reported to be about 1 in 3- to 4,000, so you'll see an asterisk there because

the incidence is reported to be increasing, and I will touch on that in a little bit. It is the only blood spot condition that is not typically inherited, so we don't see the standard Mendelian inheritance that we see with the other conditions, and it is typically due to a partial or complete loss of thyroid function because the thyroid gland either fails to develop altogether or partially, or just simply cannot function properly.

And finally, prior to the advent of newborn screening for this disorder congenital hypothyroidism was one of the most common causes of preventable intellectual disability, and this fact, along with the availability of this screen, led states to -- to add this to newborn screening panels, and we've been screening for this for quite some time.

In terms of how we screen for this disorder, there is general disagreement on what the best testing strategy is, but typically, it will involve looking at one or both of the

following hormones: thyroid stimulating hormone, or TSH, which is thought to be most specific for primary congenital hypothyroidism, or thyroxin, which I'll refer to as T4, which is thought to be more sensitive for secondary hypothyroidism but maybe less specific for primary. In other words, we may see higher false positives in -- in certain populations. So, a brief schematic: If the thyroid is not functioning correctly, what we would expect to see in congenital hypothyroidism is an elevation of TSH because it is not being processed by the thyroid, and a depression of T4 because it is not being made.

You may have mention -- or noticed on the last slide that I used the concepts primary congenital hypothyroidism and -- and secondary congenital hypothyroidism, and to get to Michele's point that she made with SCID, we may say we're screening for congenital hypothyroidism, but that's really an umbrella term for several conditions or potential findings that we may have in screening.

So, I think many of us believe that our true target is the permanent primary congenital hypothyroidism, which, as I mentioned, is caused by an issue in the thyroid gland development or function.

But there's also permanent secondary, or central, hypothyroidism. This is thought to be more of an issue with the pituitary gland and may be detected if using T4 as the primary analyte, not typically picked up if you're using TSH.

There's also something called transient congenital hypothyroidism, and it's pretty self-explanatory. It's, really, a temporary abnormality of the thyroid function, which later reverts to normal. The hard thing with this particular categorization is that what "later" means, no one's really defined, and so this can be particularly difficult to say whether it is a false positive or a transient hypothyroidism. These cases may or may not require treatment -- really dependent upon the value -- in -- and in order to determine if it's permanent, in some

cases they'll do imaging, but if not, they'll actually challenge the child at 3 years of age, take them off treatment and see how it goes.

Subclinical or compensated hypothyroidism -- I think this is something we're seeing more and more. I think you can think of it as mild congenital hypothyroidism, so where you see a persistent mild elevation of TSH but, typically, with a normal free and total T4. I mean, typically, these infants don't have any symptoms in infancy.

The other part, the iatrogenic hypothyroidism, which is not necessarily a disorder, but I wanted to mention it because there are often reasons that the lab picks up an elevation of TSH that is real. It's just that it is a finding secondary to some sort of intervention, and so that becomes difficult to figure out how to take those and -- and accommodate those into a cutoff or workflow.

Both Scott and Michele mentioned that there are several factors that can cause issues

in interpretations and setting cutoffs, and certainly, congenital hypothyroidism is -- is no different. One issue we know of is that there is an endocrine surge at birth, which elevates the TSH and results in dynamic changes of the T4. So, this can result in a high number of false positives, especially if specimens are collected early, so less -- less than 24 hours.

We know, in addition to an endocrine surge, we may see delayed elevations in premature infants. So, as you can imagine, if the -- if it's taking them a while to kind of come up to baseline, that we can miss these individuals if a subsequent screen past that initial 24- to 48 hours is not conducted.

We know there are known maternal and infant intervention effects. Certainly, if the mother has hyper- or hypothyroidism and is being treated, exposure to radioactive iodine and -- as well as some cardiac medications.

And then, there are some, kind of, unknowns right now. There's reported possible

intervention effects, head cooling, which is becoming a more common intervention in the NICU. There's some reports that this may affect the screen, as well as -- as ECMO, you know, in terms of transfusion.

So, with that in mind, states have several things to think through in terms of how they're going to make adjustments to accommodate for these issues. I mean, I'll go through a few examples of what states have done to -- to try to address this.

The first is varying the cutoffs by age at time of collection, and Dr. John Thompson presented a -- a great couple of slides on how they've done this in Washington. So, the thought behind this is that you can account for that endocrine surge, but I also want to be clear that this relies on integrity of the data coming into the program. So, if the time of collection is reported to me incorrectly, I -- I would be applying a cutoff that, maybe, isn't actually capturing the true clinical status of the child.

The low birth weight or premature serial screening protocol -- many states have implemented something like this in their program, whereby low -- low-birthweight infants or infants in -- in ICU get multiple screens. So, they get, you know, usually one either on admission or at 24/48 hours, and then a subsequent screen later on, and this is an attempt to account for those delayed elevations that I mentioned.

The other way to potentially address this is doing a routine second screen. So, certainly, there are states out there who routinely recommend, you know, a screen at the regular time but a screen later on, 1- to 2 weeks later, and again, this is an attempt to account for some of these delayed elevations.

I'm going to touch very briefly on the follow-up process in terms of communication to and from the provider. As I mentioned, that communication amongst the follow-up staff and lab is important, but certainly, communication to our providers is equally important.

So, in terms of borderline screen results -- so, these are ones that are either mildly elevated or mildly depressed -- typically, the program will request a repeat screen. In some cases, we may just request that they do a clinical TSH/T4 simply because it's a fairly common test; primary care providers are pretty comfortable ordering it. So, in many cases, I'll have the option of doing one or the other.

For a presumptive positive screen result -- Here, we're typically just recommending a TSH/T4, so some clinical labs, as well as a pediatric endocrine consult. And the urgency of -- of when this needs to happen likely depends on the values. We try to triage our responses as much as -- as much as we can, for both the family and the providers' sake.

And finally, that was really focusing on communication from the program to the providers, but I would be remiss if I didn't talk about the importance of communication from the providers to the program, especially as it relates to

potential false negatives, because we don't know what we don't know, and we can't apply the potential cases that we're missing if we simply just don't know about them. So, clinicians have to be encouraged to report these to the newborn screening program. Some states have actually mandated this in their statute, which is an interesting way to approach it.

But I will say, in terms of congenital hypothyroidism, this is probably most difficult because many of them are followed by primary care. So, we don't, kind of, have that subspecialist human relationship that we tend to see in metabolic and immune.

I'm going to touch briefly on the clinical TSH and T4 results, and really, the sole point of this is just to say that we -- we do ask for these, at least in the state of Minnesota, as part of our follow-up process, and I want to use it as an illustration, too. I think what Scott mentioned is that cutoffs and reference ranges, in terms of variability, is not something limited

to newborn screening. It is an inherent laboratory finding.

So, I'm going to put up a couple of tables, and they are both for you to read and be impressed, unlike Scott. No, you -- The purpose of these -- So, these are TSH and clinical T4 labs that we've obtained in 2016 from the state of Minnesota, as reported for infants 4 days to 2 months of age. And I'm not putting this up here for us to critique the -- the reference ranges that certain labs are using but to illustrate the fact that even post-analytically, in terms of what we're seeing from the follow-up team, there is a wide range of reference -- reference ranges that we need to look at and think how we're going to deal with.

So, what does this mean for us? It means, 1) that determining the outcome is pretty difficult, because we have -- we're looking at such a variable, you know, spread of reference ranges. And what, ultimately, this does is, it forces the program staff and the subspecialists

in which they're working with to make a decision. They can either accept the values within the context of the reported reference range, or they can choose a value over or under which they will continue to recommend follow-up, regardless of the reported reference range. Not surprisingly, this approach is likely going to alter what your reported incidence is, as well as what the reported outcomes are, and I can tell you for a fact, in Minnesota, it did.

So, in 2016, we changed our approach from A to B. This was after discussing this with a few other states, as well as our pediatric endocrinologists, and you can see that our reported incidents almost doubled. Likely, these are subclinical or transient -- at least, what we think are transient now -- but you can see how this may impact, then, what the lab is getting and how they're interpreting their cutoffs and what they're applying to cutoffs.

I mentioned that congenital hypothyroidism is an umbrella term for several

disorders, and so, again, I'm going to go back to the case definitions in that the agreement between the lab and follow-up on how you're categorizing these, as well as your subspecialists, is critical. And then, there needs to be an understanding that you may not know whether a case is permanent until age 3, and as -- as Scott said, many of us don't have the resources to follow cases for this long. So, you know, getting that information post-challenge to get, really, truly, what the final outcome is can be very difficult, and, quite frankly, is often not done very -- very often.

So, the outcome reported back to the laboratory for them to use in establishing cutoffs and defining their workflows will be dependent upon, 1) the follow-up practices, which I hope I illustrated on the previous slide, as well as the clinical expertise in the state. Pediatric endocrinologists are known to not agree very often, and they differ not only on the preferred screening strategy, but also on the

definitions of the various types of congenital hypothyroidism. One endocrinologist may call it transient, while another may call it subclinical, and certainly, in terms of clinical care can vary on the treatment approach, as well.

So, I will end with three take-home messages that I'd like to leave everyone with. The first one, which I mentioned right up front, is that population screening, especially in the context of rare diseases, is really complex, beyond the testing itself. There are very real differences and approaches to follow-up and in the clinical realm in terms of what a -- defining a case in whether or not that case is going to be treated and how long it takes to define that case.

The other point, which I hope the tables illustrated, as well, are that the concept of variable reference ranges or cutoffs is not unique to newborn screening. It's not unique to screening. It's -- it's a -- a lab concept. And so, you know, it's something that I think we need

to be aware of, and I think there's ways to, you know, try to become as -- you know, slightly more uniform, but inherent variability is -- is just going to exist.

And, finally, ongoing communication -- excuse me -- between lab and follow-up, as well as the subspecialist, is completely vital to the -- the success of any screening program.

So, with that, I'd like to thank the Short-Term Follow-Up Workgroup, which is a great workgroup set up by NewSTEPs and APHL, especially the co-chairs, John Thompson and Carol Johnson, as well as my team in Minnesota, and particularly Amy and Nancy, who are our lead endocrine follow-up individuals. Thank you.

DR. JOSEPH BOCCHINI: Amy, thank you very much.

(Off-mic speaking)

(Applause)

DR. JOSEPH BOCCHINI: Can I get the other two, Michele and Scott, back up to the podium? And then, Piero, are you still on the line? Still

able to be on the line?

DR. PIERO RINALDO: Yes, I am.

DR. JOSEPH BOCCHINI: Great. Let's open this for questions and then discussion by the Committee. So, we'll start with Beth.

DR. BETH TARINI: So, I find it interesting that -- that a lot of the four presentations this morning focused on getting the false positive rate to zero, or as close as it can be, yet much of the discussion of public that probably has influenced and encouraged us to have this discussion more broadly has been about false negatives. And so -- and it was touched upon at one point, in at least one of the presentations, by Amy, but -- but it seems to me, a system of passive referral back about some of these conditions is not necessarily adequate enough to address this problem of false negatives, especially when we're considering additional screening techniques, which may -- which may exacerbate, potentially, the problem. I was wondering if any of you have any brilliant ideas

on that.

(Laughter)

MS. AMY GAVIGLIO: All right. I'll take a stab at it, Don. So, your -- your question is, how we can supplant the current passive process of obtaining --

DR. BETH TARINI: But if you had --

MS. AMY GAVIGLIO: -- false negative cases?

DR. BETH TARINI: If you had funds galore, or you could redesign the system, what would be some initial, sort of, low-hanging fruit interventions to at least start to -- to dig away at how we can identify false negatives that we're probably missing?

MS. AMY GAVIGLIO: I think it's -- it's largely an education issue, to be honest. I think -- and I think the Milwaukee Journal Sentinel articles highlighted that a lot of providers take a screen as diagnostic. And, you know, I think we've always started with the -- the concept, in terms of education, of what is newborn screening,

but we've never started with, what is screening.

And so, really understanding that cases can be missed and the importance of reporting back -- I think that just comes down to education of primary care providers, as well as, probably, some of the specialists, especially for conditions where we may be more likely to miss them, and the fact that that can happen and the importance to the lab and follow-up program on that information when it does happen.

DR. SCOTT SHONE: I just want to add one quick thing that, at least, I'm aware of in -- in some states, where the birth defects registries have a close relationship, especially the follow-up programs, and will feed back any diagnosed -- any, you know, case that's diagnosed, and then follow-up programs can see if that was actually screen positive and referred or if that was a -- a case that wasn't identified.

You know, there -- there are challenges with that, especially for -- now, with later onset conditions, and there'll be movement in the

birth defects registry, and the new state might not communicate with the screener, and so, it goes back, I think, to a -- an educational issue. But there --there are some existing tools that could potentially be exploited to help get some traction towards that, and -- and as I mentioned, the strong relationship with the subspecialty groups --

I mean, I feel that at least in New Jersey, every 6 months, every subspecialty group meets with the program, metabolic geneticists and pediatric endocrinologists, hematologists, immunologists, and so -- all my -ologists. And so -- and so, they don't often wait for the 6-month meeting to bring up cases, but they -- they would always -- I think they would always acknowledge it. If something came up, at least that they saw, they would show that immediately, so.

DR. MICHELE CAGGANA: And also, in some states, it's in the regulation, the newborn screening statute, that false negatives have to be reported back to the program. And the

Congenital Malformations Registry in New York, that's one of the -- The newborn screening conditions are supposed to be reported by 2 years of age, and so you -- you can miss that window, and the follow-up -- You know, when you're following up things like heart defects and structural anomalies, people don't always think about the newborn screen, and if the baby's being followed and changes providers, whose responsibility is it to enter that information? And so, it's -- it's a -- it's a tough thing to -- to standardize, I guess.

DR. BETH TARINI: And one other piece, I think, of information to consider, which I think Dr. Rinaldo has done work in, are sudden infant deaths, and what are -- And I don't know that there's a comprehensive, sort of, approach to when a child has -- is diagnosed or dies of SIDS or -- or -- We can go into the whole how they report them on the -- on the death certificate, but when a child dies of an -- sudden, unclear illness, is that an undetected newborn screening

disorder?

DR. JOSEPH BOCCHINI: Amy, I was going to ask, when you went to your second plan, where you broadened the number of patients to be evaluated by looking at just below and just above, how did you select how to do that, and what sort of follow-up is recommended under those circumstances? And then, what do other states do under that setting?

MS. AMY GAVIGLIO: Yeah, we modeled this a lot after what Washington State was doing. And -- and really, we looked at, you know, data that we had in terms of how we -- what we had picked up, but we also worked a lot with our subspecialists on, kind of, what they felt was a point where they just felt like more follow-up needed to happen, a value by which they felt more follow-up needed to happen.

So, what we recommend in that case, we send them a note just saying, you know, "We understand this appears to be within the reference range of the lab you used, but our

specialists, you know, are -- feel that this warrants some -- some more testing." And usually, it's just repeating those labs in, say, 2- to 4 weeks, just to kind of monitor whether it is, indeed, coming down or whether it's staying the same or going up. After, you know, a few repeats, then we'll usually recommend a -- a consult, at that time, with pediatric endocrinologists to assess whether treatment is necessary.

DR. MEI BAKER: Mei Baker. I want to say something. Here is -- I think, that's as good a point, because the reason when I thinking newborn screening because the general principle is that we try very hard, when we set the threshold, is not to miss a case. So, a lot emphasize is set up a very conservative and over the time trying to modify the -- really emphasize the work on the false positive. I think this is -- I think maybe it's one good reason the three speakers who didn't put an emphasize on false negative, but that -- you -- you pick up advice as the -- the medium -- talk about a false negative.

And second part I want to -- to think through this is that, indeed, you have the system, and four speakers all mentioned the regional and how we do the comprehensively. And so, one thing I think each situation, like a false negative, occurred, I think we have the need to think -- Of course, we want to check our system working or not. Also, we -- We also need a study investigate that specification is read because of system of cutoff or have some unique situation for this specification, because we can -- this is more regional and informative to help us going forward. That -- that's, I think -- that's a few important, we are not lose this -- the point, too -- either.

DR. JOSEPH BOCCHINI: Thank you. Don?

DR. DON BAILEY: I don't really have a question but just an observation. These have all been very helpful presentations, and appreciate very much the awareness this has -- has brought to us.

To me, I'm struck by the need, on the one

hand, for massive amounts of data on many, many children, hundreds of thousands of children, really, so we can understand the true, where there's genotype/phenotype correlation, to the full range of expression of a -- of a biochemical marker or a genetic marker, as well as a clinical -- clinical phenotype. And on the other -- other end, the case-by-case information that we need to do, child by child by child, to really understand: What is it that's going on with this child?

And so, how we marry these two systems together, that this big, massive database and the -- and the case-by-case work, and how they're mutually informative -- That's where we really need to be focusing our efforts.

DR. JOSEPH BOCCHINI: Annamarie?

MS. ANNAMARIE SAARINEN: Thank you, all of you, for such a great talk. I'm always so happy to see Minnesota overrepresented at any meeting, so. Welcome, Amy.

(Laughter)

MS. ANNAMARIE SAARINEN: I wondered if either -- or any of you, actually, can answer how universal the cross-pollination of birth defects data with the NBS programs are. I know what it is for our state, but as you pointed out with CCHD, that's another -- as you know, another challenge, because we have kids that, you know, are coming back through primary care that end up being diagnosed with the things we often can miss with pulse oximetry screening.

So, that's just one example, but I wondered about this, because I think it's important, and the point that was made around case definitions and nomenclature. I -- I don't know what that takes, if it's just funding, if it's Dr. Zuckerman's work that influences some of this, but it's been something that's been discussed since my first interactions with this meeting, 8 years ago. So, I wondered about pathways for that.

DR. MICHELE CAGGANA: I -- I know, in New York, we -- we do work with our birth defects

registry, more for looking at structural anomalies in children. I do know that the newborn screening data is very underpopulated in that group, and that -- that -- this discussion made me think that that might be an angle to see.

Generally, if we have a false negative-type result, the clinician will call us. Our CF physicians are very good at that, immunologists, and the metabolic docs. And, of course, the first thing you do is, go back and look at your process to see, is this something we did wrong, or is this a -- You know, there could be many different causes for a false negative. It could be a lost specimen, a specimen that -- that we thought was received and never received. You know, so you have to go back and check all of these different, sort of boxes, and then you go back and you look at the analyte results.

And so, if we could survey the birth defects registry and then align that with our -- our cases, then that might be an approach that would be helpful to -- to look at.

MS. AMY GAVIGLIO: Yeah. I would just add, in terms of -- much like newborn screening programs, birth defects registries are different and operate differently, in terms of whether they're active or passive or what is considered a reportable condition. And so, not all states have newborn screening conditions as a reportable condition unless it is associated with a structural defect, though I -- I have heard some who've added those conditions, which may be something interesting to look at, certainly for us. Our connection with birth defects is most robust with CCHD, though, also, we use it with hearing loss to look for cold morbidities, but I think it's -- it's an interesting approach, and I would say, in terms of looking at it from a national landscape, it's a little bit all over the place in -- in terms of how that connection is made and how the registries themselves operate.

DR. JOSEPH BOCCHINI: Let me just ask if there are Committee members on the phone, or

Piero, who wish to make a comment or ask a question so I don't -- we don't miss some?

DR. PIERO RINALDO: This is Piero Rinaldo. I have a comment -- a -- a question for Scott. I -- I agree with you that there's always room for improvement, but I believe that, as you presented a VLCAD deficiency, there was a -- a critical piece missing, the dual scatter plot, which is exactly (audio interference) separate true positive and false positive. So (audio interference).

DR. SCOTT SHONE: I could not -- Did anybody else get that question? Because it was breaking up.

DR. JOSEPH BOCCHINI: Yeah, could you repeat that, Piero? I think we lost the last part of that question.

DR. PIERO RINALDO: My question is that Scott showed an example where, let's say, R4S didn't do the job. It was basically coding abnormal false positive. My question is about the fact that I didn't see evidence of use of the

tool that is exactly designed to prevent that.

DR. SCOTT SHONE: Sure. So, as I mentioned at the beginning of my presentation, we were incredibly limited in time. I'm happy to share that and -- and work with you, Piero, to -- to look at -- at that or any other specific case. I -- I didn't -- I didn't feel that I had the -- well, the appropriate time, much less wanted to -- to bog down the talk with going through every single step of -- of R4S. But as you know, over the years, you have walked not only me but other staff in -- in New Jersey through use of the tools. So -- so we can certainly review that, and I'll reach out to you after --

DR. PIERO RINALDO: Okay.

DR. SCOTT SHONE: -- after the Committee meeting.

DR. PIERO RINALDO: That will be great. Thank you.

DR. JOSEPH BOCCHINI: Beth?

DR. BETH TARINI: One comment: I think that for the -- When you look at the disorders

that have been added to the panel and the time since they've been added, the one what strikes me as time since on the RUSP and achievement of data centralization and progress made from a research and clinical standpoint made based on that data centralization is CF.

And I think the elephant is -- in the room is that we all -- and I don't have any current funding from the CF Foundation, but I have in the past is my disclosure -- But I think that we could learn a lot from how the CF Foundation has -- has been able to achieve such, I would say, comprehensive coverage of these children that have been screened, both in terms of their genotype, their phenotype, their newborn screening results.

And -- and we can all say, "Well, yeah, they have more money than the rest of us." But I think they -- there are also additional organizational issues that they have been able to somehow overcome that I think if we can learn from them, even a small, incremental amount, we

could probably make some headway.

DR. JOSEPH BOCCHINI: We have --

DR. ROBERT SAUL: This is Bob Saul for the AAP. I'll be glad to ask a question now or wait 'til the Committee members are done.

DR. JOSEPH BOCCHINI: Okay. Well, the Committee members are done, but you'll be third. I have -- Okay. We have Carol first, then Mike, then you, and then Siobhan.

DR. CAROL GREENE: Carol Greene. I -- Most helpful panel, and a couple of observations and a -- and a question. When we think about false negatives, there's a lot of discussion, or perhaps even a little bit of confusion when some -- And I think the example was very nicely made in -- in CCHD, that there are conditions that show up later that CCHD is known to not pick up. They're still heart defects, but they're not cyanotic. And similarly, there's the homocystinuria, with the -- with the low methionine instead of the high methionine that's never going to be picked up by a screen, and the

certain kinds of -- of hypothyroidism.

So, the other thing that really struck me is the -- you know, the example of the new kit and the changing numbers. And that makes me, really, even more nervous about a single database that -- that all the past wisdom says, this is how you know it's a true positive or a false positive, but all of a sudden, your new kit, you have completely different levels. And how does that relate to this single resource?

The question that I had is -- This was a -- a great panel on the follow-up but kind of stopped short of the -- how do the -- interact with the families and -- and -- And I'm very curious: What happens when a state makes a decision that you're going to recommend that a child be followed up in a way that's state-specific, and not specific to the Quest or the LabCorp normal values, and the physician -- So, first of all, I know a lot of states don't even turn in levels. We don't give the numbers. We just tell the state health department: This baby

was unaffected or affected. We don't tell them what the acylcarnitine profile was or what the sweat chloride was. And CF is going to make all of these other variabilities look like nothing because of the variability in the disease. But what happens when the pediatrician, then, having already told the family that the baby's all clear based on the Quest lab report, now has to get back with them and do follow-up?

MS. AMY GAVIGLIO: Yeah, that's a -- that's a fantastic point, and I would say that we make the recommendation. We -- as I mentioned, we kind of send a letter outlining why we're making this recommendation, but ultimately, is -- it is up to the primary care provider. We as a public health program, especially newborn screening, never dictate medical practice. So -- so, you know, we'll follow up once or twice and, ultimately, if they say, you know, "We feel like this is fine," then we're going to close it out as, the provider is considering this normal. So, that's how we would handle it, at least in our

state.

DR. CAROL GREENE: So -- so, follow on, that means that even with your own case definition, you have a case definition, and you accept that you're not following it when the provider says, "I'm calling this kid normal," and you call it normal, even though it doesn't fit your case -- I'm -- I'm -- I'm not criticizing. Please be aware. I'm just pointing out that this is very messy and, see --

MS. AMY GAVIGLIO: Yeah.

DR. CAROL GREENE: -- it makes all the rest of it look clean.

MS. AMY GAVIGLIO: No, I'm actually really glad you're -- you're pointing this out. I don't feel bad about it at all, because I think you're illustrating the exact point that I wanted to make, in that it is very complex, and as much as we want to shove things into a box, we are not in a vacuum, and we have to rely on the -- what is reported back to us, how it's reported back to us, and -- and, kind of, how far we want to push

a system that we're not really meant to push, which is the medical system.

DR. JOSEPH BOCCHINI: Mike?

DR. MICHAEL WATSON: So, I -- I'm actually interested in figuring out: How do we figure out which of these systems works best? I mean, I'm relatively convinced that CLIR does a very nice job bringing down false positives. My -- the only thing I'm unsure of: I don't know of -- So, in New York, do you report -- When you find a false negative, does that get put back into CLIR so that it becomes possible to calculate negative predictive values? I'm guessing it's probably not a comprehensive thing that's being done out there when you find one.

DR. MICHELE CAGGANA: No, I mean, we -- we look at the -- We look at all the processes, from when the sample was collected all the way through what the report and final outcome was. We just started using CLIR for the LSDs right now. We have uploaded a lot of our normalized data and our case data to R4S and CLIR, but we're not

using it for anything but LSDs right now, so we -- we don't have that, you know, data. Fortunately, these don't come up that frequently, and a lot of times, it's not a screening result issue.

But -- but that's certainly going forward, and I think the point I wanted to make, also, was: In order for this to work, it has to be tested. It has to be tested fairly long term, by many different states, and the way to get around, I think, this -- this system of changing machines and reagents is actually to have people upload their new data and have it keep, you know, recapitulating, so.

DR. MICHAEL WATSON: Yeah, that's exactly where I'm going, is trying -- I mean, it seems like one of the more straightforward problems that's data driven, to figure out which of these systems is the best approach to, you know, calling out something. I don't know -- I mean, I don't know if the Committee is in a position to make a -- a recommendation that that -- I mean,

it's with some trepidation, I must admit, that I say this, remembering how the second screen studies in the states went over a decade without having -- being able to get anybody to play because the consent issues.

But it seems that -- that, you know, the data's going to be out there. CLIR can't do it by itself because it doesn't always have the other data that the state has about false negatives and may not have everything related to the false positives. So, it has to be a collaborative kind of approach, but it's -- I mean, it just strikes me as one of the easier problems of -- of a data-driven analysis, to figure out what to do.

(Off-mic speaking)

DR. JOSEPH BOCCHINI: Next, we have Bob Saul on the phone.

DR. ROBERT SAUL: Let me add my perspective as a primary care physician now. I've lived on both sides of this fence, and I appreciate the arguments -- or not the arguments, the points on both sides, but -- Can you hear me?

DR. JOSEPH BOCCHINI: Yes, we can hear you well.

DR. ROBERT SAUL: Okay. The primary care providers are, in many ways, still very much out in the field and unengaged, despite the fact that we have lots of nice tools and despite the fact that, oftentimes, these patients, from what the various conditions that are discussed here, and even other ones, are sometimes funneled to -- more to the specialists, be they the -- the metabolic geneticists or the endocrinologists or -- or those sorts of things.

But in my experience, here in my clinic, which runs the biggest Medicaid clinic in the state of South Carolina, and talking to other PCPs around the country, is, still, most of them feel like we don't have a good integration with our newborn screening programs. And I think we talked -- I -- I heard the conversation about making sure we educate the PCPs. I think, at the same time, we need to be sure we have the understanding of what it's like to be a PCP and

how we can better broach that interface.

Now, institutionally, you know, the AAP has been doing this ever since the ACMG guidelines came down, but we all know that it's -- it's people to people. And in my state, if I call the state lab about a condition, I'm likely to get a text -- or a phone message, and they won't call me back. Now, that's not a condemnation of South Carolina; it's a -- it's a problem with staffing.

But in -- I think that -- I -- I suspect the situation here is not a lot different for some people. Now, I suspect it's not for the three ideal programs I heard today, but it still is an issue that impedes, I think, the -- the appropriate implementation of the newborn screening project on a national basis.

DR. JOSEPH BOCCHINI: Thank you for that comment. Let me just -- Next is Siobhan.

DR. SIOBHAN DOLAN: Siobhan Dolan from March of Dimes. I really appreciated the follow-up conversations and discussion, and I kind of

wanted to suggest and ask us to think about the real continuum from the patient perspective, which is actually that some of the information that may help solve the conundrums in the follow-up period may have actually been diagnosed prenatally, because at the same time that there's expansion in the newborn screening domain, the prenatal carrier screening world is actually growing, as well. And for those of you who may not get these bulletins, in March of this year, the American College of OBGYN put out a bulletin suggesting that expanded carrier screening, which, in some cases, is well over 200 conditions, is a -- is a viable option.

So, at -- you -- I -- and we're not going to solve this today, but I also want us to just think about how, from the patient perspective, by the time they even get to newborn screening, they've already had a tremendous number of decisions to face around aneuploidy screening, around carrier screening, and it's just really complicated, and it's really -- I think patients

end up, certainly by 20 weeks prenatally, extremely confused, and then to get to the newborn screening period and starting that odyssey again -- And actually, some of the information may solve what comes on -- comes up in the newborn screening period.

So, there's some educational efforts, I think, around patients that could be a first pass to have them understand and maybe even get in writing what happens prenatally to inform the post-natal and newborn screening follow-up period, where applicable, and then, also, just the idea of having the electronic medical records from the mother's workup into the newborn. And I know, again, that's a big challenge, but I -- I just wanted us to be aware, in this context, that a whole bunch is happening before that baby even gets their newborn screen, and -- and how can we use that to the advantage of helping babies.

DR. DIANA BIANCHI: Add to --

DR. JOSEPH BOCCHINI: Thank you. I appreciate that. Yes.

DR. DIANA BIANCHI: Yeah, so I'm Diana Bianchi, Director of NICHD. I want to echo want Siobhan said, but also, it's even worse than that, because now Baylor, as well as Natera, are offering non-invasive prenatal screening for single gene disorders. So, it's not the carrier situation; they're actually doing testing for affected fetuses. This is very late-breaking, and something we -- you know, we're going to have to deal with, as well.

DR. JOSEPH BOCCHINI: Thank you. So, unfortunately, we have to move on because we're -- we're out of time. But I think that the key thing for the Committee now is that we've -- we've heard some -- from experts that we -- we see much of what's going on in -- in particular states, but now the -- the potential role for the Committee we need to define, and -- and whether the Committee has a role in trying to deal -- I think Don put it nicely. We've got this large database, and then we have individual patients, and we're talking about situations where an

individual patient could be missed and how to address that in a way to minimize that or eliminate that if possible.

And so, lots of things are in place, and the question is whether this committee has a potential role in either organizing or making recommendations, providing guidance, and so we certainly want to hear from the experts about that, in -- in terms of whether the -- they feel the Committee has a role in this, as well as members of the Committee. So, perhaps in each of the workgroups this afternoon, spend a few minutes thinking about whether the workgroup in -- in each of those areas may potentially have a role. And obviously, we're going to have more information in August, perhaps, with the APHL survey results, which might be really helpful, as well as some input, so that we can kind of see whether we have a significant role in this area.

All right. So, we are running a little late, but we do have public comments now, and we do have five individuals. I want to thank the

panel. That was really excellent, and Piero, as well, from your distant site.

DR. PIERO RINALDO: I'm checking out now. I have to go.

DR. JOSEPH BOCCHINI: All right. Thank you very much. So, we now have five people with us here today who have requested to make public comments. As I call your name, please come forward to the microphone to provide your comments. You need to keep your comments to approximately 4 minutes each.

First on is Jill Jarecki. Dr. Jarecki is the chief scientific officer at Cure SMA, and she will be discussing newborn screening for SMA. Dr. Jarecki?

DR. JILL JARECKI: So, thank you, Dr. Bocchini and Advisory members, for the opportunity to talk to you today. As you said, I'm the chief scientific officer at Cure SMA, and I'm testifying on behalf of the spinal muscular atrophy patient community regarding our nomination of SMA to the -- for inclusion on the

Recommended Uniform Screening Panel.

As you know, in recent years, there have been significant advances towards developing a treatment for SMA, and these reached a new height on December 23, when the FDA approved Spinraza, the first-ever therapy for SMA. Clinical trials of Spinraza showed effectiveness across all SMA types, resulting in the FDA's broad label for the drug.

Data from the randomized, sham-controlled Phase 3 ENDEAR study showed a statistically significant reduction in the risk of death or permanent ventilation in infants with SMA. In fact, Spinraza decreased the risk of death or the need of permanent respiratory support from 68% in the sham control group to 39% in the drug cohort. In addition, 51% of treated infants gained mile motor -- motor milestones, compared to none in the sham control group.

Both human natural history data and animal modeled data suggest that early drug intervention is required for greatest efficacy in

SMA. Natural history data indicates that there's only a small opportunity for optimal intervention in SMA type 1, which, as you know, is the most common and severe form of the disease. It has been shown that type 1 infants undergo rapid and severe loss of motor neurons in the first 3 months of life, and this often results in the loss of more than 90% of motor neurons by 6 months of age.

Importantly, results from Biogen's open-label study of pre-symptomatic infants, called NURTURE, demonstrate that infants receiving treatment pre-symptomatically obtain more motor milestones and better outcomes when compared with infants in the ENDEAR study, who received treatment after symptom onset. As of October 31, 2016, no pre-symptomatically treatment -- treated infant had died or required permanent ventilation, compared to 39% in the sham controlled group -- 39% in the treated group in the ENDEAR trial. Furthermore, 89% of treated infants in the NURTURE trial have gained motor

milestones, such as the ability to sit, stand, and walk.

Therefore, it is of the utmost importance that SMA be added to the RUSP, to ensure patients receive treatment as early as possible to obtain the best possible outcomes. Our community strongly urges the Advisory Committee to advance the SMA nomination that was submitted on February 28th to evidence review during today's deliberations.

We believe that there -- the evidence is strong to support this, including two ongoing SMA newborn screening pilots in New York State and Taiwan, sensitive and specific screening assays and diagnostic tests, good understanding of SMA natural history, including genotype and phenotype correlations, and, most importantly, a life-saving treatment for SMA that has been shown to be more effective when delivered pre-symptomatically in the NURTURE clinical trial. I thank the Committee for the opportunity to address you today and for your consideration of

the SMA nomination.

(Applause)

DR. JOSEPH BOCCHINI: Dr. Jarecki, thank you for your comments. We appreciate them, and as you know, we will be looking at the nomination packet today. Thank you.

Next, we have Debra Schaefer. Ms. Schaefer is a caregiver and will be providing comments today on newborn screening for SMA.

MS. DEBRA SCHAEFER: Good morning, members of the Advisory Committee. Thank you for the opportunity to testify today. My name is Debra Schaefer. Two of my granddaughters have been affected by spinal muscular atrophy, also known as SMA, which is the leading genetic cause of death for infants. On behalf of the SMA community and Cure SMA, I'm here to comment about the urgent need for newborn screening for SMA.

My granddaughter Madison -- this is -- passed away in 2012, at 7 months of age, from SMA type 1. My granddaughter Bailey, who was born in January 2014 and also affected by SMA type 1, is

alive and thriving due to the early treatment she received via a clinical trial for a drug called Spinraza. On December 23, 2016, the FDA approved Spinraza, making it the first-ever approved treatment for SMA.

This drug has enabled Bailey, now age 3, to flourish, despite having the same disease that took her sister's life at just 7 months. Spinraza has helped Bailey with her respiratory function and strength. Before she started on the drug, she had lost movement in her legs and could no longer lift her arms or hold her head up. She now has her arms and legs in the air anytime she's lying down. She can roll on her own and can lift her bottom off the floor. She's able to sit without support and propel herself in a manual wheelchair, as well as bear weight on her legs.

When I see Bailey with her mother, I see typical 3-year-old mischief. When in her chair, she rolls up to tables so she can take everything off them. She wheels away from me or her mother when we're waiting to check out at the store and

gets close enough to the shelves so she can grab whatever candy she is eyeing. If she's not ready to leave, she grabs the wheels so we can't push her anywhere. These typical frustrations have been a huge blessing to experience, as they are so different to Madison's experience.

With Spinraza now approved by the FDA, newborn screening would allow infants born with SMA to immediately begin receiving treatment. Because of our family history of SMA, Baily was diagnosed in utero and was able to begin treatment at 3 months of age. However, most children born with SMA are not so fortunate. Research shows that babies with SMA type 1 typically face 3.6 months of diagnostic delays after showing symptoms, but with newborn screening, all children born with SMA would receive the same opportunity that Bailey had.

In conclusion, the SMA community strongly urges the Advisory Committee to move the RUSP nomination for SMA into evidence review, with concerted focus on the availability of a

treatment for SMA and the demonstrated benefits of early intervention and the success of the technology and screening for SMA. I thank the Committee for the opportunity to address you today and appreciate your consideration.

DR. JOSEPH BOCCHINI: Ms. Schaefer, thank you for your testimony, and thank you for sharing your personal family experience. Thank you.

(Applause)

DR. JOSEPH BOCCHINI: Next, we have Kristin Stephenson, who is Vice President for Policy and Advocacy at the Muscular Dystrophy Association. She will be discussing the SMA nomination to the Committee for consideration.

MS. KRISTIN STEPHENSON: Hi. Thank you for the introduction and for the opportunity to be here with you today. As you said, I'm Kristin Stephenson with the Muscular Dystrophy Association, and while MDA has an interest in multiple disorders that are either on the RUSP or that we believe would be good candidates for the RUSP, I do want to limit my comments today just

to SMA, given the fact that it's part of the discussion this afternoon, and look very much forward to hearing that conversation.

Over the past year, we've had the opportunity to collaborate with Cure SMA and with many people in the SMA community on nominating SMA for your consideration to be added to the RUSP, and we're really grateful for the way the whole community has come together to work on this effort. You've had the opportunity today and over the past months to hear from compelling speakers and individuals, like Ms. Schaefer and Dr. Jarecki, who have been committing themselves to this effort and who are personally touched by SMA. You've heard about the progression of the disease, the diagnostic odyssey, and the drug development space for SMA.

So, given that, I don't want to recount everything that you've already had the opportunity to hear. I want to keep it very simple and just share our view, which amplifies that of what you've heard, which is that SMA is

an excellent, and perhaps ideal, candidate for newborn screening.

As Dr. Jarecki set out, SMA is a lethal disease, with early onset, rapid progression, and a small window for optimal treatment. There's a therapy currently available that is being tested in babies and is showing efficacy, and there's a diagnostic test that is already being employed in the U.S. and abroad that is also effective. Thank you for your time and your consideration, and we look forward to continuing to work with you as you consider the nomination.

DR. JOSEPH BOCCHINI: Thank you very much, Ms. Stephenson.

Next, we have Dr. Michele Lloyd-Puryear, who -- well-known to this committee. She is serving as newborn screening consultant with the Parent Project Muscular Dystrophy and will be discussing newborn screening for Duchenne Muscular Dystrophy. Michele?

DR. MICHELE LLOYD-PURYEAR: Hi. Thank you very much for letting me address the Committee

today. I'm speaking on behalf of Parent Project Muscular Dystrophy, and we -- we would like to thank the Committee for the time allowed here, and I -- I'm going to cut my -- since you have my comments, I'm cutting this as short as possible. I'm representing PPMD and Annie Kennedy, who's in the office -- the audience here, and also Jerry Mendell from Nationwide Children's Hospital. And the three of us have been providing leadership for the newborn screening project of PPMD. We most recently addressed the Committee in February 2017, and I'm here to provide a short update on the therapeutic pipeline and some of our efforts that, I think, would be of interest to the Committee around the newborn screening infrastructure that we're supporting.

So, in February 2017, after we addressed you, the FDA approved Emflaza, or deflazacort, both tablets and oral suspension, to treat patients with DMD, 5 years and older. And this is a corticosteroid that works by decreasing inflammation and reducing the activity of the

immune system. Corticosteroids have been commonly used to treat DMD across the world; however, this is the first time FDA has approved any corticosteroid for the treatment of DMD, and it's the first approval of the use of this drug in the United States.

But -- and this is a caveat -- deflazacort is only approved for use in patients 5 years and older. Currently, the company is working to study the efficacy and safety of their product in younger boys, as well.

That company also has another product called ataluren. It's -- it's also currently under review at the FDA, with an anticipatory regulatory review deadline of -- in October of this year. The European Commission already granted marketing authorization for this drug, within the use -- for use within the European Union. But, again, it's for treatment for patients with DMD for -- 5 years and older.

But together with Sarepta's drug, eteplirsen, we now have treatments for patients -

- for a quarter of the patients with different kinds of mutations for DMD, and along with the first line of treatment of the corticosteroids with these two other treatments for specific mutations, we're able to treat, as I said, about a quarter of the patients.

We're still working with PerkinElmer on validating the newborn screening immunoassay for creatine kinase that was developed by -- through the efforts of Stuart Moat but developed by PKI. It's developing a kit.

And we're working with the California Department of Health newborn screening program and their biobank and retrieving dried blood spots for patients screened through California who are -- are identified with the several Duchenne care centers in California and -- and then having a control of -- of children who don't have DMD but were screened at the same time to test that immunoassay. We expect that to begin by the end of the month, or at least within June of this year.

And then, one other development is, we had organized -- we reported on this before -- but organized six workgroups to address specific newborn screening issues, ranging from the evidence review for Duchenne Muscular Dystrophy and examining the follow-up system needed to support newborn screening for this specific disease. One workgroup, though, looked at the LC issues surrounding screening, on a population basis, rare conditions. And -- and we tried to tease out specific LC issues that were not necessarily part of the evidence review process that the current -- the Committee currently uses.

We've written two papers, one specific to DMD and one addressing rare conditions in general. When these are ready for publication, which they almost are, we'd like to bring them back to the Committee to suggest ways of incorporating some of these LC questions into the Committee's evidence review process.

And so, I just want to end by saying, the Duchenne community remains hopeful, but we also

know that we have an extraordinary amount of work that we must do to transform our existing national Duchenne care and support infrastructure into one that fits into the public health model for newborn screening, and we -- we are still working hard to accomplish this. We are committed to paving a path forward for Duchenne newborn screening in the United States. Thank you.

DR. JOSEPH BOCCHINI: Michele, thank you for the update. Appreciate it.

Last, we have Ms. Torrey Smith. Ms. Smith is a parent and will be discussing foster children and CHD testing and getting medical information into the right hands.

MS. TORREY SMITH: Okay. Thank you so much for allowing me to speak today. My name is Torrey Smith, and I am a mom to seven children who came to me through adoption. After I adopted my oldest and only daughter when she was 12, we decided to open our home to foster care. After about a year of taking classes and getting our home prepared, we were finally licensed to bring

children in.

In the first 5 years, it brought me 5 boys that I adopted, from two different birth mothers. My first two boys came to me because of domestic violence and mental health issues. My next three sons came to me because of prenatal drug use. I would love to tell you that part of our training is understanding that -- what prenatal drug use can do to a baby. I would love to tell you that foster parents are told that there may be lifelong needs that require us to be on top of screenings and follow-ups, and when the baby appears perfectly healthy that we still need to be on top of that. I would love to tell you that all this happens, but it does not.

As a mom who has never given birth to any of her children, or even been there for the first few days of their life, I had no idea of any of the screenings that were taking place. I didn't know the questions to ask the pediatrician. I didn't know the screenings my babies received or the results. I was handed these babies, the ones

that the American Academy of Pediatrics says are a singularly disadvantaged and vulnerable population, known to be at a high risk for persistent and chronic physical, emotional, and developmental conditions because of multiple and commutitative (sic) adverse events in their life. We are handed these babies and told that if we love them enough, all will be well.

I believe this to be true -- I believed this to be true, as many wide-eyed foster parents believe today. I took in baby after baby, adopting a few along the way, and I noticed something. They almost all had asthma-like symptoms. They seemed to catch every single cold or bug that was going around. They cried more than usual, or they were the exact opposite and didn't react to things at all. I did therapies, many of them where I was praised for how well I was doing with the child, told time and time again how the love and attentiveness could change the future for these babies and children, and on a certain level, this is very true.

But all of this changed for me in December 01st of 2011. My then-youngest-son, who had been born 13 months before to the same birth mother as my 2 youngest before him, with the same story -- an older birth mom who was overweight, with hypertension, had used illegal drugs and alcohol throughout her pregnancy, did not receive any prenatal care. Best guesses said that the baby were all 4- to 6 weeks early, and they needed various medical interventions.

But unlike his two brothers before him, he didn't spend 3- to 4 weeks in the NICU. I was told he had passed all of his tests, though I was never told what those tests were, and he was sent home with me on day 3 of his life. We had thought how amazing this was, and he seemed to not have any issues his brothers before him did, except for the lungs. All three had persistent coughs and took twice as long to recover from illnesses.

But on that day in December, my beautiful, most amazing, and loved child stopped breathing. I picked him up, laid him on the

floor, and began CPR. Soon, police and paramedics were in my living room, and I watched as they tried to get him breathing again. I rode in the ambulance, the most silent ride I have ever taken. I was then taken into that room in the hospital, the one that I'd only ever seen on TV, the one for families who are told horrible things. When the pastor came in and asked our religious preference and if he could pray with me, I went into the fetal position, because I was sure that they had to have this wrong.

The nurse came back to get me, and the questions began. "What happened to him?" she asked me. "Would anyone want to hurt him? Could he have gotten hold of anything that he shouldn't have?"

I was told that they had worked on him for over an hour and wanted to let me say goodbye before they called his time of death. I will never forget that room and my tiny, most beautiful son, laying on a gurney that was made for an adult, so still. Everyone moved as I ran

to him, running my fingers through his hair, telling him that he could not leave me, begging him to come back to me.

It was then that they heard a heartbeat. They pushed me aside and rushed him up to the PICU, but the questions didn't stop. I was told that I may lose my other children while they tried to figure out what happened to my baby. Sterling lived for 2 days, while test after test was run -- expensive tests, tests that would prove that he was not abused or neglected, tests that would also show no brain activity.

On December 03, 2011, Sterling died in my arms, and I held him while answering the coroner's questions. And I then handed my baby over to a stranger and was taken home to a house that, while full of my five other children and family and friends, suddenly felt so empty. I endured questions from DCFS while also making funeral arrangements and trying to grasp that my baby was dead. I fought feelings of not wanting to be here anymore, because I had no idea what

had happened to my son. I worried that his brothers could have something wrong with them, too, and spent my nights going from bed to bed, making sure that they were breathing.

For nearly 8 months, I worried, and then the phone rang, and it was the coroner telling me that my son had multiple congenital heart defects that they believe stopped his heart that day, which led to not enough oxygen to his brain and his death. I began researching congenital heart defects and finding so many stories like ours.

Pulse oximetry was just being brought into newborn screening, and I fought far -- I fought hard for every baby to have this test, but I learned that that would never have detected his defects. The more I searched, the more walls I hit. I hear not everyone can have an EKG or an echo; it's too expensive. So, I began handing out signs and symptoms cards to newborns at our local hospital, but I still wanted to do more, which led me to advocacy and becoming a part of Baby's First Test Consumer Task Force on Newborn

Screening.

I have also been told that stories like mine are becoming less and less, but I have to tell you: With minimum effort, I found another foster mom who had a baby die in her care, as well. All of her children were removed from her home while they investigated his death. Nearly 2 months to the day that that baby died, his 15-month-old biological sibling in another foster home stopped breathing, as well. It was then that they found out that both babies had congenital heart defects. These babies also had prenatal histories, but much like my son, no prenatal care, illegal drug use, moms had seven to nine kids back to back.

I would love to see more research and attention given to our foster babies and children. They are at such a disadvantage from their peers. Everyone involved in the care of our foster babies and children, from foster parents to case workers to the pediatricians, must know that they may have missed prenatal care, which

includes critical screenings. Adding onto this is a mother who may not be eating right, using illegal drugs and alcohol, as well as being under tremendous stress and maybe even domestic violence. Our foster care system is set up to protect these kids from that. Screenings and follow-up does -- follow-up is often very far down on the list.

Foster parents are the first line of defense for these kids. We are their voice, and we should have a better understanding of what our kids need to be the healthiest that they can be. Thank you very much.

(Applause)

DR. JOSEPH BOCCHINI: Ms. Smith, thank you for sharing your personal story, and thank -- thank you for all you do for many disadvantaged children. So, thank you.

(Applause)

DR. JOSEPH BOCCHINI: So, we're going to have a lunch break. We're a little bit late, but we do need to be back promptly at 1:00 to do our

best to get started on time for the afternoon session, because we have a busy session this afternoon. So, thank you all very much for this morning, and we'll see you at 1:00.

(Whereupon, the above-entitled matter went off the record.)

DR. JOSEPH BOCCHINI: All right. Let's go ahead and have everyone take their seat, please. If you'd take your seat so we can start the session?

All right. Let's go ahead, and we'll call the afternoon session to order. The first business is to record the attendance, so we'll go around the room and by phone: Don Bailey?

DR. DON BAILEY: Here.

DR. JOSEPH BOCCHINI: Mei Baker?

DR. MEI BAKER: Here.

DR. JOSEPH BOCCHINI: I'm here. Carla Cuthbert?

DR. CARLA CUTHBERT: I'm here.

DR. JOSEPH BOCCHINI: Jeff Brosco?

DR. JEFFREY BROSCO: Here.

DR. JOSEPH BOCCHINI: Kellie Kelm?
DR. KELLIE KELM: Here.
DR. JOSEPH BOCCHINI: Fred Lorey?
(No audible response)
DR. JOSEPH BOCCHINI: Michael Lu?
DR. MICHAEL LU: Here.
DR. JOSEPH BOCCHINI: Dieter Matern?
DR. DIETRICH MATERN: Here.
DR. JOSEPH BOCCHINI: Steve McDonough?
(No audible response)
DR. JOSEPH BOCCHINI: Kamila Mistry?
DR. KAMILA MISTRY: Here.
DR. JOSEPH BOCCHINI: Diana Bianchi?
DR. DIANA BIANCHI: Here.
DR. JOSEPH BOCCHINI: Beth Tarini?
DR. BETH TARINI: Here.
DR. JOSEPH BOCCHINI: Cathy Wicklund?
MS. CATHERINE WICKLUND: Here.
DR. JOSEPH BOCCHINI: Catharine Riley?
DR. CATHARINE RILEY: Here.
DR. JOSEPH BOCCHINI: Bob Ostrander?
DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: Robert Saul, webcast?

DR. ROBERT SAUL: Here.

DR. JOSEPH BOCCHINI: Mike Watson?

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: Britton Rink?

(No audible response)

DR. JOSEPH BOCCHINI: Kate Tullis?

DR. KATE TULLIS: Here.

DR. JOSEPH BOCCHINI: Susan Tanksley?

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Chris Kus?

DR. CHRISTOPHER KUS: Here.

DR. JOSEPH BOCCHINI: Adam Kanis?

DR. ADAM KANIS: Here.

DR. JOSEPH BOCCHINI: Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. SIOBHAN DOLAN: Siobhan.

DR. JOSEPH BOCCHINI: Siobhan Dolan?

(Laughter)

DR. SIOBHAN DOLAN: Here.

FEMALE SPEAKER: Just can't look at it.

DR. JOSEPH BOCCHINI: I can say it if I'm not looking at it. That's the problem.

FEMALE SPEAKER: That's exactly it. That's a good tip.

(Laughter)

DR. JOSEPH BOCCHINI: If I look at it, I'm in trouble. All right. Cate Walsh Vockley?

MS. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: And Carol Greene?

DR. CAROL GREENE: Here.

DR. JOSEPH BOCCHINI: All right.

(Off-mic speaking)

DR. JOSEPH BOCCHINI: So, we'll try again. Fred Lorey?

(No audible response)

DR. JOSEPH BOCCHINI: And Steve McDonough?

DR. STEPHEN MCDONOUGH: I'm here. Can you hear me?

DR. JOSEPH BOCCHINI: Did I miss Anna? Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

FEMALE SPEAKER: We can hear you, Dr. McDonough.

DR. JOSEPH BOCCHINI: We're good.

DR. STEPHEN MCDONOUGH: Thank you.

DR. JOSEPH BOCCHINI: All right. So, we're going to start this afternoon's session off with a discussion of the SMA nomination. Dr. Beth Tarini is going to open the discussion on behalf of the Nomination Prioritization Workgroup. As you know, she is Committee member and Associate Professor and Division Director, General Pediatrics and Adolescent Medicine, University of Iowa Hospital and Clinic, and she's going to provide a summary of the nomination packet and the deliberations of nomination and the Prioritization Committee Workgroup with, then, followed by a discussion by the full Committee and then a vote.

Beth? Oh, we need to -- There are a few people that need to recuse themselves: Carla Cuthbert, Cathy Wicklund, Mei Baker, and Don Bailey. And so, Mei, you will need to disconnect

your phone, and Catharine will contact you when this portion of the meeting is over so that you can get back on the line.

DR. MEI BAKER: Well, I'm going to hang up, and Cathy, later on, could you send me the phone number for the laboratory (audio interference) --

DR. JOSEPH BOCCHINI: I'm sorry, I didn't understand. Could you repeat that?

FEMALE SPEAKER: I think she hung up.

DR. JOSEPH BOCCHINI: Oh, she did hang up. Okay. All right. Okay. Beth?

DR. BETH TARINI: Okay. Thank you for the honor of presenting to the Committee, and thank you for my subcommittee/workgroup members for assisting me with this presentation, and finally, thank you to my research coordinator, Ann Adkins (phonetic), for doing a -- a wonderful job with these slides.

So, I'm going to present today to you about spinal muscular atrophy, otherwise known as SMA. The nominator for this condition was Cure

SMA, with cosponsoring organizations from the Muscular Dystrophy Association, as well as the SMA Newborn Screening Working Group.

For a brief overview, SMA presents with muscle weakness and atrophy resulting from progressive degeneration and loss of the anterior horn cells in the spinal cord and the brain stem. The onset ranges from birth to adolescent and also extends into young adulthood, and the clinical features span a continuum, without a clear delineation of subtypes to some degree. In essence, there is some degree of overlap amongst the subtypes, and the subtypes are listed here.

And for this committee, we're going to focus on types 1 through 4, which you see here, range from type 1 being the most severe, Werdnig-Hoffman -- otherwise known as Werdnig-Hoffman disease, the severe infantile type, which onsets between birth and 6 months, and the maximum muscular activity achieved is never sitting without support, problems sucking and swallowing, and a median survival of 24 months. And type 2,

infantile chronic, also known as infantile chronic -- age of onset is, on average, 6- to 12 months, and these children, at best, would sit independently and lose this ability by mid-teens, with 70% alive at age 25. And then, types 3 and 4 you see here, with a later onset -- age of onset, as well as a -- a more developed maximum muscular activity and both having a normal life expectancy.

So, the genetics and epidemiology of this disorder: It is autosomal recessive inheritance. It has a variable phenotypic expression, as you've just seen. The incidence is estimated at 1 in 10,000 live births, with a carrier frequency of between 1 in 40 and 1 in 60. The -- the underlying genetics are: The SMN1 exon 7 is absent in the majority of patients, independent of the severity of SMA, and it is the SMN2 copy number that modifies the severity of disease. And so, you see here, putting the genetics and epidemiology next to the subtypes, that as the copy number of the SM2 copies increase, you'll

see a change in severity.

So, in 2008, the Secretary's Advisory Committee -- the Nomination Prioritization Workgroup of the Subcommittee reviewed SMA for consideration of full evidence review, and at that time, the -- the decision was that it was premature for evaluation based on the submitted evidence, and at that time, the Workgroup recommended no evidence review and the implementation of prospective pilot studies of the screening method by one or more traditional public laboratories. And they were heard, so, hence, the resubmission occurred.

And so, here are the key questions that the Prioritization Nomination Subgroup reviewed, and I'll go through each of these one by one and summarize what the nominee has presented us.

Is the medication -- Is the condition medically serious? The answer to that is an affirmative, capital -- all capitals YES. As I described earlier on those slides, a child with SMA type 1 is very severely affected and does not

live much beyond, on average, 2 years of life.

Is the case definition and spectrum of the disorder well described to help predict the phenotypic range of those children identified based on a population-based screening? And we do see that there's a continuum of clinical features. It correlates loosely with genotype, and these type designations can be determined clinically based on the highest-achieved functional milestone. Not -- That's the definition of these types.

They -- they -- And this is not surprising, because this is a disorder that is not screened; it's diagnosed -- has been historically diagnosed clinically, so the characterizations are largely based on phenotype or clinical presentations. And -- however, SMN2 copy number is predictive, although not determinative of SMA clinical severity. And then, of course, as I mentioned, you have types 3 and 4, which are the less severe, late-onset forms.

Are there prospective pilot data, U.S.

and/or international, from population-based assessment available for this disorder? So, again, remember, just a moment ago, I said that was one of the concerns behind the refusal to move forward with evidence review in the past, in 2008. And indeed, there are. There is one pilot study from Taiwan in which the screening was detection of an SMN1 deletion by real-time PCR, single nucleotide polymorphism genotyping assay on a StepOnePlus RT-PCR 96-Well System. And there's a second tier in this -- in this pilot, as well, which was a digital -- digital droplet PCR to exclude false positives and to also detect the SMN2 copy number.

In addition, there is a New York SMA pilot study; also, detection of the SMN1 deletion is the screening paradigm. This is done by a custom TaqMan teal-time polymerase chain reaction, or PCR assay, on a real-time PCR platform, such as an ABI 7900 or a QuantStudio 12K Flex Real-Time PCR System. And that also has a second tier, that study, with targeted

sequencing for infants of positive SMN1 deletion, also to detect SMN2 copy number.

There is also an assay in development by PerkinElmer, the 5 Flex qPCR, and this would allow for real-time PCR assay targeting, both SMN1 and 2, the SNPs and -- the SNPs and exon 7, using a dual-labeled lock nucleic acid TaqMan probe, et cetera. There's no second tier necessary because in these -- because of the -- my understanding, because of the real-time sequencing.

Does the screening test have established analytic validation? The -- the answer we came to was, yes. The Taiwan project's been submitted for peer review publication. All the positive cases have been validated by two other methods.

The rundown of the numbers of children detected is as follows: From November 2014 through September 2016, over 120,000 infants were screened, for a positive predictive value of a hundred percent and a false positive rate of zero. Fifteen infants screened positive by the

first-tier test, seven by the second-tier test, resulting in an incidence of one in just over seventeen thousand. Carriers were not detected.

In New York, all positive cases have been confirmed by outside -- by an outside diagnostic laboratory, and from January through December of 2016, there were just over 3,200 infants screened, with a positive predictive value of a hundred percent and a false positive rate of zero percent. One infant screened positive by both the primary and second-tier testing. Carriers were detected or are being detected and reported.

Are the characteristics of this screening test reasonable for the newborn screening system -- among other aspects, a low rate of false negatives? So, the data we have to -- had to review was that the specificity for the detection of SMN1 is a hundred percent. And both screening pilots have a 5% false negative rate, because neither will detect a compound heterozygous case, which I'll discuss in a moment. The pilot newborn screening programs, however, have not reported

any false negatives to date.

And the next question was: Are those who are most likely to benefit from treatment identifiable, especially if the treatment is onerous or risky? So, we have both animal models of severe SMA -- mice models -- showing that induction of SMN expression in the early postnatal period substantially improved survival, whereas a later induction is less effective. These have borne out in these early-stage trials, which we'll summarize in a moment, in which pre-symptomatic or early symptomatic restoration of SMN during the -- the maturation phase will likely produce the best response to therapy.

And this, if you -- Let's see if this -- If you see here, this is the compound heterozygous issue, is that you have SMA with typical or uncommon features. You have an SMN1 deletion. If they're homozygous -- I'm sorry, if they're not homozygous, and you repeat the clinical exam, and then they end up with proximal weakness, you can do an SMN1 copy count, but if

you have one copy and you perform a sequence mutation, you can identify this 5qSMA confirmed on the other allele. So, this is the compound heterozygous problem, or challenge, if you will.

And so, confirmatory tests in the diagnostic process: SMN deletion testing and SMN2 copy number determination analysis takes about 5- to 8 days, and this testing is available at CLIA-certified labs throughout the United States.

Are there defined treatment protocols, FDA-approved drugs, if applicable, and treatment available? And, indeed, there are. Pulmonary care is available. Gastrointestinal nutritional care, orthopedic and rehab care, as well as palliative care, but most importantly, there are drugs in the pipeline and also currently in -- have passed through FDA approval. And you can't see it on this slide, but the blue line is Spinraza, which you've heard referred to before, and below that are all other candidate drugs that are in the SMA drug pipeline. But we're going to focus on the Spinraza.

This was the first drug approved by the FDA for spinal muscular atrophy, in 2016. Its other name is -- Nusinersen? Did I say it right? -- administered through intrathecal injection. The wholesale acquisition cost for the first year of treatment is 750,000, and $375,000 in subsequent years.

There are two studies using this drug. The first is the ENDEAR study. This is a Phase 3 randomized, double-blind, sham-procedure controlled trial. SMA is diagnosed genetically. You had to have two copies of SMN2 and an onset of symptoms at age less than or equal to 6 months, between, and -- and an age less than equal to 7, and then there's the NURTURE study, which is a Phase 2 open-label, single-arm study, and that was originally diagnosed as a 5qSMA, 2 or 3 copies of SMN2 in pre-symptomatic infants age less than or equal to 6 weeks.

And here are the summarized results: The final results of Phase 3 ENDEAR, in which there were 80 treated and 41 controls, and comparing

the treatment group to the sham control, there were clinically and statistically significant percentage of motor milestone responders, greater improvement in total milestone score, and achievement of motor milestones unexpected for infants with SMA type 1. And, importantly, this continued improvement occurred over the course of the study. There was also prolonged, event-free survival, which is -- was tied to death or permanent ventilation and overall survival. The risk of permanent ventilation was 34% lower in the nusinersen-treated infants, and there were no adverse events considered related to the treatment.

The interim results of the Phase 2 NURTURE trial: Nusinersen had 20 -- remember, this is a single arm -- 20 cases, or 20 children. The data cutoff for this analysis was October 31st, and the median enrollment was 317-1/2 days, ranging 254 days. At that point in time, all infants were alive, and none required respiratory intervention, and they saw continued benefits --

beneficial effects of Spinraza, most infants achieving motor milestones consistent with what normal development would be expected. And some enrollees achieved standing unaided, as well as independent walking. As well, this -- in this trial, the treatment seemed to be well tolerated, with no specific safety concerns.

And here, you see the slide where the green -- So, the left axis -- the Y-axis is the mean total milestone score, and the X-axis is scheduled visit day. The green line you see at the top, which means higher mean total milestone score, is the NURTURE trial, and then the blue triangles and the gray below you see is -- are the ENDEAR trials, as well as, the -- the red square is the C5 3A (phonetic) trial. So, this gives you a visual of what was described.

Are there defined treatment protocols, FDA-approved drugs, and treatment available? So, I just talked to you about the treatment, the FDA-approved treatment. The one thing to note is that there are currently no formal consensus on

when to treat SMA patients who are diagnosed pre-symptomatically, and that, it is my understanding, is in process.

So, the recommendation from the Workgroup is to move spinal muscular atrophy forward to full evidence review, with a note of a few issues to consider as it moves forward to evidence review -- not that I'm telling Alex how to do his job. So, the -- there are some considerations as evidence review unfolds from this workgroup or the following. There's no -- there are no recommendations or guidelines for specific SMA types management strategies. There may be a burden associated with carrier identification, and there is this issue of the 5% compound heterozygous cases to be considered. And these were our references.

And with that, I'll open it up. Dr. Bocchini?

DR. JOSEPH BOCCHINI: Thank you, Beth. So, the -- the Committee has had a chance to review the nomination packet originally

submitted, plus the additional information that was requested by the Nomination Prioritization Workgroup and -- and the response, and then the recent submission -- more recent submission from the nominators. And so, now you have the review by the work -- by the workgroup, and this is now open for discussion.

DR. STEPHEN MCDONOUGH: This is Steve McDonough. Can you hear me?

DR. JOSEPH BOCCHINI: Yes, Steve.

DR. STEPHEN MCDONOUGH: We need to get on with adding SMA to the RUSP as soon as possible. I would like to offer a motion to move this to evidence review.

I have a teenager in my practice who has SMA type 2. I have known her and her family since birth. She is highly intelligent and attends middle school, where she's very popular. She's also never lost use of the wheelchair, comp assist device, best therapy, and twice in the past few years has nearly died from pneumonia and had to be transferred to Minnesota for pediatric

intensive care. We have requested insurance coverage for the FDA-approved medication and are awaiting decision. Because she has had spinal rod surgery, she'll need to have a reservoir placed in her spine for the medication to be given.

In conversations with her Minnesota pediatric neurologist, he indicated considerable enthusiasm for SMA newborn screening, because the evidence is so strong for clinical benefit.

DR. JOSEPH BOCCHINI: Thank you, Steve. So, that -- You made this in the form of a motion?

DR. STEPHEN MCDONOUGH: Yes, sir.

DR. JOSEPH BOCCHINI: Thank you. Is there a second?

DR. JEFFREY BROSCO: This is Jeff Brosco. I'll second.

DR. JOSEPH BOCCHINI: Thank you, Jeff. So, it's been moved and seconded. Now let's have any additional discussion, comments. Annamarie?

MS. ANNAMARIE SAARINEN: Not to delay the vote, I just wanted to share that our Minnesota

State Newborn Screening Committee heard a very robust update and presentation on SMA from three different providers and two advocates, I believe. I know, Amy, you were at the meeting, too, just about 2 weeks ago. And I'm -- I'm not sure if Dr. McDonough's patient's neurologist is at the University of Minnesota Children's Hospital, but if he is, he might be my daughter's neurologist, who was the person who actually gave the update on SMA.

And I -- I guess I can vouch for how compelling the evidence was and reiterated many of the points in Dr. Tarini's presentation. And thank you for being very thorough and pointing out the few remaining things that the Committee needs to consider.

DR. DIANA BIANCHI: I just wanted to share that NICHD is going to be funding, probably, two awards. We have a pool of three contractors coming from three state screening programs, working with affiliated universities and research groups that are preparing these

proposals for an 18-month pilot testing period. The timing probably, if we vote to move forward today, won't necessarily get information in time, but they still will be valid pilot state screening projects that will screen at least 50,000 infants.

DR. JOSEPH BOCCHINI: Thank you. So, Carol?

DR. CAROL GREENE: Two points that were raised by Dr. Tarini that I just want to share from the point of view of genetics. I don't think that they should slow down or change the nomination.

One is the issue of, some are going to be missed because they're heterozygous in the -- in the -- There are plenty of conditions currently on the newborn screen where we don't pick up all forms, and it doesn't seem necessary, to me, that you have to wait for something that's perfect that's going to pick up a hundred percent. That kind of improvement can go along. If you can pick up 95% and there's a treatment, I think that

would make sense to go forward.

And the other is carriers, which, of course, is going to be a huge burden, and it's going to be a major issue to deal with, but we've dealt with worse. And as it was already pointed out, a lot of that carrier testing is going to be more and more done even before the baby's 20 weeks gestation. So, I don't think that should get in the way, either.

DR. JOSEPH BOCCHINI: Thank you. Dieter?

DR. DIETRICH MATERN: I -- I agree, and I'm -- I was on the Committee, so I'm supportive of the -- the recommendation, but I think in New York, they find 1 in 64 carriers. So, it -- There -- there's some work to be done by the evidence review to help us understand what happens to those families.

DR. JOSEPH BOCCHINI: Good. Carol?

(Off-mic speaking)

DR. JOSEPH BOCCHINI: You -- You want to come up, too, Nancy? Yeah. Yeah.

MS. NANCY GREEN: Thank you, Joe, and

thank you, Beth, for that excellent presentation. It's good to see that the criteria are still working so well.

I -- Could you just clarify two points that you mentioned? And you -- There or may not be data on that, and -- and certainly something that the evidence group -- review group will have to address, and one is the issue of genotype/phenotype correlation, because you did mention the later onset, and, you know, that is something that the Committee has dealt with in the past around other conditions.

And the other has to do with insurance coverage. So, from my own experience at Columbia, I understand that this is an enormous problem. Again, that doesn't necessarily affect evidence review or even Committee decision. In -- in fact, it may move along what turns out to be a very difficult program for families who apply for the treatment, and -- but the hospital can't even buy the agent because it's so expensive. So, the patient is reviewed for appropriateness, the --

you know, a committee of experts and parents, you know, decide who is eligible and whom it's likely to benefit, and then -- then -- it goes to their insurance company, and then, only with that approval does treatment go forward. And apparently, that is not a pretty picture. So.

DR. BETH TARINI: And your question about the genotype -- What specifically was your question?

MS. NANCY GREEN: Just how predictive --

DR. BETH TARINI: Oh.

MS. NANCY GREEN: -- the genotype would be.

DR. BETH TARINI: I don't know the degree of overlap. Does anyone else on the Workgroup know that? The -- I -- I think that -- I think that the issue is, you end up with -- and I don't know how they've -- I don't think there was a proportion in the data that I've seen -- right? -- about if you had a child who was asymptomatic and had two versus three copies.

(Off-mic speaking)

DR. BETH TARINI: Okay.

(Off-mic speaking)

DR. BETH TARINI: I mean, I don't know if we've seen it.

(Off-mic speaking)

FEMALE SPEAKER: But 90% of children that have two copies of SMN2 will have type 1 SMA, and then, you know, very few -- about 10% of type 2 patients will have 2 copies --

DR. BETH TARINI: Mm-hmm.

FEMALE SPEAKER: -- and then -- then it's a 50/50 --

DR. BETH TARINI: Two to three?

FEMALE SPEAKER: Yeah.

DR. BETH TARINI: Mm-hmm. So, there's a 10% -- So, to rephrase --

(Off-mic speaking)

DR. BETH TARINI: Okay. To answer your second question: We did discuss the cost, but -- I mean, we -- it did -- since it floated by our eyes, we did discuss it, but it is my understanding, whether you believe this is

correct or not, that this committee does not do -- make its decision based on costs, and so it was noted but not incorporated into the decision.

MS. NANCY GREEN: Okay. Thank you.

DR. BETH TARINI: Mm-hmm.

DR. JOSEPH BOCCHINI: So, now, I've got Kellie, then Jeff.

DR. KELLIE KELM: Hi, Kellie Kelm, FDA. Question I had is, you -- you sort of take us through the methods that Taiwan and New York have used and describe them in terms of confirming some of them analytically. Do you have any information on whether or not either of these programs have actually prospectively identified diagnostic cases of SMA?

DR. BETH TARINI: I -- Is that what -- what -- I must -- So, I'm sorry, it wasn't clear then. They did -- These were prospective -- right? These were all prospective. I'm looking to my group. And so, the -- on this -- I can go to the -- Can you put the slides up so they can see them? Can you switch to the computer?

So, here, you have, in the Taiwan study, 15 by the primary test and 7 by the second-tier for the incidence of 1 in 17, and in New York, there was 1 child that passed both. So, those were confirmed. Those -- my understanding, those cases went on to be confirmed.

DR. JOSEPH BOCCHINI: Jeff.

DR. JEFFREY BROSCO: Just a quick comment that I was also part of the nomination group and that many of these issues came up about carriers, about the 5%, about the cost, and there was a lot of discussion. We felt that discussion wouldn't stop us moving forward with an evidence review, but it's likely to come back to this group later on. So, there are some substantial issues to -- to be dealt with still.

DR. JOSEPH BOCCHINI: Further questions, comments?

(No audible response)

DR. JOSEPH BOCCHINI: If not, the -- we have a motion seconded to move this forward for evidence review. Now we'll take a -- a -- a vote.

We'll go alphabetically, so I'll start by voting yes. Jeff Brosco?

DR. JEFFREY BROSCO: Yes.

DR. JOSEPH BOCCHINI: Kellie Kelm?

DR. KELLIE KELM: Yes.

DR. JOSEPH BOCCHINI: Fred Lorey?

DR. FRED LOREY: Yes.

DR. JOSEPH BOCCHINI: Michael Lu?

DR. MICHAEL LU: Yes.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETRICH MATERN: Yes.

DR. JOSEPH BOCCHINI: Steve McDonough?

DR. STEPHEN MCDONOUGH: Yes.

DR. JOSEPH BOCCHINI: Kamila Mistry?

DR. KAMILA MISTRY: Yes.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Yes.

DR. JOSEPH BOCCHINI: And then, Dr. Bianchi?

DR. DIANA BIANCHI: Yes.

DR. JOSEPH BOCCHINI: Beth Tarini?

DR. BETH TARINI: Yes.

DR. JOSEPH BOCCHINI: So, that is unanimous. Obviously, we have four members who are unable to vote, but of those voting members, it's unanimous, so. So, thank you all very much, and thank you, Beth, for summarizing things in such a good way, make it very clear where the Nomination and Prioritization Workgroup stood. And I want to thank the nominators for putting together such a nice packet that provided the information that we needed to meet the -- the -- the key and core questions that the Committee has for moving a condition moved forward to evidence review.

So, now it'll go to review, and we do have a 9-month process now, through which we hope to be able to bring back fruit from the evidence review and the information necessary for the Committee to then make a decision about whether to add this condition to the RUSP.

So, next on our agenda is the report on medical foods for inborn errors of metabolism. This is a project that has been ongoing, and Sue

Berry has been the lead in putting together a white paper for the Committee which discusses the current issues that continue to exist related to providing medical foods to family -- families. And this has been worked on by she and a subcommittee of the Follow-Up and Treatment Workgroup, under Dr. McDonough's direction. And this was a project that was given to the Workgroup by the Committee in 2016. So, Dr. Berry will now present the final draft of the report for consideration by the Committee.

DR. SUE BERRY: Okay. I'm assuming I just advance through. All right. Thank you very much, Dr. Bocchini and the Committee, for the opportunity to review with you the issue of medical foods for inherited metabolic diseases.

As Dr. Bocchini mentioned, this is an area of interest that the Committee has been addressing for -- I hesitate to say it -- many years is the only way I can say, a long time. It's a critical element. I hear this conversation frequently. If we can't provide medical foods to

treat children who we screen for, what are we doing? And I think that's a fundamental question that we hoped to be able to address a little more effectively.

So, I'm going to present to you only a very brief summary. We have talked about this a lot, and I hope you've had the chance to review the document that our group prepared.

A reminder: What is a medical food, and why is this a problem? Well, it's a regulatory problem. It -- what does -- where does it belong in terms of how it's supported, how it's funded, what classification it has? I'm not going to read this to you, because it's repeated many times, but it's a very specific set of products that are used for very specific things. It's not something you can go to the drugstore and buy or to the grocery store and buy. They're specially prepared, and they're only available under medical supervision.

They're not drugs. They're not drugs. Drugs are for -- they're, by definition, for

diagnosis, cure, mitigation, treatment, or prevention of disease. It seems -- This is where we got a little hedgie, I would say, because of course, in a medical sense, we use medical foods to treat inherited metabolic diseases. Like drugs, medical foods are supposed to be used under medical supervision. They are the primary intervention for these specific conditions.

All right. So, as Dr. Bocchini indicated, we were asked, as a major project for the Follow-Up and Treatment Workgroup, to provide a policy analysis that summarizes the current state of coverage, talks about what work has been done by this committee previously to -- to bring this very difficult problem to some kind of conclusion, and to provide some recommendations about additional actions.

All right. You've heard, even this year, two really outstanding presentations that tell you about the intractability of the problem, because access remains highly variable. It depends on the age of the person. If you're an

adult, tough luck in a lot of cases. It depends on the disorder. Sometimes they're named in statutes, so that those disorders are covered but others are not. Depends on what state you're in, because each state has its own rules. And it depends on the nature of your insurance coverage. Some will cover it, some will not. It's even inconsistent when you think it should be consistent, such as, is it covered under federal insurance policies?

All right. So, we presented a draft of our work at the last telemeeting, and subsequent to that, I was going to summarize the few things that we added we think adds depth to this paper, and I'll -- I'll tell you why. We thought that was important as I move forward.

We added sections that are a little more descriptive with regard to the use of medical foods in these Recommended Uniform Screening Panel conditions. We talked in more specific detail about inborn errors of metabolisms, what they are, and why they're treated with medical

foods. We talked specifically about how medical foods differ from regular foods and why you need medical supervision. You can't just give anybody medical foods. It turns out, you can make them sick or die, and that's not a good thing, either. They have to be used under medical supervision.

We reviewed some of the consequences of not using medical foods, and we talked about the number of persons impacted by these decisions in -- in its -- in its lowest estimate. We added details of some of the variations of coverage from state to state. Thank you to the Catalyst Center for their outstanding report, and to ACMG and the National Coordinating Center for making sure that that was available for us, and to this committee. And we talked about some of the information about costs to family, and of course everybody thinks about financial costs, but there's a lot more than financial costs in thinking about the impacts these have.

All right. So, I'm going to speak to you about a possible change in our approach to the

way that we sometimes handle these kinds of reports. All of our previous efforts in discussing medical foods on this committee have been directed towards creating a message that is shared with the Secretary of Health and Human Services. Up to this point, that has not been successful, because, in the end, you have to ask the Secretary to do things that is in the purview of the Secretary to do.

You can't ask the Secretary to prepare legislation. You can't ask the Secretary to sprinkle money somewhere that does this. You -- you -- you have to ask for what you can ask for, and I think this -- this, in the end, after some considerable discussion, probably requires a broader approach. I'll let Dr. Bocchini comment further on that as we move forward, but we wanted to think about this in a wider way.

So, what we have done -- all of this material that's in the paper comes down to a series of principles that we thought, and we'd like to ask the Committee to affirm in accepting

this document, and I'm going to go through these, because I think they're important to realize.

The first one is that the medical foods should be covered as required medical benefits. It shouldn't be something that's optional. It shouldn't be something that you put in some and not in others. I know, in today's environment, that's a really hard thing to ask, because pre-existing conditions, all the things you can think of that -- that -- that make that a concern remain real, but it's still, I think, a principle we should affirm.

Second is that affected persons should have access to essential benefits, irrespective of the source of their health coverage. It shouldn't depend on what state you live in or whether you're on Medicare or whether you're on Medicaid or whether you have a great policy or terrible policy, and federally supported programs should cover medical foods. TRICARE has made that decision based on how it was handled in this year's reauthorization for national defense, but

that is not universally true for federal coverage. And we shouldn't have any distinction about whether states decide they want to cover medical foods or not.

We as a society should ensure that individuals of all ages, who are diagnosed with an inherited metabolic disease, should be able to access comprehensive coverage for their medical foods. That's the bottom line. We have to cover medical foods, and people need to be able to access them, and it shouldn't stop when they're 21 years old.

All right. So, I'm going to open this up for discussion. I am not the discussioner. That is the Committee's job to do. But I think that the issues that will probably need to be addressed are whether you wish to accept the draft text -- of course, we will accept revisions and amendments, and I'm not the world's best writer, and I've had a lot of people looking at it, but you know, we will accept any suggestions around that. But are we in a position to endorse

the principles? What strategies should we have for disseminating this, and what are our next steps?

I will mention that in the paper, we suggest one avenue might be a stakeholders meeting to iron out some agreements about what could be covered and to have appropriate stakeholders included in that so we can come to some final conclusions.

So, with that, I will conclude what I hope was a brief presentation and turn it back over to the Committee for discussion. And thank you for that opportunity. I'm very grateful.

DR. JOSEPH BOCCHINI: Sue, that was a great summary. Thank you. And I -- I want to thank Dr. Berry and Cathy Camp, Carol Green, and Christine Brown, who were the four people who really were in the subcommittee or subworkgroup committee that helped bring this to this point.

So, I think -- Could we put that last slide back up? I think that the first two steps ought to be a discussion by the Committee related

to acceptance of the draft text and endorsement of principles. So, I'd like to open that up for Committee comment and discussion, and then follow that by the organizational representatives. So, this is open.

(No audible response)

DR. JOSEPH BOCCHINI: I'm assuming this means that there's no issues with the -- I think that the latest draft was included in the agenda book, and if there are no questions or comments?

DR. STEPHEN MCDONOUGH: This is Steve McDonough. I have a couple of comments.

DR. JOSEPH BOCCHINI: Yes, sir.

DR. STEPHEN MCDONOUGH: When we began this effort, a year ago, to address medical foods, I was hopeful the Secretary could be convinced to instruct Medicaid and other agencies to cover medical foods. I was hopeful that a large number of influential organizations who've adopted this as policy could convince the Secretary to do the right thing, to lead by example.

The problem of leading by example, however, is that you need leadership, which has been lacking, from the unfortunate tenure of Secretary Sebelius to the current people leading the agency. So, we are left with the hope that someone will convene a meeting that will convince others to do the right thing.

I will support this recommendation and say that it's successful. However, the children and families deserve better than this, but it is what it is.

DR. JOSEPH BOCCHINI: Thank you, Steve. It's an important comment. Other comments? Oh, I'm sorry. Annamarie?

MS. ANNAMARIE SAARINEN: I have, I think, more of a question than a comment, but I'll thank Sue, again, for all her very fine work with her colleagues on this. I know you've been working on this stuff for so long.

DR. JOSEPH BOCCHINI: Could you speak -- be a little closer to the microphone? Thank you.

MS. ANNAMARIE SAARINEN: Yeah, thank you,

Sue. This is Annamarie. Thank you for all your hard work on this. I know it's near to your heart, and I think everyone on the Committee can concur, and -- and -- and I certainly endorse the principles. I think the strategic part is the hard part, and so that'll be interesting, I think, from Dr. Bocchini's perspective, how the Committee can support or help move things along in that regard.

My question is, coming on the heels of what we just talked about with SMA and the costs that are, as a new condition, being looked at for treating children that would be on this therapy -- And I know, in our Minnesota presentation, I think -- I think there were two large payers that have already decided that they will reimburse for SMA at the -- at the current treatment for Spinraza, though I imagine more will come onboard. But if the Committee is going to weigh in or actually have a policy position on medical foods, does the Committee need to weigh in and have a policy position on reimbursement for

pretty much anything that falls under the newborn screening panel? That currently might not be very clear.

I hate to use CCHD as a model, again, but that's one thing that comes to mind, but there are other things that I think one would question the equitable access to care and reimbursement for other conditions that aren't necessarily in the medical foods category but are part of a newborn screening. So, that's my long question. I'm sorry.

DR. SUE BERRY: Are you asking me?

(Off-mic speaking)

DR. SUE BERRY: I -- I don't know that I'm in a position to comment on the relative value of making sure something gets paid for, for any rare disorder. This is going to increasingly be an issue, in my view, for all disorders, whether they're newborn screened or not, in the rare disease space, as they call it.

If you can -- I was telling somebody that one of the kids that we have, who's going to

have, like, a cc here and a cc there of a -- a new ammonia scavenger, is going to pay $614 a day wholesale for her medication. This is a tiny little 14-month-old.

Are there resources to cover all this? I don't know. I don't know, but when we -- when we set -- I think -- Emotionally, I think, the response is, is if we screen for it, we want to make sure we can take care of it.

(Off-mic speaking)

DR. BETH TARINI: To add to that: We don't just screen for it, we require --

DR. SUE BERRY: Require. Mandatory.

DR. BETH TARINI: -- we -- we mandate the screening, which --

DR. SUE BERRY: Yeah.

DR. BETH TARINI: -- takes it one step further. There are things we screen for in clinic, for instance, but they're not mandatory. So, to only strengthen your point.

DR. JOSEPH BOCCHINI: Carol, then Bob.

DR. CAROL GREENE: So, I think that is a

fascinating question and actually goes to the heart of something that -- that I've personally lobbied for in -- in terms of how that is -- is framed is -- a -- a little bit of a nuance, and not everybody agrees with me, and it's not in the paper, but one way to say it is that medical foods should be paid for in the same way as any drug would be paid for, which gets around the question of, can you mandate -- I mean, I'd like to see them as essential benefits, but I do see the -- I do see there's an inherent inequity, potentially, in there.

With that said -- That's me personally, as opposed to now trying to -- to provide an answer to the question, why are medical foods different than drugs or different than surgeries or different than visitors -- visits to a -- a -- a cardiologist, and that is, medical foods got singled out as a special category in order -- and it's summarized in the paper -- to maintain access. And the fact that it is a special category is then used as an excuse to not cover

it.

So, something like a drug for SMA is a drug, and you negotiate with the insurance company, as you do for any drug, as you do for insulin for a diabetic. So, my way of phrasing it is that medical foods are as essential to somebody with PKU as insulin for a diabetic -- or metformin or whatever it is. And it's because it's a special class that it's been a problem for decades, because it's denied on the basis of being not a drug and therefore not covered.

DR. JOSEPH BOCCHINI: Bob?

DR. ROBERT OSTRANDER: Bob Ostrander, American Academy of Family Physicians. One comment or suggestion I might add is that in the summary page, in addition to defining what the medical foods are, that we include the section that discusses what they are not, because the big bugaboo -- or one of the big bugaboos with getting this moved forward is -- is going to be the latch-on cost for nutritional therapies for other conditions, and that's fairly clearly

stated out in -- in the medical foods definition piece. And I think we can highlight that in our summary, because that's going to be one of the early objections: You know, what about gluten free, what about sugar-free candy, the whole -- the whole business? And if that's when it becomes an essential benefit, then we really are out of resources.

My second comment is, when it comes to convening this meeting, that we -- that you all, since I'm not a "we," actually suggest that the Secretary convene that meeting. And it would -- I don't know that that will happen, but this is what our job is, to be advisory to the Secretary, and I think we could advise the Secretary to convene a meeting of stakeholders about this issue.

DR. JOSEPH BOCCHINI: So, my -- Carol?

DR. CAROL GREENE: And I'd love to see -- A -- a way that might be done -- by the way, to second what Bob just said about the idea of asking the Secretary to convene the meeting, that

would not necessarily be part of the -- the paper itself, but that could be in a cover letter sending the -- you know, if the Committee were to so choose, that the Committee could send the Secretary a paper, with a cover letter saying, "Please, please, convene the meeting."

DR. JOSEPH BOCCHINI: So, as -- as Dr. Berry alluded to, I -- I think that the goal that we kind of came to in our prior discussions related to -- to medical foods was that -- that this white paper needed to have a broad exposure, and that rather than making a specific recommendation that we would state the principles that this committee believes are appropriate for the use of medical foods. And as Carol said, I think the key issue here is that drugs are used to provide life-saving treatments; medical foods are the same. They are to provide life-saving treatment, and yet they are not been -- they haven't been treated that way in terms of reimbursement.

And our goal is to -- is to make those

broadly available so that CMS and others are aware that this problem has not been solved. My -- my goal was to send a letter to the Secretary, attaching this, indicate that this is an unsolved problem and needs to be addressed.

And if it's the Committee's wish to ask that a meeting be scheduled, that certainly is one -- one option. There may be others that the Committee would like to consider related to that, that -- that might bring the stakeholders together, but I think that is a very reasonable next decision or next step towards attempting to resolve a problem that has existed for a long time.

Are there other thoughts? Dieter?

DR. DIETRICH MATERN: I just wonder, given the -- the -- the discussions around the renewable of the Affordable or American Care Act, is that an opportunity to bring in a voice to politicians and remind them of this? And another image I cannot forget is from the State of the Union Address, where you had a Pompe patient not

only in the room but also being pointed out.

DR. JOSEPH BOCCHINI: Well, my -- my thought, in composing a letter to the Secretary, that I would include the -- the fact that the President did point out Pompe disease and a treatment for it as an example of the importance of therapy for conditions that are identified through the RUSP and -- and that inborn errors of metabolism fit that same category, but the treatment is different but needs to be considered the same in terms of reimbursement. Yes?

DR. BETH TARINI: I -- I'm not sure, from a strategic perspective, unless we think that a meeting is going to really, sort of, push this over the top -- but I have this sense that one meeting, even if -- that one meeting by the Secretary -- convened by the Secretary is not going to do it, that if we -- I mean, I would be in favor of asking the Secretary what it is we want achieved, which is significant attention to resolving this issue, not provide him the actual answer on how to do it, because that may not be

the answer to do it. We can provide examples. And if we do that, we may actually end up giving an out that we -- that isn't -- perhaps, not the most effective course of action. So, I would be in favor of a -- of -- of a, sort of, looser cover letter which focuses, really, on the long-term goal, however it is to get accomplished.

DR. JOSEPH BOCCHINI: Natasha?

MS. NATASHA BONHOMME: I think, with either approach, whether it's a meeting or more of that broader and yet strategic approach that Beth is discussing -- I think really figuring out when would be a good time to pull in payers into this discussion, because that's really what it's about. And so, you know, I think us, in terms of the stakeholders who come to this meeting and who have been talking about this for quite some time -- we know what the issues are, but I think there may be some things that we can learn from the payers in terms of how these decisions are taking place and that they can hopefully learn from us in terms of why this is so critical.

And so, I would -- I would hate the see the discussion progress without figuring out a way to pull them in. And I know that's not easy, but I think, thinking of multiple ways or avenues that we can try to get those payers into the discussion, or at least putting this on their radar, would -- would be really beneficial.

DR. ROBERT OSTRANDER: All right. Bob Ostrander, AAFP, again. My concern with just sending a generic letter to the Secretary is, is that it will languish, and this -- because of the way this committee is set up and charged, we can't approach the politicians on Capitol Hill. We can't convene a meeting of stakeholders or do press releases or -- or generate public sentiment. All we can do is advise the Secretary to do something. And I have fear that if we don't advise something specific, and just bring something to attention, that it's not going to move that needle at all.

So, again, I would be -- It doesn't have to be a meeting, and it doesn't have to be a

motion today from you, but I would suggest that you do offer a specific action that might raise -- and that would -- could include holding hearings. It could -- You know, "We recommend you hold hearings." "We recommend you convene a meeting of stakeholders that would include the payers."

I mean, that motion could take a number of forms. But I think if you -- if you send a letter saying, "Please pay more attention to this," it's easy enough for the Secretary to say, "Okay, I have." If you say, "We -- we really would like -- We would recommend this," then the answer has to be, "Okay, I will," or, "No, I won't, and here's why." And, you know, I'm not a political strategist in any way, shape, or form, but I think we should frame it in a way that would require a response.

DR. JOSEPH BOCCHINI: Are there other thoughts about that from the Committee?

(No audible response)

DR. JOSEPH BOCCHINI: More specific

guidance or broader, sort of, end -- end goals? Don?

DR. DON BAILEY: This is Don Bailey. I don't really have an answer to this. I'm just raising this more as a question. So, I'm just looking at the principles again, which I personally like -- like them all, but I'm wondering, strategically, and building on Beth's comments is -- is, are some of them -- by endorsing all of them, would -- would some of them -- would it cause everything to be discounted?

And so, I'm -- I mean, it seems like the first and most important thing is that we want -- is that medical foods be considered as the -- and this goes along with what Carol says -- that medical foods be considered in the same reimbursement category as -- as prescription drugs.

DR. SUE BERRY: Please add that reimbursement piece and not call them drugs --

DR. DON BAILEY: Okay. Yeah.

DR. SUE BERRY: -- because if we have to go through the drug thing, we're going to be in trouble. So.

DR. DON BAILEY: Yeah. So, they'd be reimbursed in the same way that prescription drugs would be.

DR. SUE BERRY: Love the FDA.

DR. DON BAILEY: I mean, there would be wording to that effect.

(Off-mic speaking)

DR. DON BAILEY: If -- if we did --

DR. SUE BERRY: Yeah.

DR. DON BAILEY: If -- if that were the overarching statement, message, that went forward, these other -- I don't know if these other things, then, would be necessary, or if they -- if these things might be more red flags that might cause other things to be -- And I don't really know the answer to that, but I'm just throwing -- What -- Do you have a thought about that, Sue?

DR. SUE BERRY: We have thought a lot

about whether to lump these together or split them apart, or whether to leave something in or leave something out, and I guess we ended up thinking that they have to be covered, and they have to be covered for everybody of all ages, and I think those are the two essential elements. You know, whether it's -- whether you say states can't get out of it or not -- I don't care if you put that in there, because I don't think they should. Whether you say, "Lead by example, feds," that would be one strategy to ask about. It's -- it's -- You know, that -- that -- that's more a strategy than it is a principle.

But I think the principles are that they should be covered, that they're essential benefits, and that they should be accessible to all affected persons with this category of disease. And however you pen that out so that nobody mistakes it for sugar candy is fine with me.

But the bottom line is, is they do -- There is a very specific -- it goes into a lot of

arcane details in the -- in the paper about why medical foods are different from other specialized products, and I think our -- the heart of what we want to say is that they should be covered and for persons of all ages.

DR. DON BAILEY: Yeah, I think that would -- Yeah, to me, that would be a very strong statement to send forward.

DR. JOSEPH BOCCHINI: So, I think that makes sense to narrow it to the specific things that we want, without raising other issues that could potentially be used to sidetrack or sidetrack it. So, I guess the --

DR. DON BAILEY: And I -- And I'm not saying they will sidetrack it. I don't really know --

DR. JOSEPH BOCCHINI: Right.

DR. DON BAILEY: -- the answer to that. I would be interested in other people's on the Committee's perceptions, but I'm just throwing this out as a question.

DR. JOSEPH BOCCHINI: Yeah.

DR. SUE BERRY: I think the business of mentioning federal coverage was a holdover from our -- our concept that this -- that the Secretary could assist in leading by example. Perhaps it can be framed slightly differently. That's where that one came from.

DR. JOSEPH BOCCHINI: Beth?

DR. BETH TARINI: This is Beth Tarini. I -- I think that -- I -- I agree, you don't want to raise the flag unnecessarily, but if they're going to raise it, you want to see that you've seen it. So, if -- if you think that these, you know, other issues are going to be used as, "Oh, you just don't understand it because, you know, it's federal versus state, and there's these regulations, and there's these exclusions" -- If they're going to be used as, sort of, a walk-around the issue, then -- then I think they need to be there somewhere.

Perhaps the, sort of, middle ground is, this is -- is to state -- and, you know, the principle should be simple and -- and as succinct

as possible and as clear as possible and as broad as possible, and then just the continue -- but I -- I would lose this. I said, and these principles are based on certain things that, sort of, must happen in our view and our experience, et cetera, et cetera, et cetera, but I wouldn't -- They don't all have to stand out as principles, but they should be pretty close to the top because, otherwise, they're going to say, "Oh, you don't understand about regulations," which you will understand.

DR. SUE BERRY: Painfully so.

DR. BETH TARINI: Yes. Unfortunately. My understanding, also, is that this is a -- a timely moment, because the AAP and the AFP and the AMA have all set forth resolutions.

DR. SUE BERRY: Thank you for mentioning that.

DR. BETH TARINI: I wasn't sure --

DR. SUE BERRY: Professional organizations did --

DR. BETH TARINI: Right.

DR. SUE BERRY: -- in fact, create endorsement that echoed this.

Dr. BETH TARINI: Yes.

DR. SUE BERRY: The AAFP, the AAP, the SIMD, ACMG via the AMA --

DR. BETH TARINI: Yes.

DR. SUE BERRY: All had strong endorsements this year in their resolutions for medical foods.

DR. BETH TARINI: So, the iron is hot.

DR. SUE BERRY: The iron is hot. And others have always supported this. I know March of Dimes have been stalwarts in all aspects of care for newborn screening.

DR. JOSEPH BOCCHINI: Yeah, that's why, in part, if -- if it's accepted and finalized, and we make the Secretary aware that we've done it, then we've got it posted on our website. So, it's available to those organizations, as well. Bob?

DR. ROBERT OSTRANDER: This is Bob Ostrander. I hate -- hate to keep monopolizing

and chiming in, but this has been a pet project of mine, as well. I think, as we're all talking about this and writing this letter, it's worth focusing some on the fact that although these are medically necessary treatments, and in that way, like drugs, they are indeed foods, and then people have a right to freedom from want and freedom from starvation.

And it makes it -- for certain groups, I think that would make it even more fundamentally important and acceptable than saying -- Because there are some people who don't think medical treatment is a right. There are very few people who don't think food is a right. So, I think it's worth, you know, bearing that in mind as we frame things and -- and the tones that we use here.

And then, the other thing -- and -- and Sue pointed it out -- you're going to have to be very careful about throwing the word "drugs" in there for that other reason, because we -- the last thing we want is FDA oversight and regulation in the way that they do to approve

drugs. I mean, that adds a whole bunch of costs and problems, so, you know, medically necessary treatments, I think, is a good phrase to use, but, you know, using anything that compares it with medications is a hot potato.

DR. SUE BERRY: I know, and you have to be careful with the word "treatments." You have to call them interventions or something else, because treatments is something drugs do. I -- I've been -- had this drilled into me.

(Laughter)

DR. SUE BERRY: The -- the language is essential. It's -- it's -- The -- the key to this is precision in language. That's why it's really important that we discuss this thoughtfully and use the right words, because the wrong words will trip you up. You know, they'll find a way to -- People will get into regulations. That's why we -- we're so careful in framing the regulations in this.

DR. DIETRICH MATERN: I know I'm very new but regulations are currently, presumably, on the

chopping block. Do we understand why they don't pay for medical foods? And if not, if there are regulations that need to be changed, why don't we suggest they're being changed?

DR. SUE BERRY: I -- I don't know that I have answer for that, so.

DR. DIETRICH MATERN: But do -- but do we know why it has been denied so far, to include medical foods?

DR. SUE BERRY: It's because they're not drugs, so insurance doesn't pay for food. That's the bottom line.

DR. DIETRICH MATERN: So --

MALE SPEAKER: So that could be changed.

DR. SUE BERRY: You can say it's medical foods, it's special, people die without it, but that's not enough. Carol, do you want to add to that?

DR. CAROL GREENE: And -- and Cathy might be able to add even better, but, yes, in -- in -- the -- the drug -- the insurance companies, by the way, see this as a very small number, not

nearly as expensive as some of these major drugs. And what they have said in so many words, at least at the state level, when we were in a meeting with them, is: if we were all required to cover it, that would be easy. It wouldn't even jack up the prices. It's a small number. It's only if I cover it and they don't that everybody will flock to me, and then mine is more expensive. So, if somebody would just level the playing field, we'd all be happy, no big deal. It wouldn't really be that much money.

And the reason that they don't cover it is precisely because it is not a drug, and the reason that there's no regulatory solution to that is because there is no other category. It's either -- In terms of coverage, it's either a drug or a device, or it's not a drug or a device. And if you were to try to create a new regulation, you'd have to either create a new category, which is not going to happen -- that's actually what happened the last time -- or you'd have to make it a drug, in which case we would

instantly be with none because nothing on the market has been -- had the kind of trials that a drug needs. So, if you make it a drug, it's covered, but we don't have any, and there's no regulatory response to solving the problem. And if Cathy wants to add anything --

FEMALE SPEAKER: No.

DR. CAROL GREENE: -- I think she's the real expert here if the Committee has a question about that.

MS. CATHY CAMP: Thank you. Is this on? Can you hear me?

(Off-mic speaking)

MS. CATHY CAMP: Yeah. Thanks. To answer that question, with respect to FDA and what they can and can't do, I'm not an expert from FDA, obviously, I was at NIH, but I do know the medical foods people very well at FDA, and they made a very concerted effort, with their guidance to industry, to clarify their thinking on medical foods and what medical foods are and what they're not.

And if you read their guidance carefully, they've been very careful to say that medical food is something that's required for a condition whereby you cannot -- you cannot adapt a normal diet. So, they distinguish between providing a product -- even if it's in a can -- for a person with diabetes versus a product for a person with PKU, because a normal diet can be modified for people with diabetes, and they cannot be -- cannot be modified for people with PKU.

But I think that the Committee could go to FDA and say, "Can you help us solve this problem?" Because there may be a way that they can come up with further clarification or with a way that they could come up with some kind of a statement, perhaps, that says that these products should be covered for people with inborn errors. And I'm -- I'm seeing a look over there, and that's something that if --

(Laughter)

MS. CATHY CAMP: There's no reason why, I don't think -- You could ask the Secretary,

certainly, to include FDA medical foods people in the discussion with respect to how this'll move forward.

DR. JOSEPH BOCCHINI: Kellie, you want to add anything?

(Laughter)

DR. KELLIE KELM: Well, it's difficult, because, you know, obviously, current regulatory climate is changing, to be realistic. I mean, there -- there are people that are interested, and I think, depending on what you guys are recommending, you know, you obviously can reach out and try to include them, but I can't comment on what they would be able to or what they would not be able to do. Obviously, we have a new commissioner, just started a couple days ago, and so can't comment on how -- what the regulatory climate will be.

DR. JOSEPH BOCCHINI: Thank you. Carol?

DR. CAROL GREENE: I -- I think it's a fascinating discussion, and I've been around for long enough that I've been around -- I mean, I'm

not old enough to have been around when the first -- it wasn't even TRICARE then, but the first time that the -- the armed services covered it, whatever it was called then, the first time Kaiser covered it -- All that is before my time.

But I -- all the time I've been working in this, it's been not covered, and at each time, there's a different potential avenue for how to solve the problem. And the avenue that might be available to solve the problem in May of 2017 might be different than what is available in January of 2018.

And that's one of the reasons that I personally like so much the idea of starting with a basic where we -- what's the issue and where we have been and what's been tried, and lay it all out on the table, so that people wouldn't have to reinvent the wheel. And I love the way that Sue came up with affirming basic principles, and then, after that, they become strategies. So, I -- I really do like the idea of -- of having it laid out and look forward to finding out whether

the Committee agrees with the -- the -- the paper and the principles, and then the rest is strategy.

DR. JOSEPH BOCCHINI: No other comments? Then I think that -- The consensus, I believe, is that there is general agreement with the white paper and that the suggestion is that the -- the specific -- the principles be tightened to reflect, very specifically, what we're -- what we're -- what we believe is the principle in terms of the use of medical foods and how they should be covered.

And with that, I -- I believe we have, sort of, a consensus, and if that's the case, if there's no other comments, I'd like to go ahead and take a formal vote to accept the -- the -- the -- the white paper, with -- with those specific sets of guidance, and then, following that, if we can have further discussion on how to go forward with this -- I think we -- we've laid out the general ideas, but we -- we certainly can provide more direction. That doesn't have to be

done immediately, but I think it would be good to get overall consensus from the Committee as to how we feel about next steps once that's done.

So, let's go ahead, then, if there are no other comments, with the vote to accept the white paper.

DR. KELLIE KELM: Dr. Bocchini, can you just -- You talked about tightening them. So, are you talking about modifying the white paper? Can you just maybe comment a little bit more about --

DR. JOSEPH BOCCHINI: Yes.

DR. KELLIE KELM: -- what you mean by that?

DR. JOSEPH BOCCHINI: So, the -- the -- basically, accept the white paper the way it is. If there's any mild, sort of, language changes that people want to make to clarify things but not really change the -- the -- any of the -- of the ideas that are in the paper, that would be fine. But then, as far as the -- the -- the principles that were stated -- I don't know if we can go back to that -- that one slide that had

the principles? There were -- there were four.

DR. SUE BERRY: And I -- I -- I took some of the extra words out that were in the paper to make it easier to read on the slide here.

DR. JOSEPH BOCCHINI: Mm-hmm.

DR. SUE BERRY: And I realized that I cut out something about age on this. So, remember, age -- It should be age unrelated.

DR. JOSEPH BOCCHINI: Okay.

DR. SUE BERRY: I -- I cut it a little too much.

DR. JOSEPH BOCCHINI: So, I -- I mean, the principles and -- and -- were that -- I mean, the specific principles were that medical foods must be covered as required medical benefits, be covered in all ages, and -- and then, the way Don put it, we really had it down to two -- two statements, one that the -- that it was a -- a -- a required medical benefit and -- I guess for all ages, and that was it. And is everybody comfortable with just modifying the language to make it those two statements?

(Off-mic speaking)

FEMALE SPEAKER: Can you just repeat the --

DR. JOSEPH BOCCHINI: Oh, so the two statements? I'm sorry. Could we --

FEMALE SPEAKER: Okay.

DR. JOSEPH BOCCHINI: -- put that back up again? One was, medical foods must be covered as required medical benefits -- actually, you could make it one statement -- for all ages.

DR. SUE BERRY: Yeah. And -- and the fuller statement that's in the paper, I should have copied it verbatim. I'm sorry, I was just doing this for the presentation purposes, and I apologize for that. In the -- in the statement, it's a little wordier, and it basically says for all ages and all -- And it's a little more specific about how they're diagnosed and some other things like that.

MALE SPEAKER: Would you --

DR. DON BAILEY: Yeah, the first statement in the paper itself's very clear, I

think --

DR. SUE BERRY: That's what that should say.

DR. DON BAILEY: -- except it doesn't -- it actually doesn't say ages. It says: Medical foods which require ongoing medical supervision, whereby dietary intervention cannot be achieved by modification of a normal diet alone, that are authorized by a medical provider for management of an IEM, must be -- must be covered as required medical benefits, and we could add "across the lifespan." And to me, that's the essence of what we're trying to push for here, and the other things are -- You know, the regulations might not be subject to state exclusions. That could all change depending on --

DR. SUE BERRY: Just leave that part out.

DR. DON BAILEY: -- upcoming legislation and so forth, and so we don't -- So, I think -- I mean, I'd be interested if the Committee -- if the group that's presenting this agrees with that, but I think the first statement is -- is a

-- is obvious. Yeah.

MALE SPEAKER: (Off-mic speaking) authors are --

DR. SUE BERRY: So --

MALE SPEAKER: -- comfortable with those changes (off-mic speaking).

DR. CAROL GREENE: Speaking only for myself -- Carol Green -- I am comfortable with that change. The rest, to me, are subsidiary. They're part of how you try to achieve that. So, I'm very comfortable, especially, like, adding "across the lifespan."

MALE SPEAKER: Mm-hmm.

DR. SUE BERRY: Yeah. That's because that got subsumed at that statement at the end, where basically, it talks about individuals of all ages. So, it would be easy just to take -- Actually, the thing you want to say is just that first statement.

MALE SPEAKER: Yeah.

FEMALE SPEAKER: Yeah.

MALE SPEAKER: Exactly.

DR. SUE BERRY: You know, medical foods must be covered as medical -- as required medical benefits for persons of all ages.

MALE SPEAKER: Right.

DR. SUE BERRY: And the rest of it you can --

DR. DON BAILEY: To me, the rest of --

DR. SUE BERRY: -- take out.

DR. DON BAILEY: -- it is -- is -- is varying strategies, depending on, you know, future legislation, a variety of other things, but this is core.

DR. SUE BERRY: And, you know, the affected persons should have access to these essential interventions, irrespective of the source of their health coverage is, perhaps, only a redundancy? I think it just says the same thing again. So, we can change that by adding those three or four words, take out the other three because they're subsidiary. I don't know if you want the italicized piece, but we could leave that out. We can -- we can just say: individuals

of all ages who are diagnosed with -- You can take out the insurance and guidance part. You'd just say: Individuals of all ages who are diagnosed with an IEM should be able to access comprehensive coverage for medical foods. Just that last part of that, and have those be the two statements.

DR. JOSEPH BOCCHINI: All right. Comfortable with those? Any -- any concern about that?

(No audible response)

DR. JOSEPH BOCCHINI: Okay. So, does that clarify where -- where we are?

(No audible response)

DR. JOSEPH BOCCHINI: Okay. Everybody's -- Okay. So, we'll go ahead, then, with the vote to accept this report on medical foods for inborn errors and make the adjustment on the principles. So, there --

(Off-mic speaking)

DR. JOSEPH BOCCHINI: Is there any conflict of interest?

(No audible response)

DR. JOSEPH BOCCHINI: Does anybody need to abstain?

(Off-mic speaking)

DR. JOSEPH BOCCHINI: Kellie?

(No audible response)

DR. JOSEPH BOCCHINI: All right. Dr. Lu?

(Off-mic speaking)

DR. JOSEPH BOCCHINI: And Kamila. Okay. So, does this require a motion, or is this just that the Committee accepts?

FEMALE SPEAKER: Require a motion.

DR. JOSEPH BOCCHINI: All right. Do I have a motion?

DR. DON BAILEY: I move the Committee accept this report with the modifications to the principles, as -- as stated and hopefully recorded by our recording system here.

DR. JOSEPH BOCCHINI: Thank you, Don. Do I have a second?

DR. JEFFREY BROSCO: I second. It's Jeff.

DR. JOSEPH BOCCHINI: Jeff, okay. So,

it's been moved and seconded, and now we'll do the vote. Don Bailey?

DR. DON BAILEY: Yes.

DR. JOSEPH BOCCHINI: Mei Baker?

(No audible response)

DR. JOSEPH BOCCHINI: Did Mei get back on?

FEMALE SPEAKER: She is on, but she was getting -- There she is.

DR. MEI BAKER: Can you hear me now?

DR. JOSEPH BOCCHINI: Yeah. Can --

DR. MEI BAKER: I --

DR. JOSEPH BOCCHINI: Yes, we can hear you. How do you vote?

DR. MEI BAKER: Yes.

DR. JOSEPH BOCCHINI: Okay. I vote "yes." Carla Cuthbert?

DR. CARLA CUTHBERT: I abstain.

DR. JOSEPH BOCCHINI: Abstain? Jeff Brosco?

DR. JEFFREY BROSCO: Yes.

DR. JOSEPH BOCCHINI: Fred Lorey?

DR. FRED LOREY: Yes.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETRICH MATERN: Yes.

DR. JOSEPH BOCCHINI: Steve McDonough?

DR. STEPHEN MCDONOUGH: Yes.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Yes.

DR. JOSEPH BOCCHINI: Let's see, Dr. Bianchi?

DR. DIANA BIANCHI: Yes.

DR. JOSEPH BOCCHINI: Beth Tarini?

DR. BETH TARINI: Yes.

DR. JOSEPH BOCCHINI: And Cathy Wicklund?

MS. CATHERINE WICKLUND: Yes.

DR. JOSEPH BOCCHINI: Okay. I want to thank Sue, especially, and all the rest of you who participated in bringing this together. This was really a good -- good body of work, so thank you. I think this is going to be very helpful going forward.

Now, as far as next steps, I think I've outlined that we want to post this, when it's

finalized, on our website to make it available. We want to send a letter to the Secretary, making the Secretary aware that this is an important problem that the Committee believes has not been addressed and needs to be addressed, and -- and then, I will be happy to discuss further with the Committee any additional recommendations that -- that might be made in terms of specific recommendations to the Secretary or being broader in terms of an overview of what we want to achieve rather than how to achieve it. And if there are comments now, that's fine. If not, we can take them later.

(No audible response)

DR. JOSEPH BOCCHINI: Everybody needs time to think. Okay.

DR. DON BAILEY: Well, I think this is a systems-level issue that's not going to be solved by -- by one simple declaration by one person or one group, so it's going to require a -- a systemic and coordinated approach at the highest levels. And I don't really know what the ultimate

mechanism to make this happen is, but I do think sending this forward to the Secretary in as, you know, positive but as strong a language as we can and -- and -- and -- and then try to move forward from there. Beth, do you want to --

DR. BETH TARINI: Is the legislation coming up for renewal? The Newborn Screening Saves Lives Act? Has it ever -- Is it --

(Off-mic speaking)

DR. BETH TARINI: Nineteen? Oh, okay. Never mind.

(Off-mic speaking)

DR. CATHARINE RILEY: The Committee has a charter through 2019.

(Off-mic speaking)

DR. BETH TARINI: I was -- Right, I was trying to link as many ongoing activities as possible, the -- the AFP, this, AMD, this, and any other legislation, other than the budget.

(Off-mic speaking)

DR. BETH TARINI: To make it look timely to act.

MS. CHRISTINE BROWN: I'm Christine Brown with the National PKU Alliance. There will be a bill introduced in the Senate, hopefully within the next 2 weeks, called the Medical Nutrition Equity Act, which is championed by Senator Casey from Pennsylvania and Senator Grassley from Iowa, so we do have bipartisan support, and in the House, right now, our lead champion continues to be Congressman Delaney out of Maryland. And if I get a bill number before this goes forward, I will pass that on.

DR. JOSEPH BOCCHINI: All right. Thank you. That will conclude this general meeting for today. We will now have a short break, and at 3:00, the workgroup meetings will begin. Catharine, do you want to --

DR. CATHARINE RILEY: Sure.

DR. JOSEPH BOCCHINI: -- tell people what's where and where they need to be?

DR. CATHARINE RILEY: Sure. If we could get -- I know there's a -- The -- the last slide just has the room numbers for the workgroups if

we could get that up there? For those interested, the workgroups are open. They'll be meeting in three separate rooms. We're going to have some -- some HRSA escorts so you can find the rooms. For those who've been here before, you -- There's two conference rooms here, so.

We're ending a little early, so the -- the HRSA staff that are going to help with that are going to be down shortly, but if you're part of the workgroups, if you kind of can just stay in here, we'll make an announcement, and we'll head over there to the rooms about five 'til 3:00, but until then, you can -- you know, restrooms and cafeteria. There's a -- I think the cafeteria closes at 3:00. But we can escort you, also -- If you kind of wait here, then we'll make an announcement, and we can escort you to the rooms, and we'll have the room numbers up here for those who want to make their way.

(Whereupon, the above-entitled matter was concluded.)

DAY 2 PROCEEDINGS

DR. JOSEPH BOCCHINI: We're going to need a minute or so to get all of the electronics ready, then we'll start.

(Period of silence)

DR. JOSEPH BOCCHINI: All right. Good morning, everyone. I'd like to welcome you to the second day of the May meeting of the Advisory Committee on Heritable Disorders in -- in Newborns and Children and call the meeting to order.

We'll start with a roll call, so Committee members first. Don Bailey?

DR. DON BAILEY: Here.

DR. JOSEPH BOCCHINI: Mei Baker?

DR. MEI BAKER: Here.

DR. JOSEPH BOCCHINI: I'm here. Carla Cuthbert?

DR. CARLA CUTHBERT: Here.

DR. JOSEPH BOCCHINI: Jeff Brosco?

DR. JEFFREY BROSCO: Here.

DR. JOSEPH BOCCHINI: Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH BOCCHINI: Fred Lorey, by phone?

DR. FRED LOREY: Here.

DR. JOSEPH BOCCHINI: Michael Lu is being represented by Joan Scott today.

MS. JOAN SCOTT: Here.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETRICH MATERN: Here.

DR. JOSEPH BOCCHINI: Steve McDonough?

DR. STEPHEN MCDONOUGH: Can you hear me? Here.

DR. JOSEPH BOCCHINI: We can hear you. Kamila Mistry?

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH BOCCHINI: Melissa Parisi?

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Beth Tarini?

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: Cathy Wicklund?

MS. CATHERINE WICKLUND: Here.

DR. JOSEPH BOCCHINI: And Catharine Riley?

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: Now organizational representatives in attendance: Robert Ostrander?

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: Robert Saul, by phone?

DR. ROBERT SAUL: Here.

DR. JOSEPH BOCCHINI: Michael Watson?

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: Britton Rink, by phone?

DR. BRITTON RINK: Here.

DR. JOSEPH BOCCHINI: Kate Tullis?

DR. KATE TULLIS: Here.

DR. JOSEPH BOCCHINI: Susan Tanksley?

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Chris Kus, by phone?

(No audible response)

DR. JOSEPH BOCCHINI: Adam Kanis?

DR. ADAM KANIS: Here.

DR. JOSEPH BOCCHINI: Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. JOSEPH BOCCHINI: Siobhan Doyle (sic)?

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: Cate Walsh Vockley?

MS. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: And Carol Greene?

(No audible response)

DR. JOSEPH BOCCHINI: So, completing roll call, Catharine Riley has a couple of housekeeping things to tell us.

DR. CATHARINE RILEY: Good morning, and welcome, again, for day 2 of the Advisory Committee meeting. Just a reminder for security that all visitors or guests do need to be escorted if you are leaving outside of the -- this pavilion area or cafeteria or, kind of, this main area on the fifth floor.

And then, for Committee members and organizational reps, when you have a question or a comment, could you please state your first and last name for our recorder? Just, we want to make sure we accurately represent this for the records. So, appreciate that. Thank you.

And for the Committee members, for any of those who have not turned in annual -- your annual ethics paperwork, if you could submit that to me before you leave today, or -- or we'll follow up. So, thank you so much.

DR. JOSEPH BOCCHINI: Next on the agenda is recognition, and I just wanted to highlight that we do have three members of the Committee who are here for their last meeting before they rotate off the Advisory Committee. And I want to recognize these three individuals because they have made numerous contributions to this committee for more than the regular term.

And I think all of you remember when this committee -- the -- the legislation sunsetted, and we were made a discretionary committee by the

current -- the -- the -- the -- the Secretary, and so we froze the positions and the -- and the duration of time that people served. So, all of these individuals served well past the usual time, and -- and so, they did so willingly and continued to make multiple contributions, both in leadership roles on the workgroups and -- as well as by providing comments and -- and recommendations at individual meetings.

So, I want to thank them all for -- for their work. They will receive, each, a certificate at the close of their term from -- from HRSA, which will then just remind them of their service to the Committee.

But, specifically, for Don Bailey -- Don has been a -- a -- a really strong member of this committee. Don always kept reminding us that the primary focus for all we do is the family and the children in the family, and -- and brings us back to that with everything that we look at. In addition, I think he's very capable, in the middle of a -- of a busy meeting, to, kind of,

work through complex issues and summarize the key elements that are necessary to really move ahead and -- and move the Committee forward.

So, for all of that, Don, I want to thank you for your many years of service, and we'll certainly miss that going forward.

(Applause)

DR. JOSEPH BOCCHINI: Next, Fred Lorey. Fred is -- is the consummate public health laboratorian. Fred has been involved in a number of the efforts that this committee has made related to laboratory work. He has been involved in -- in a number of discussions, taken on a number of leadership roles, and -- and actually, because of his expertise and involvement in -- in research work in -- in his role in California, he was able to provide us with lots of insights into many of the issues facing laboratories, facing putting new conditions that have been approved by the RUSP or into the -- in the workflow of the lab and -- and -- and has been very -- very helpful to the Committee.

He has -- When he retired from California, he -- from his work in California, he became a consultant and now is around the world, lending his expertise to countries that are trying to develop their newborn screening programs.

So, Fred, want to wish you the best, and thank you for all of your contributions to the Committee, as well.

(Applause)

DR. JOSEPH BOCCHINI: And third is Steve McDonough. Dr. McDonough is a real champion for patients. Dr. McDonough's a general pediatrician who focused many of his efforts on children with special-care needs, and through that, he has become a strong advocate for those children.

And he came to the Committee with -- with the drive to have the Committee act, to have the Committee move -- move issues forward, and to always ask for some degree of accountability for all of the things that we have -- we've tried to move forward. And so, he has been an incredible

advocate and has certainly helped this committee make decisions and then provide efforts for accountability for some of the decisions that we've made.

So, Steve, thank you for all that you've done, both around the table here at each meeting and in the leadership roles that you've taken through the years on the Committee. So, thank you.

(Applause)

DR. STEPHEN MCDONOUGH: Mr. Chairman?

DR. JOSEPH BOCCHINI: Yes.

DR. STEPHEN MCDONOUGH: Could I make a brief statement?

DR. JOSEPH BOCCHINI: Yes, you may.

DR. STEPHEN MCDONOUGH: Okay. Thank you. It sure has been an interesting experience, serving on the Committee. One of the benefits has been meeting people who are better than me, and that has been especially true for Don Bailey and Dieter Matern.

I'd like to thank those who truly

inspired me, the children and families of those who came before this committee, from the parents who saw their children die because screening was not done on a timely basis to the parents of children with GAMT and SMA. When I thought that the evidence was there, I tried to give you a voice and a vote on the Committee. I did what I could, as long as I could, and I wish you good fortune in the struggles ahead.

DR. JOSEPH BOCCHINI: Thank you very much, Steve. Don or Fred? We'll give you equal -- equal time.

DR. FRED LOREY: Well, this is Fred.

DR. JOSEPH BOCCHINI: Yes, sir.

DR. FRED LOREY: I just want to say, it's been a great experience, and I'll miss everybody, and outside of the Committee meetings, there really is a great deal of interest and respect for the Committee and what it does. I'm asked about it all the time. And I think we don't always get that feedback, so just for the other Committee members, know that, and keep on going.

DR. JOSEPH BOCCHINI: Thank you, Fred. Don?

DR. DON BAILEY: Yeah, all I can say is, it's just been an honor to serve on the Committee. I think the Committee is doing outstanding, important work, and if you think of all the committees you could serve on, the ones that actually result in something that makes a difference with children -- This is one of the -- this is one that does. So, it's been quite a -- quite an experience, and I'm looking forward to continuing to do work and do more screening in other ways. So, thanks very much for the opportunity.

DR. JOSEPH BOCCHINI: Thank you. So, next on the agenda is a discussion about the implementation of critical congenital heart defects in -- for -- into newborn screening. And we have a panel presentation today, and I'm going to introduce each of the panel members.

Careema Yusuf is a manager for the Newborn Screening Technical Assistance and

Evaluation Program, NewSTEPs, at the Association of Public Health Laboratories. Prior to joining APHL, Ms. Yusuf was a senior health care analyst at the National Committee for Quality Assurance, where she managed and coordinated the National Collaborative for Innovation in Quality Measurement research project activities that are tasked with development of child health performance measures.

Amy Gaviglio has been serving as a genetic counselor and supervisor to Minnesota Newborn Screening Program for the past 10 years. She has extensive experience in newborn screening-related education and training, targeted at a variety of audiences, ranging from parents to providers, legislators, hospital staff, and midwives. She is interested in education as it relates to newborn screening centers on issues in health equity, in health communication, obtaining broad informed consent at the population level, and utilizing new tools to reach today's parents, and developing

sustainable education plans for hospital staff.

And then, our third presenter is a member of our committee, Annamarie Saarinen. So, I'm not sure who is going first.

MS. CAREEMA YUSUF: Good morning, and thank you very much for this opportunity. I'd like to thank Dr. Bocchini and the members of the Committee for the opportunity to share with you the status of screening of critical congenital heart disease in the United States. To begin with, I'd like to say that the development of this presentation was supported through a cooperative agreement with HRSA.

So, the Newborn Screening Technical Assistance and Evaluation program -- or NewSTEPs, was designed to provide data, technical assistance, and training to newborn screening programs across the country. APHL, in collaboration with the Colorado School of Public Health, implement NewSTEPs, and newborn screening programs share information with NewSTEPs around the newborn screening activities that they

perform, and we use this data and information to help with continuous quality improvement.

Part of the information that they share with us is the status of newborn screening conditions that are on the RUSP, and one of the ways that we share this data with the public is through a number of graphics. I will show one of them here.

This is, like, a measles chart. It is a chart that shows all the newborn screening programs in the country, and then all the different conditions. There are 34 conditions on the RUSP, the core conditions. The table at the bottom has a key, and the key provides you with some information about what the different symbols mean in the chart. I'd like to say that the highlighted column actually is supposed to be CCHD, as we're talking about that today.

Another way that we provide information to the public is through this -- another visualization using maps. Here, you see a heat map, and this heat map shows the universal

screening status of all the 34 core disorders as of April. The darker the color, the higher the number of the core RUSP conditions that are being universally screened.

So, what is the status of screening of CCHD currently? Just a reminder: CCHD was added to the core RUSP back in September 2011, and this is a screenshot of the letter to the Committee from the then Secretary of Health and Human Services, agreeing and deciding to add CCHD to the RUSP.

In the same letter, the Secretary also adopted additional activities that were proposed by the Committee, and these activities include research around technologies for screening and diagnostics, surveillance of CCHD, the development of screening standards and infrastructure needed for implementation of a public health approach to point-of-care testing, and then the development of appropriate educational and training materials for families, public health, and health professionals.

So, the next set of slides I'm going to show you is just a progression of the adoption of CCHD within the country. We'll start off with 2012, when just a handful of them were universally screening. 2013, more states adopted this to their screening panel, even more in 2014, 2015, and 2016.

I seem to have lost my slides. Okay, no problem. So, just to show you right now: Currently, in 2017, the map looks very much the same. There are two programs who are pursuing universal screening, the first being Idaho. They are pursuing legislative approval. And the second is Wyoming. They did receive legislative approval, and they have recently gotten that, and they're working through their public health rules and regulations around CCHD screening.

My other slide was going to show information about the data that we are collecting for CCHD screening. It is varied across the country, because CCHD is a point-of-care screening and is not done in the public health

program. So, what we try and do at NewSTEPs is collect information about what kind of data are they collecting if they are universally screening.

And so, there are various, I guess, options that folks can get. They can either get aggregate data from the hospitals on whether children passed, failed, or did not get the screen. They have information on -- at the individual level. You can get information around whether the child passed, failed, or it was not done, and there are also some programs that get individual, actual oxygen saturation data and time. So, there's a wide variety of data and how the different programs are collecting it. Currently, 14 programs don't have data coming into the public health program.

So, I just wanted to highlight that, you know, NewSTEPs is trying to describe the differences. We're collecting that information, and we're also working with CDC, currently, to identify those data collection challenges and

come up with some standard metrics for CCHD screening at the newborn screening program.

And that's all I have. I just want to say thank you to the newborn screening programs who continue to provide us with data, and I'll hand it over to Amy. Thank you.

(Applause)

DR. CATHARINE RILEY: Could I -- I just want to make a point. So, there were a couple of slides that will be available in the presentation after the meeting. So, thank you.

MS. AMY GAVIGLIO: Perfect. Thank you, Careema. Thank you, Dr. Bocchini and the Committee. I've been tasked today to -- to delve a little bit deeper into what CCHD screening looks like in -- in the United States from a state program perspective.

So, I'm going to start with a -- an image that Careema got stuck on, I guess, and I think we -- we often like these visuals because I think we -- we look at them and -- and feel like we get a good idea of what's going on in the -- in the

states. But in -- in the world of CCHD, the devil is really in the details, and there are a lot of details, just based on the nature of CCHD and -- and the fact that it is a point-of-care test.

So, I'll briefly remind everyone what CCHD screening is all about. So, it utilizes pulse oximetry to detect lower oxygen saturations, which are often associated with critical congenital heart disease. And the way "critical" is defined, typically, is that it requires some sort of intervention, whether it's catheterization or surgery in the first year of life.

Another important point is that this is not specific to CCHD. This screen is detecting hypoxemia. We're looking at oxygen saturations. And this can be associated with a number of things. It can be associated with non-critical congenital heart disease. It can be associated with several pulmonary conditions: pneumonia or persistent pulmonary hypertension of the newborn. It can be associated with bacterial infections,

like sepsis, and of course, it can be associated with CCHD.

Originally, when CCHD was recommended and the AAP came out with their recommendations, there were seven primary targets. That has since been upped to 12, which I'll show you here. So, the first seven that are bolded, those were the original targets, thought, pretty likely, that we would pick those up by pulse oximetry, and the bottom five are those additions that we feel like may be picked up, but also, we may miss those.

So, I'm going to talk a little bit about CCHD screening and -- and compare it to some other conditions. As Careema mentioned, states have taken a lot of different approaches in -- in terms of how to deal with CCHD screening, in terms of what screening algorithm they're going -- going to recommend, how or if they're going to do any active follow-up on these cases, as well as if they can collect data, and if they can collect data, what kind of data are they going to collect, and what are they going to do with that

data.

So, this is an example of three algorithms that are currently in use throughout the United States. So, the top one is the original AAP, aka Kemper, aka Granelli algorithm, and so this requires a saturation above 95% in either the right hand or foot.

The New Jersey program -- and we -- this is actually the algorithm we use in Minnesota, as well -- made a modification to that algorithm in that they require the sat value to be above 95% in both the right hand and foot. So, it's a -- an "or" to an "and."

And then, Tennessee actually takes a different approach altogether, in that their first screen is just a post-ductal screen; they're just looking at the foot measurement first, and only if that is above 97% do they go on and do pre- and post-ductal. So, you can see there's a pretty good variation in -- in even the screening algorithm itself.

CCHD is also unlike any other newborn

screening condition that we currently screen for, both in terms of the blood spot conditions and even in terms of the other point-of-care condition: newborn hearing screening. One of the things that makes it unique is that pulse oximetry screening is actually the third line of defense, and this is very different for us.

We're used to being the first line of defense, in that we're the people who are going to pick this up, you know, unless there's a -- a positive family history. But with pulse oximetry screening, you have prenatal screening for CCHDs, and then you have the clinical exam, and that may pick it up and, quite often, will pick things up prior to the 24 hours, when pulse oximetry screening is recommended.

So, it's just important to -- to keep this in mind, and I know -- I'm sure everyone heard of the Jimmy Kimmel -- his story. And, certainly, that is a success for detection of CCHD, but that was picked up clinically, so not necessarily a success for pulse oximetry

screening, and that makes it, I think, complicated to -- to delineate how effective we're being with pulse oximetry.

The other unique aspect is that there are other public health programs that are quite involved in looking at CCHD, as well. These are the birth defects registries, and -- and in most states, identified cases of the primary targets are mandated to be reported. And so, you have another state program that is offering surveillance of these conditions.

The other component is that the necessity of the screen itself has the potential to vary by individual and location, dependent upon access to care, both prenatally and clinical care. So, it's interesting to think of this screen as maybe being more necessary in certain locations and maybe not as necessary in other locations where there is high levels of prenatal and clinical care available.

So, what have been our successes thus far with this screen? We know, absolutely, that

infants who may have otherwise gone home undetected have been picked up by screening, and we also believe -- and -- and note that I say "believe" -- many, if not most of the eligible infants appear to be getting screened, and I'll talk a little bit more about why I'm saying "believe" and not "We know this for sure."

We also know that -- and I think Annamarie will probably touch on this, as well, is that because we're looking at hypoxemia, we know that other significant disorders are being picked up that are making a difference, maybe not -- it may not be CCHD, but it could be persistent pulmonary hypertension of the newborn, pneumonia, or sepsis, which are very real and very significant conditions.

Another success is, when CCHD was first added, there was some fear that it would, essentially, shock the system in terms of having a high level of echocardiograms or transports, and this does not appear to be the case. This is anecdotal; I -- we've talked to a few people

about this, but it seems as though we're not really putting too many kids through the system that don't need to be through the system.

I think another success, quite honestly, with this screen is that it has forced public health programs to kind of de-silo themselves. We -- we really like to work in our silos, but the addition of this disorder, that had such a clear component in another public health program, I think, has really resulted in much stronger relationships, which I think is ultimately going to be better, not only with CCHD but for the -- many of the other newborn screening conditions, as well, as we discussed yesterday.

So, what are our existing challenges? Data, data, data. Both -- And -- and really, in many different ways. I think programs are having some difficulty getting buy-in from hospitals to report this data, understanding the timeliness of this data, how timely do we need to get it, the quality of the data, and, of course -- which is always kind of an issue for us in -- in state

programs are -- are the so-called border babies, so the babies who are born in one state and screened in another.

And challenges in getting the data really span the entirety of the process, from trying to get the initial screening results or information for why the child was not screened, trying to get the echocardiogram results after a failed screen, and also trying to delineate all of the non-cardiac findings. It's not too hard to get, at least when you've picked up a true CCHD case, but trying to figure out what else might have been going on is proving to be quite difficult.

I'll mention case definitions again, and these are currently being developed, but we really haven't had them until now, so reporting and -- and ensuring that what I'm calling a CCHD or -- or a -- a case is -- is what someone else is comparing -- or calling a case, as well. And, again, this is not -- this challenge in particular, is not unique to CCHD screening. It's -- it's really something that we need across the

board in newborn screening, but understanding that there are limitations of this screen. We will not pick up all of these conditions, and we may not even pick up some of the conditions that are now on that, kind of, primary target list. Coarctations of the aorta, for example, are -- are missed quite often with pulse oximetry screening.

There's also some concern right now about the screening devices themselves. Pulse oximeters have typically been developed as monitoring devices and not as screening devices. So, there are some concerns that have been published more recently in the literature over the accuracy and precision of the currently available screening devices.

Because of our -- our challenges with getting data, we also, at this time, don't know, really, what the best practices are or the best algorithm, which is, I think, why many of us are -- are, kind of, just sticking with what we started with.

And we also often don't know if the algorithm is being followed correctly. In Minnesota, we're getting all of our CCHD data electronically, all of the raw pulse ox results, and we have built in the algorithm into the software, so you -- you get the preductal, the post-ductal, it applies our algorithm and gives you an outcome, and then you -- you -- you hit "Yes, I want to accept that outcome," or "No, I don't."

In -- in 0.6% of cases, they are still misinterpreting the algorithm, so they're actually getting the answer and saying, "Nope, I'm going to tick -- pick something else. I'm going to pick the wrong answer," even when we -- we have a pop-up that says, "Are you sure you want to pick the wrong answer?" So, it -- it -- it remains, kind of, a mystery as to why the algorithm doesn't -- isn't being followed.

Infants in the NICU -- These -- I think we're still not entirely sure how to handle these -- these infants and, you know, if they're being

monitored, do they also need to be screened? If they're already getting an echo, do they need to be screened? And there's quite a bit of disagreement still on how to handle these babies.

Certainly, out-of-hospital births -- The algorithm has the potential to take about 3- to 4 hours. If you're going to go through it all the way, or if you need to go through it all the way -- and -- and most midwives are not spending that much time with a visit, so how -- how best to incorporate the screen into their existing workflows --

And I think, really, where our biggest struggle has been is just knowing what our role and responsibility is with this screen. Is it our responsibility, at the program level, to provide this individual-level quality -- quality assurance? Should I be looking every day to see if the algorithm was misinterpreted and -- and trying to follow up on those children? Is our role more system-level quality -- quality assurance -- which is, you know, very different

than, I think, what we're -- we're typically used to in terms of follow-up, like I said, both in terms of blood spot and newborn hearing screening.

So, some program needs going forward: certainly, support for this data collection and analysis. Without this information, we're just not going to know how well we're doing and how we can do better. So, more data, of course, will allow for better evidence-based recommendations. And I think, ultimately, we need, kind of, a -- to step back and take a fresh perspective at CCHD screening. I think, when it was added, we either tried to fit it into the newborn hearing screening mold or the blood spot mold, and neither of those molds are the right fit. And so, we really have to think differently about what metrics and expectations we should place on programs in order to really analyze the effectiveness of this screen.

So, I -- I want to end, and I want to say that, without a doubt, CCHD screening has value.

We know it is picking up kids. We -- we've all heard stories of it picking up -- up kids. We just can't quantify that value yet. But overall mortality does seem to be going down for CCHDs if you look at death certificates, and -- and that's obviously what our ultimate goal was. But there -- the question remains, I think, for programs, really, what is our role, and how best can we approach this with that end goal in mind?

So, I'd like to thank the CCHD Technical Assistance Workgroup members, especially these ones listed here, who provided a lot of thoughts to me about what to include in this talk -- that is a fantastic group that I have the honor of co-chairing with Lisa Hom -- of course, the NewSTEPs staff, and -- and the Minnesota CCHD team. So, thank you.

(Applause)

DR. JOSEPH BOCCHINI: Thank you.

MS. ANNAMARIE SAARINEN: Good morning. Thank you, Amy and Careema. Thanks to the Committee for giving some time on the agenda to

do a quick update on CCHD screening. I think there might be an opportunity at one of the upcoming meetings to get a little closer to some of the data that Amy had mentioned.

And I will just say, before I start talking a little bit about the impact of what happened here in the United States and other places, that I -- I think, as an advocate -- and those of you who know, from years ago, my showing up at these meetings and doing what we saw parents do yesterday, that it was half about the emotion and half about the data. And in the absence of that, as my children say, we have the "pirates code." It's sort of, like, you know, guidelines, not really rules.

And until we figure that out, how to better enable state programs to get what they need and to allow it to not be a burden for the providers, we're going to continue to have discussions today that are exciting when you see a map, but when -- not so exciting when you say, "Do we really know exactly how many kids we're

picking up and when and how, and are we actually improving outcomes because of the earlier intervention?" And I think some of that data's becoming just newly available, and again, hope we'll hear more about that in an upcoming meeting, but I just wanted to say that, given the -- the relatively short time that's passed, I think there's been a remarkable amount of progress.

So, for those who don't know, about 8 years ago, I had my third child, little Eve, who looked perfectly healthy, and I had a blissful pregnancy, with no problems. I was a little bit of an older mom. I had my last two girls at around 40, and so I had had numerous -- I think about 4 -- level 2 ultrasounds, so I -- and live in a, you know, urban area, academic health center, access to great care kind of a thing, so. We thought everything was perfect, and she really looked perfect.

But it was a little bit of serendipity and good luck that allowed us to get a diagnosis

in time for Eve to get the care she needed. The rounding pediatrician had heard a murmur, and she was planning on still discharging us with the murmur, because they're quite common in babies, and when she found out there was an echo tech from the University of Minnesota Children's Hospital over at our hospital, our community hospital, that day, evaluating another baby with that cart that they drag around from one place to the other, she said, "You know what? Why don't we just take a look at Eve, so that you don't go home and, you know, worry for a week." And frankly, I wasn't worried. She's my third kid. If it doesn't bleed or doesn't look broken, we're all not too worried about it.

So, anyway, an hour later, there was a pediatric cardiologist standing in our doorway, telling us our daughter was in heart failure and she needed to be moved immediately to the NICU over at Children's. And I looked at the X-ray and saw that her organs were being pushed down into her stomach cavity because of the size of her

heart. And to think that we were just looking at that baby and going to pack her up in her car seat and go home was horrifying.

So, gratefully, she got the care and the surgery she needed: two surgeries, one for her Wolff-Parkinson-White syndrome to stop the SVT that was happening pretty much around the clock, and the other a very complicated surgery to repair her mitral valve. So, mitral valve disease prolapse is not on that list of even expanded conditions, but I do know for a fact that however rare that is, that that does show up as mildly cyanotic in any of the babies that it's popped up in since then.

So, here's the snapshot of the timeline that I've not updated since 2012, but I -- I wanted to show it, because it provides, sort of, that context of how fast things moved shortly after I started researching whether pulse oximetry was a valuable tool, as an advocate, and going back to our physicians in Minnesota and saying, "Are you interested in doing a pilot

project with the Minnesota Department of Health?" and that's when I met our fine Amy Gaviglio, way back in 2009.

And fortunately, she and Mark McCann were quite interested in actually doing a pilot to explore this. And at the time, there were a couple of other places that weren't really doing studies but were, kind of, looking at it, and one was Children's National here in Washington, D.C., under Dr. Gerard Martin, and the other was in Washington State. And those are the only -- other than a very small little project that had been done in Tennessee, that -- those were about the only things that had been happening in the United States to look at pulse oximetry.

But at the time, Dr. Rinaldo, who, as you know, served on this committee, I think, thought the timing might be right, even in the absence of any data from our pilot study at that point -- we had just started -- but the nomination was made, as you -- as you know, in January of 2010, to this committee, and it was brought forward into

evidence review, and things moved rather quickly from there.

Let me see, I'm going to show the slide of the -- Secretary Sebelius's letter back to Dr. Howell. Our process -- at -- at that time -- because this was, again, a new, kind of a different thing, the point-of-care screening. There was a -- a workgroup convened. I don't know if Dr. Puryear is still here today, but she -- she put a lot of work into assembling a -- a group to meet here in Washington, D.C., to work through, you know, kind of: What -- what remaining questions do we have? We've got this letter from the Secretary. How do we translate that into something actionable?

And fortunately, at the -- I -- I feel like, in my memory, it was the eleventh hour, but, like, 2 weeks before the meeting or something, we reached out to a physician in -- in the UK, Dr. Andy Ewer, who hadn't yet published but had done about a 2-year, very robust study in -- in the UK, well -- very well-designed study,

pulse oximetry screening, and then Anne Granelli, for whom the protocol, as mentioned, was, sort of, named the aka Kemper and Granelli protocol. And both of them, one from Sweden and one from UK, flew over on their own dime to participate in that meeting at the invitation, and -- and their insights were, as I recall, very, very helpful. They answered a lot of questions that, I think, maybe we wouldn't have been able to otherwise answer, even with all the experts in the room.

So, then, I think, you know, attention being paid to this idea of a new point-of-care test to detect something that was, you know, the most common and deadly birth defect was -- was starting to spread around the world once the U.S. sort of -- even without our full implementation, the -- the news had spread that we were -- had added it to our panel. So, given the high occurrence rate of congenital heart disease in other parts of the world, I think for the countries that had an -- an intervention strategy, or kids could get access to care, there

was suddenly great interest in whether or not this was something that they could implement in their countries. So, there were a number of countries, at that time, that had started just, sort of, looking at it, maybe small pilots, but I think accelerating things because of what had happened here in the U.S.

There were a few faces you might recognize in this photo that were presenting on this subject matter at international conferences and symposiums -- the International Society of Newborn Screening, the International Conference of Birth Defects in the Developing World, to name a couple that happened that same year -- and so in -- Since I'm a visual learner, I always like putting together, sort of, what I thought the evolution of things was.

So, we had this early evidence coming out of Europe, these four, in particular, very large population health studies that were part of the evidence review process in the U.S., and -- sorry -- that then, you know, helped advise, I think,

our decision in the United States. And then, as we started rolling out, as you see -- I'm going to show the -- the map changing over the years and our -- our six implementation grants, that's when the, sort of, global interest started picking up, even outside of Europe, where we've seen Asia, some projects in South America, and a few projects, even, in -- in India and in the Middle East.

So, in 2012, there were a little over a dozen countries that were actually starting to pilot CCHD screening. Around 2012 and '13, a physician and his team out of the University of Fudan Children's Hospital in Shanghai put together a study which would become the largest-ever population health study of newborn pulse oximetry screening ever published.

This ended up being published in April of 2014. And their protocol is a little bit different, because they were using murmur as an additional indicator, so their data is a little bit different than what we'd seen in other ones,

but because of the large size and the multiple centers that it involved, this study, as it -- when it got published, gained a lot of international attention and traction.

And then, Andy Ewer's study, as it was published, was also getting a lot of attention around the world, because they were screening quite early in the UK, about 8 hours of age, and, largely, just because that's when new moms are discharged in the UK. So, this press release that looks like -- dated May 2014 was when the -- the UK -- the NHS decided to forge ahead, but I can tell you, having just seen Dr. Ewer, that they are still not yet fully implemented in the UK. They're still evaluating their data, but they're getting very close to implementing. And there's a -- actually, a -- a photo of Andy Ewer presenting some of Lori Garg's data, out of New Jersey, at an international forum on -- on CCHD screening just very recently.

So, again, as an -- as an advocate, I -- I've been very interested and excited to see how

this rolls out in other parts of the world, so it can help save lives and improve young lives through earlier detection. And through the process of -- of, kind of, looking at data from elsewhere and collaborating where it's been possible, I, sort of, put together what -- along with Andy and Girard and other people that are kind of on the front lines of this still -- what are the things that other countries have had to look at when they're developing their programs.

So, one is looking at your -- the existing burden of disease. In some places, that's not altogether obvious. There's still a lot of information missing about how many children are being diagnosed with CCHD, how many die from congenital heart defects, and I -- I think the idea that, perhaps, a simple screening that might not be an economic burden to a region, that can actually help them improve their record keeping and their birth defects statistics was -- was something they -- they -- they felt might be helpful in terms of their overall programming.

As folic acid implementations have happened in some of the lower-resource countries, neural tube defects and other birth defects have gone down, but congenital heart disease then rises on the scale of, you know, where it is relative to other things that are taking the lives of children. So, as a public health priority, I think congenital heart disease is getting more attention now than it was not really very long ago.

And then, in other countries, too, they'll be looking at, say, what their rates of prenatal screening are, what those rates of prenatal diagnosis are, and much like in the United States -- I can speak for China and the Philippines, anyway -- to say, it's kind of similar. The rates of detection from ultrasound are quite high in Beijing, Shanghai, Manila, places where there's a lot of it done, and the techs are pretty good and they see a lot of women. When you go out into outlying areas, the detection rates fall, and there's your window of

diagnostic opportunity.

That reminds me, while I'm on it, to think about the Jimmy Kimmel thing. That, actually, is an interesting opportunity, from an advocacy standpoint -- right? -- because even though that baby wasn't detected with pulse oximetry screening -- his child was, I think, around 3 or 4 hours of age, had clinical symptoms, but given, you know, high profile, Cedar-Sinai, wealthy family, where they are, those -- those are the cases that'll -- I think we hear a lot about, like, "Oh, those -- they always get detected." You know, the mom goes for lots of ultrasounds, she's at a great place, but this is a case where, you know, his son had a very, very serious congenital heart defect, and it went undetected before birth and, fortunately, was detected clinically.

So, here -- then the -- then the other ones -- You know, it might sound crazy to say capacity for pulse ox supplies and staff, since we all think pulse oximeters are such a standard

thing. Many of the places that I've been around -- and the data will show -- just simply don't even have pulse oximeters. So, that's a consideration: How do we do this screening if we don't even have the basic equipment to even do it? And then treatment infrastructure: Are we going to be able to screen for something that if we find critical find defects, we cannot refer those babies anywhere to get treatment?

So, these are just some basic surveys that we've seen out there on the landscape, looking at, you know, echo -- the same things we looked at here when we were implementing screening. Did they have the ability to stabilize a baby if they are noted as having not just hypoxemia but suspected heart disease? What's their prostaglandin availability? What's their pediatric echo capacity? Do they have someone that they can have look at that heart, either remotely or for -- per referral? And then medical transport.

And I think these are just generally -- I

-- I would say these goals are pretty well aligned with our goals in the United States, but the things you'll hear: How do we get access to quality equipment that's actually going to work on newborns? Do the screening protocols that the United States used work in our setting? How long do we have the babies in -- in our birth setting? Do they get discharged 4 hours after the baby's born, or do they stay for 3 or 4 days?

And then training and education materials, just being able to roll out a program that can reduce the false positive and false negative rate to an acceptable level in places where referrals and treatment may be difficult and, maybe, fall into the hands of the parents to actually manage, instead of in our country, we're used to being able to have that clinically managed and use medical transport services. So, they're just some babies that I was with in the last week, in -- in China.

And then, getting to the, sort of, new, extended value of pulse oximetry screening that

Amy touched on in the paper from the AP Workgroup about a year ago -- I also pointed out these, sort of, secondary conditions that we weren't paying a whole lot of attention to back when CCHD screening was implemented. Now the data's showing, particularly in other countries, that these have become really important. Oftentimes, we'll see for every failed screen that -- that's a congenital heart defect, we have at least one that's a sepsis or a pneumonia. This comes directly from one of the recently published studies in Asia.

And so, the global health community has really been paying attention to pulse oximetry, not so much as a screening tool for CCHD, although non-communicable diseases have risen on the global health agenda, but they are interested in it from a -- from the perspective of how this can impact low-hanging fruit, like pneumonia, which is the number one killer of children under 5 years old, and an exponential percentage of that -- those stats are in infancy.

And this is the, sort of, chronically updated map by Children's National. There's a group of five or six of us that contribute to this on a, sort of, as-it-happens basis, or at least on quarterly updates.

So, it looks very different than it did not too long ago. You can see where you've got actual, formal mandates or recommendations from the government where, basically, universal screening is happening. There are countries that don't have an actual, formal policy or mandate, but they are over 90% screening. And then the yellow is -- You see a lot of it. Some places on this map that are yellow have only done a few smaller pilot studies, but some are doing very large population health studies and are very close to adding CCHD as a standard screening in their countries, with China being one of them.

And I think there was a meeting in March, in China, that the China CDC and the Ministry of Health participated in, where data from four different projects was presented, and they have,

sort of, enthusiastically endorsed moving forward with pulse oximetry screening for the country and are using a model quite similar to the one we used in the United States, in that they're assembling a workgroup or a commission to work on the remaining implementation hurdles, figuring out what their formal protocol will be, and how they will implement over the coming 24 months to 36 months in that country.

So, we've gone to -- to 90 -- 10 countries that now have 90% or more of newborns screened, and 48 countries, up from a -- just a dozen a few years ago, that are doing very large pilots or government-sponsored work. Here's just a few more pictures from China.

By the way, I am so, so privileged to know the doctors, the nurses, and the public health folks in some of these other countries. It has been one of the greatest, greatest privileges of my life to be able to work with these people and learn with them, and happy Nurse's Day, International Nurse's Day, by the way. I'm

grateful for all they do for babies every single day.

And I just wanted to land -- I don't want to -- I don't want to land on a downer, but this is one of the projects sites that we've done some collaborative work, and -- and it's Beichuan, in the Sichuan Province, China, and today is the anniversary of the devastating earthquake that claimed almost 80,000 lives, and our -- The project investigator we work with at this hospital in Beichuan lost her son that day. The entire mountain collapsed on two schools in this town. And so, I was standing right in -- where you see this rubble 3 days ago, I guess, on Wednesday -- I've lost track of time this week, I'm afraid.

But it's profoundly moving, and I will tell you that the people in this area have such respect for every baby's life, and they want so badly to make sure there are no preventable deaths. And newborn screening's an important part of that for -- for the public health community in

this province. So, I just wanted to share that and honor the many lives that were lost and the people that we have had the opportunity to work with there.

And I don't know if I'm able to click on this thing, because I can't see the button down there -- Oh, wait. Okay, I'm going to do it. Watch. Pandas!

(Laughter)

MS. ANNAMARIE SAARINEN: Yay! I'll end with that. Thank you so much for letting me share that update.

(Applause)

DR. JOSEPH BOCCHINI: So, Annamarie, if you would stay at the microphone, and if we'd bring Amy back, and Careema, and let's open this up for discussion from -- from the Committee and raise any questions or comments.

But, certainly, this is a remarkable story, and it's -- it's pretty remarkable, from your first visit to this committee, to the Secretary's decision in 2011, to see where we

are, both in the United States and internationally, and then all of the work that still needs to be done to understand where we are and the effect of what we're doing, and yet, we -- we know we're having significant impact. So, this is a pretty remarkable story, so thank you, all.

Questions? All right. Cathy?

MS. CATHERINE WICKLUND: Cathy Wicklund. Thanks, you guys, that was a great presentation. And my question is, do you guys have any concrete ideas about how to collect the data to be able to actually have more evidence, you know, that we are, you know, preventing deaths or -- So, do you have any, like, "If you had funding ..." Do you have any specific, concrete ideas or solutions?

MS. AMY GAVIGLIO: Yeah, I don't know if I have a concrete idea, but funding is certainly part of it. It -- it seems to be a resource limitation. It -- it's very -- It takes a lot of time to get data from someone else, especially someone else who sees reporting of data as, kind

of, a -- a lower level -- and -- and, indeed, it is. Clinical care comes first. So, I think, you know, just, funding and resources and -- and probably a better infrastructure and support for programs.

I think, when EHDI was added, our -- our newborn hearing screening, there -- there was already a -- a big support system and -- and an infrastructure that came along with -- with the inclusion of it on the RUSP. And so, it was a lot easier, I think, for states to -- to kind of just find themselves in that infrastructure.

But with CCHD, I -- I think there wasn't that. We, kind of, were just sent into the wind and kind of try to figure it out. So, I think -- Yeah, I -- I would say, having a more robust, like, infrastructure, like EHDI has, as well as an increase in resources and -- and funding. EHDI also has a couple grants associated with it from the CDC and HRSA, which has helped a lot in terms of funding for data collection and follow-up.

MS. CATHERINE WICKLUND: Can -- Can I

ask, like, another question?

(No audible response)

MS. CATHERINE WICKLUND: Oh, no, I totally forgot what I was going to ask.

(Laughter)

MS. CATHERINE WICKLUND: Darn it. Oh, I know. So, in thinking about to -- being able to do some of these point-of-care kind of tests through newborn screening versus, like, professional guidelines that might come from a professional society, saying, you know, "This is what we recommend that every baby get at a certain time" -- Do you guys feel like this is, like, the way to go? Like, do you feel like the benefits of going through a state department, health department, and the RUSP outweigh some of the cons, maybe, of trying to organize all of this or, you know, the -- the idea of, like, what is the role of the public health department? I mean, do you have some insight into that now that you've been doing this?

MS. AMY GAVIGLIO: Thanks for the easy

questions, Cathy.

(Laughter)

MS. AMY GAVIGLIO: I -- I think it's a fair -- it's a fair question. I think it depends on -- on a little bit about what the goals are. It -- it appears that having it as standard of care -- and certainly, there are states that have taken that approach, where the health department really is not involved, and they've taken that, kind of, more medical approach. It -- it seems to be making a difference there, as well, in terms of if you look at mortality rates.

So, then, the question becomes, is -- is a program role to try to get more data to improve the recommendations in terms of what the algorithm should look like, who should be screened, when they should be screened. So, I don't know if that's really answering your question, but I -- I think, potentially, there's a role for both -- both kind of approaches, and I'm not sure that one necessarily is better than the other at this point. But, yeah.

MS. ANNAMARIE SAARINEN: Well, do you want the advocacy answer?

(No audible response)

MS. ANNAMARIE SAARINEN: Okay. So, the advocacy answer is, there's a lot of conversation around this, and I was always about, like, don't legislate medicine, right? But I think, in reality, had this followed the road of -- of clinical practice and going through just getting the relevant health bodies to endorse, I think adoption would have been considerably slower. And I do think that the states that have yet to -- that, you know, have formal, either, policy language or -- or a law are doing it as well as they're doing it because it came from the RUSP. And I think that accelerated everything, and maybe -- I think it would have come around eventually, but I think it would have taken much, much longer.

And also, there was a bill introduced last session that was specifically a CCH funding bill for the public health component of CCHD, and

it was modeled quite similarly to the EHDI appropriation that was introduced a time when a bill wasn't going to go anywhere, sadly, because of where we were, you know, election cycle and, you know, new Congress and all that. So, I don't -- I can't say what'll happen with that, but there is one -- That got a bill number and exists in the world, so that's potentially, something that could -- could resurface.

And I think, as something that was a largely almost exclusively unfunded requirement in most states, it's -- it -- it is just dang near impossible to do the kind of data collection that's required to show what we'd all like to see.

DR. JOSEPH BOCCHINI: Beth, and then Dieter.

DR. BETH TARINI: So, I just want to thank the presenters. I think that this is an excellent example of the impact that the Committee can have, and while I think we can celebrate the progress that has been made, I want

to bring us back to focusing on what we need to do to move forward.

So, it seems -- I've heard from all three presenters the importance of data, so I would argue, we in the United States are not actually far ahead, if not even behind, some of the international countries who don't know who's affected, don't know who we've actually identified. I -- I mean, I literally can't go and -- and pull this data out anywhere, yet.

And -- and so, that's a problem. And it doesn't seem like we've made tremendous progress on this front -- although it may be that I'm just not seeing deeper into the weeds -- since Dr. Sontag presented on this in August of 2015.

So, my question is, how can this committee help APHL and others actually get this data? Is this a, the states can't do it, the states can't input it, the hospitals can't do it? I mean, at what point can we the Committee actually now have an effect? Like we were discussing yesterday, what can be -- with our

discussion on medical foods, what can be our leverage for this -- for this condition, going forward, now that it's actually been legislated and screened in all these states?

MS. CAREEMA YUSUF: That's a great question, Beth. I think the struggle that I see is that each state has mandated it differently. So, some have been asked, please go ahead and do the screening, but then there's no legislation or guidance or resources around data collection. And as Amy described, it's really difficult because of all these pieces that are there. So, I don't know a really good answer for that.

I will say that at NewSTEPs, we do have a data repository. We do have the capacity to collect data. We are working on those case definitions to collect that individual data. So, I mean, we're there, we're available, but it's now just helping the -- at the state level.

DR. BETH TARINI: This is just a follow-up, but I don't know that the states legislate any data to be collected on any condition.

FEMALE SPEAKER: Some do.

(Off-mic speaking)

MS. CAREEMA YUSUF: Some do.

DR. BETH TARINI: On certain conditions?

FEMALE SPEAKER: On certain --

FEMALE SPEAKER: Yeah.

FEMALE SPEAKER: On CCHD specifically.

FEMALE SPEAKER: Yeah, so in Minnesota --

DR. BETH TARINI: Well, we don't say you have to collect MCAD data.

FEMALE SPEAKER: Correct, but --

DR. BETH TARINI: Which, I'm saying --

FEMALE SPEAKER: Right.

DR. BETH TARINI: -- this unearths a larger problem, then. If this is the lesion of -- that there's no legislation -- I'm saying this example -- to move any data collection, then we have, perhaps, a bigger problem.

MS. AMY GAVIGLIO: I think some -- It -- it -- it may be worded a bit differently, but in terms of newborn screening blood spot statutes, there's usually some sort of provision to

maintain a registry, so maybe in that way. It's not specifically saying: You must collect data on these conditions.

In Minnesota, we have two separate statutes for newborn hearing screening and -- and CCHD, where it does mandate the reporting component, more -- not so much for the states to a repository but from the birth facilities to us. So, that does exist sometimes.

MS. ANNAMARIE SAARINEN: I don't -- Is there anyone from the Michigan program here at all?

(No audible response)

MS. ANNAMARIE SAARINEN: Nobody? I was wondering if anybody from Michigan was here because I -- I think --

(Off-mic speaking)

MS. ANNAMARIE SAARINEN: No -- Is anybody from Michigan program here at all?

(No audible response)

MS. ANNAMARIE SAARINEN: I think, Beth, maybe we could circle back, you know, outside of

the -- the -- the Committee with some of the work -- and Amy's quite familiar with some of the work that's been done in Michigan.

DR. BETH TARINI: They use the -- Are you talking about the HL7, and they're building the database? When I was there, they were doing this in -- in Michigan.

MS. ANNAMARIE SAARINEN: Yeah, partly, but -- Right. There's --

(Off-mic speaking)

MS. ANNAMARIE SAARINEN: They -- they tried to establish a system that would integrate with what they already had, but --

DR. BETH TARINI: An immunization registry.

MS. ANNAMARIE SAARINEN: Yeah, but I actually think what -- and not to take anything away from how -- how Minnesota did this, as well, but a lot of it is on the front end, as -- as part of rollout. It's the provider-side education that's the, I -- I think, one of the hardest parts, because you can mandate, you can say,

like: This is -- this is a new screening. This is either what's optimal or what's required of you. But if the hospitals don't get it from the very beginning, like -- Because they're kind of like -- They're doing the -- In their minds, they're like, "We're screening. What do you want from us?" Right? And so, if you don't give them some sort of a incentive to say, "This is why you need to do it, and here's the simplest possible way that we've figured out to have you do it," that's going to -- You can never come back, 2 years later, and fix that. Well, I shouldn't say "never," but the whole change --

DR. BETH TARINI: You'll be doing --

MS. ANNAMARIE SAARINEN: -- management piece.

DR. BETH TARINI: -- more work on the backend.

MS. ANNAMARIE SAARINEN: Yeah.

DR. BETH TARINI: Yep. I agree.

DR. JOSEPH BOCCHINI: Dr. Matern?

DR. DIETRICH MATERN: Yeah, I have a

question for Amy, as well. Given that in Minnesota, we have a law that requires the birth facilities to return the results to the state, how is it actually working out? And I know that the state sends, I think, twice a year, a report back to the birth facilities about how they're doing with blood spot collection, timeliness, et cetera. I don't remember if any data are included there regarding pulse oximetry results and returning of results for CCHD and for hearing loss, as well.

MS. AMY GAVIGLIO: No, that's a -- a good question. So, in terms of how it's going, I would say it's going slowly, and part of that is the approach that we decided to take, which is to obtain these results electronically, and directly from the devices, which we felt was important based on our experience with the newborn hearing screening and the high level of missing and inaccurate results reported to us.

So, just, I think, this week, we finally got our last hospital up and running. It has

taken us over 2 years to get our 91 birth hospitals connected. So, I would say, that's basically how -- how it's going, though, that it is working beautifully in terms of, I can see exactly what time and day and what the saturation values are. I can look and see that the algorithm is being interpreted correctly. So, we do have, at this point, a pretty nice, robust data source. The problem is that I've spent so much time trying to get the data, there hasn't been time to look at the data.

In terms of -- And your second piece was --? Sorry.

DR. DIETRICH MATERN: It was about the reports you send out twice a year.

MS. AMY GAVIGLIO: Oh, yes, yes. So, the way that the system works that we're using, they actually -- the reports are built in, so they can log in and pull up reports themselves whenever they want, and so that is how they're getting their feedback. If -- if we identify trends -- for example, we see a -- a -- a, you know, large

chunk of babies where we did not get results, or we see that they're screening, you know, four or five, six, seven times, we'll follow up, kind of, ad hoc when we're noticing trends outside of those reports.

MS. ANNAMARIE SAARINEN: Actually, I think, Dieter, that's -- that's a really important one, Amy was going with the roles of public health. That's actually a really important role, as -- because we can -- if we can see things across 91 hospitals, and you've got a false positive rate, for -- for whatever reason, that's 10% higher at 1 hospital than is the norm, then the public health -- I mean, that -- that's a trigger -- right? -- for them to go and say, like, "Okay, what's going on here? Are you maybe not using the right equipment or the right types of probes? Maybe you're not applying the sensors properly." There's a way to go in and, kind of, intervene and see what might be happening, you know, at that place, and without the data, there's -- there's no way to, kind of -- to, kind

of, address those things.

DR. DIETRICH MATERN: One more comment: I think, in these twice-yearly reports, you actually provide information about how your particular hospital is doing compared to all the other ones. So, it, kind of, allows the hospitals to see how it is going, and also, kind of, maybe, makes them be more concerned about not being number one.

MS. AMY GAVIGLIO: No, and -- and that's a -- a great point. I think now that we actually have everyone reporting, we will be looking at adding some sort of addition to our -- our quality assurance reports that -- that does provide that comparison, and we just haven't been able to do it previously because we didn't have the entire state reporting. But, absolutely, moving forward, that makes a lot of sense.

DR. DIETRICH MATERN: One more comment is about cost. Sorry. It seems like, in Minnesota, we -- you guys figured it out pretty well, right?

MS. AMY GAVIGLIO: Well, I -- I like to

think so.

DR. DIETRICH MATERN: I mean, it sounds pretty good. I mean, we have a -- we have a law or two that make the hospital -- put some onus on the hospitals to actually return data to you. You get the information now electronically, so I hope you can go into the mode of actually reviewing it. You might be able to add it to the report, so that the hospitals know where they are. I think you should publish that so everyone else know how it's going, but please include the cost incurred by MDH -- the Minnesota Department of Health -- and what the hospitals had to do, to do all this. Because, again, it is something that there's a law, and there's no money coming along with it, and we're spending a lot of effort on both --

MS. AMY GAVIGLIO: Yep.

DR. DIETRICH MATERN: -- sides, public health and the hospitals, to actually provide that information, provide that care.

MS. AMY GAVIGLIO: That's absolutely a fantastic point. We're actually working with the

state of Michigan to do a cost analysis of how long and how much it has cost to do the type of reporting we're doing, which is the individual-level reporting. So, we're absolutely looking at that, and I think that's a great point, that that needs to be reported and published.

DR. JOSEPH BOCCHINI: All right. Carol Greene?

DR. CAROL GREENE: Thank you, everybody, again, for a terrific update. I'm curious about, in the follow-up, in the example given, when the algorithm is not followed and you follow up with them, in what way is the algorithm not followed? Is it, for example, that they know the baby had pneumonia, and they have an echo, and the baby doesn't have a heart defect?

So, I'm curious about how you -- What happens when you follow up? I'm wondering how you get follow-up to know what's the false positive rate? If you're getting the raw data, how do you find out, later on, whether the baby had a heart defect or not? How do you find out about the

false negatives? How are you --

Because I think there are some complex issues, that sometimes people were careful to say, we're not -- I mean, clearly, in other countries, this is making a huge difference, and in some parts of the United States, but you were very careful, sometimes, to say that the death rate is going down, but we're not sure if it's the screening, and sometimes saying, we know the screening is successful because the death rate's going down. So, I'm just curious to know how we're actually figuring that out.

MS. AMY GAVIGLIO: Okay. There were a lot of questions in there. I'll try to address all of them. In terms of misinterpretation of the algorithm, what -- it -- it's not typically the situation you mentioned, where they have, you know, known pneumonia or sepsis, and they're planning to do something, anyways. In -- in our opinion, that's a -- a viable option, and that person is probably no longer, you know, quote/unquote, eligible for screening.

And typically, what it is, is that the pre- and post-ductal saturations are, kind of, over 3% difference, so that would be considered a rescreen, which needs to happen about an hour later, and they put it as a pass and are done screening. So, typically, it's that situation.

Occasionally, I've seen where it's actually a fail and they've put it as a pass, so it -- it's more of that. In those cases, we will follow up and just try to get a little bit more information in terms of why they might have done that.

In terms of follow-up, in terms of false positives -- So, I can only speak to how we do it in our state, which, as we mentioned, was likely to be different in all the other 49 states. When we have a -- Each week, we run a report, and we actually have a public health nurse who is part-time with us and part-time with birth defects, and so she will follow-up on any of the fails. We actually will report failed cases to birth defects. Right now -- So, we're serving, kind of,

as a case finding mechanism for them, which allows us -- them to go in and abstract. We have an active birth defects registry, so they'll go in and abstract and get us the information on what was the final outcome in terms of whether it was a CCHD or something else.

For false negatives -- again, that's where that link to birth defects is helpful. So, we ask -- We'll ask them to report all of the cases and then do a match, and look to see who we had in terms of pick-ups and who we did not have. And so, I -- I know, just last week, I had a report of a -- a missed tetralogy of Fallot from birth defects. So, we'll be looking at that, try to figure that out. Did that answer all of --

DR. CAROL GREENE: It was an excellent answer. It also points out the importance of looking at different states, because most --

MS. AMY GAVIGLIO: Yeah.

DR. CAROL GREENE: -- I mean, very -- I don't know what percentage of birth defects registries are active --

MS. AMY GAVIGLIO: Yeah, no --

DR. CAROL GREENE: -- not all, and I'm pretty sure that most programs don't have a nurse shared -- They don't have nurses, much less shared with birth defects.

MS. AMY GAVIGLIO: Yeah. No, fair point.

DR. JOSEPH BOCCHINI: Bob Ostrander?

DR. ROBERT OSTRANDER: Bob Ostrander from the American Academy of Family Physicians. I started coming to these meetings right around the beginning of this whole process, and I'd like to, sort of, ask some questions, both of the presenters and throw this out to the Committee members, some -- a more 30,000-foot view of this.

I remember, when we started -- excuse me -- some of our -- some of the dilemma was, was whether -- Did this really fall into the category of heritable diseases? I mean, everything does, I guess. But this isn't typical of much of what we've done, because I think the vast majority of this disease is somatic mutation or sporadic, and it's probably not heritable through the germ cell

lines.

So, as I'm looking at what appears to be one of our most impactful actions, it strikes me that it's partially outside our purview. Again, it was one of the most impactful things that this committee has done, and I think it needs, one way or the other, to inform our future actions.

And in -- in addition to that, I think the secondary benefit to the pneumonias and things is something we have to think about as we are deciding what conditions to recommend to the RUSP. If other conditions like this come up or if others note, as I did, that this is a really important condition that's congenital but not primarily heritable, I wonder if we can, you know, get our condition on the RUSP through the Secretary's Advisory Committee and -- and have the same terrific impact we've had with this.

I think it's also worth us taking into consideration the other reasons that this was rapidly adopted by so many states and was so impactful, and it strikes me that part of that

is, is that it's something that people like the non-scientists can wrap their heads around. I mean, every legislator and everybody in the public knows somebody who is born with a, quote, hole in their heart, close quote, and I think when we pick -- when we -- when we promote something that's accessible to people intellectually, we have more impact. And the lesson that I would suggest this may bring to us is, how do we make some of our more obscure things more intellectually accessible? And I think, honestly, this group does a terrific job, and the -- and the -- the folks that are out there in the field working on it do a terrific job, but that -- those are the lessons that I see coming from this. And I'd be especially interested in people's comments on other conditions that might be congenital and impactful but not heritable.

DR. JOSEPH BOCCHINI: So, I think that was a really -- I -- I think you summarized the discussions that we had related to critical

congenital heart disease and being congenital but not always heritable, and -- and I think -- As part of that discussion, I think it was the -- the -- the significance of the -- of the specific defects and the potential role that the Committee could play in addressing those by making a recommendation for something that was -- was a significant congenital disorder. That played a significant role, I think, in -- in the decision-making process.

And I don't know if other Committee members at the time want to --

DR. ROBERT OSTRANDER: I -- My question is -- is, should that be a one-time exception because it was so important, or should we -- should we be looking for opportunities to do things that are equally impactful?

DR. JOSEPH BOCCHINI: Yeah, I certainly believe that we should, and -- and -- and so, I think if -- if other things come along, with a similar issue being raised, that there's no -- no reason why we would not. I -- I think we would

look at that.

And then, to go back to the other issue that was raised with this, the determination of whether this committee would have a -- a -- a -- a more significant impact, rather than have something be more of a professional society set of recommendations for what would become standard of care, is also something that is -- was an overarching issue related to this decision, as well.

Oh, Beth, you had -- Beth Tarini?

DR. BETH TARINI: Beth -- Mm-hmm. Beth Tarini. I -- Are there other conditions -- and I'm looking at Dieter -- that are de novo, and so are not truly heritable in that sense? Other conditions that --

(Off-mic speaking)

DR. BETH TARINI: So, I -- I guess -- Yeah.

MS. CATHERINE WICKLUND: So, can I just make a comment? The -- there's genetic predisposition to heart defects. So, I think we

just need to be clear that, like, it depends on what you're trying to define as being heritable or not. If you're talking about single-, you know, gene Mendelian inheritance, that's one thing, but there are heritable components to heart defects. We give recurrences for them, and there's other syndromes that are associated with them. So, I just want to be --

DR. BETH TARINI: So, it's not -- It's not an exception.

MS. CATHERINE WICKLUND: It's -- it's --

DR. BETH TARINI: In your mind.

MS. CATHERINE WICKLUND: -- not, no. And, I mean, in that sense, I look at it as, there are heritable contributions; there are multiple factors that play a role. You have predisposition, and then environmental factors on top of that.

DR. JOSEPH BOCCHINI: Yeah, and I can't remember, I think there was something, like, 30- or 40% would be related to specific heritable --

MS. CATHERINE WICKLUND: It depends on

the specific heart defect itself --

DR. JOSEPH BOCCHINI: On the defect. Right.

MS. CATHERINE WICKLUND: -- as to recurrence risk --

DR. JOSEPH BOCCHINI: Right.

MS. CATHERINE WICKLUND: -- associated syndromes, that kind of stuff.

DR. JOSEPH BOCCHINI: Right. We have Melissa, and then Jeff.

DR. MELISSA PARISI: I just want to make a comment about heritability of congenital heart defects to follow up. You know, as we are doing more research to try to understand the underlying molecular basis of congenital heart disease, we are finding that a fair number probably are due to de novo genetic changes. The exact number's not been determined, but there's an active cohort of over 10,000 newborns that have been sequenced with -- I shouldn't say newborns, but newborns and children with congenital heart defects who are being sequenced as part of the Pediatric

Cardiac Genomics Consortium, funded by NHLBI and now partially by NICHD, to really try to uncover what the genetic contributions are to congenital heart disease.

DR. JOSEPH BOCCHINI: Jeff?

Dr. MELISSA PARISI: I know, also -- just to make one final point that Kellie's been whispering over to me that, you know, congenital hypothyroidism is another example of a condition that's on the newborn screening panel that, to our knowledge, does not have a genetic basis, although we don't really know if there are, you know, potentially, de novo genetic changes that might be contributing to congenital hypothyroidism. So, it's not unique in that regard.

DR. JOSEPH BOCCHINI: Jeff?

DR. JEFFREY BROSCO: In -- in thinking about the question whether it was worth going through this to have it part of the RUSP or not --

(Audio interference)

DR. JEFFREY BROSCO: -- publishing data a couple of years ago showing that you can reduce health disparities by making something part of the RUSP, because you make it universal, and it gets to every baby, and it's not dependent on where you are, the quality of care where you live, and so on. So, I think there's a strong argument to be made for putting things on the RUSP when it's appropriate.

DR. BETH TARINI: Say -- say it again? When it's a what? I didn't hear it all.

DR. JEFFREY BROSCO: Putting things in the RUSP when it's appropriate, because I think it reduces health disparities by making -- improving universal access.

DR. BETH TARINI: I mean, I think that the most clear example that -- that I -- that I think is, sort of, being touched on here is an infectious screen. Right? Is HIV screening -- If someone comes forth with HIV screening to the RUSP, what do we do with it? I mean, I'm not trying to make problems that aren't there, but

that, to me, is just into the other realm, because by your standard, if -- if -- if it's about disparities, and it's -- it's infectious and it's not genetically inherited, then what do we do? But I think -- We don't have to debate this now, but I agree with you on the disparities, I just don't know that that's our first charge.

MS. ANNAMARIE SAARINEN: Dr. Bocchini? I just wanted to recall something that Dr. Howell said back in the day, because we had this -- a little bit of this discussion at at least one of the meetings when -- either when this was under review or early acceptance. And I -- I remember him stating, very clearly, that the work of this committee isn't to limit itself to something that's defined as heritable. The work of this committee is to help identify things that would otherwise go unnoticed in a newborn, which is why we call it newborn screening.

And I couldn't agree more with Dr. Brosco's comments about disparities and the

benefit of the universal nature of what this program does, what the state programs do. And as with the other screenings, I think CCHD is exactly the right kind of thing to help try to level the playing field, because the places that need it most are, sort of, the ones that are the slowest to adopt it. If you look at those two states that are left on -- on the map a little bit, those kids have a much lower prenatal detection rate than the kids in Massachusetts --

DR. BETH TARINI: Oh, I agree.

MS. ANNAMARIE SAARINEN: -- and those kids, if they come to the emergency room and collapse, are an airlift from Seattle or Denver. That's their nearest heart center.

DR. BETH TARINI: No, I -- I guess --

MS. ANNAMARIE SAARINEN: So.

DR. BETH TARINI: I'm not saying the disparities --

MS. ANNAMARIE SAARINEN: No, no, I know you --

DR. BETH TARINI: -- shouldn't be used, I

just think, as a first screen -- no pun intended -- disparities is not the -- is not how we have historically decided --

MS. ANNAMARIE SAARINEN: Agreed.

DR. BETH TARINI: -- whether or not we are going to consider a screening. But it certainly does have that unintended, if you will, consequence.

MS. ANNAMARIE SAARINEN: I -- I think that it was the heritable component that I wanted to address more than that. I just was trying to, like, reiterate that I -- I truly believe that the work that newborn screen -- that the RUSP does, it does help reduce disparities for those who wouldn't otherwise have access.

And then, also, for Cathy's comment, my -- my son, who's 21, will need his mitral valve replaced within 5 years or so. So, he's on the Marfan spectrum. So, there's clearly a genetic link between -- and he was diagnosed after Eve was diagnosed, but there's a genetic component to too many of the CHD cases.

DR. MEI BAKER: This is Mei. Can I (audio interference)?

DR. JOSEPH BOCCHINI: Yes, Mei, please.

DR. MEI BAKER: Okay. And I just want to remind everybody, the current panel congenital hypothyroidism is not heritable. Right? And also, I think not a discussion about the congenital CMV, so I think this -- I think, right now, I feel the term is more used -- congenital has been more, kind of, cover the things we -- we are thinking or we already done.

DR. JOSEPH BOCCHINI: Thank you. Jeff?

DR. JEFFREY BROSCO: Just want to make a comment, because Beth said the word "historical," so.

(Laughter)

DR. JEFFREY BROSCO: Newborn screening absolutely, positively started as a disparities argument, and that is, some kids were getting screened for PKU and some weren't. And so, the whole idea was, we wanted to try to standardize it across. And it wasn't really thought of as a

genetic and heritable disorder until the '70s and '80s. Even though people understood it to be a genetic thing, that wasn't a major part of it. It was, first and foremost, about disparities.

DR. JOSEPH BOCCHINI: All right. Well, thank you for a great presentation. It's good to -- Oh, one more. I'm sorry, go ahead.

(Off-mic speaking)

DR. TERESE FINITZO: Terese Finitzo, and I've had the opportunity to work with multiple states on point-of-care reporting. And I want to speak to -- to Beth and to several people's comments about, what -- what was the success and why the success. And I think that Amy's playing down her reasons for success.

In -- in our experience, the stronger the Department of Health is able -- and I really want to underline that word -- able to be in promulgating the rules and the requirements, the more successful the program can be. And that's not to say -- again, that word, "able," is so important, because some departments will say to

me, "We can't tell hospitals how they must do this." But if they can, if they can give them strong guidelines, they're going to be successful.

And the other word is, Amy used the word "slow" implementation. Ninety-one hospitals is not slow. She's done -- Minnesota's done a remarkable job, and I -- I think that that's the biggest impact on success, is to give the state departments of health the capability -- whether it's financial or legislative -- to be able to stipulate how they want the data.

And then, the final point is, make it easy on the hospitals. No one's having to go into a third or a fourth system to report this data; it's being done as seamlessly as it can right now. It can get better, we all know that, but make it easy. So, thank you.

DR. JOSEPH BOCCHINI: Thank you. All right. Again, thank you all very much. Great presentations and good discussion.

(Off-mic speaking)

DR. CATHARINE RILEY: Hi, this is Catharine Riley. Just wanted to make a quick announcement: For those on the phone, if you can mute your lines when you're not asking a question or making a comment, that will help. We're just getting a little bit of feedback in the room. Thank you.

DR. JOSEPH BOCCHINI: All right. Next on our agenda is Dr. Alex Kemper. Dr. Kemper is Professor of Pediatrics at Duke University. He's a health science -- health services researcher who focuses on issues related to the delivery of preventive services. He is a member of the U.S. Preventive Services Task Force and serves as chair of the Committee's Evidence Review Workgroup.

Dr. Kemper will be going over several products his team has been working on related to the Committee. They are -- include consumer-friendly summaries on recently approved conditions, evidence review -- evidence-based review process, and his work on developing

methods to assess cost of expanding newborn screening. So, Alex? Thank you.

DR. ALEX KEMPER: Thank you very much. It's -- it's hard to follow that -- that inspiring talk about the critical congenital heart disease screening implementation with a -- with a methods talk, so I apologize --

(Laughter)

DR. ALEX KEMPER: -- in advance. And do you guys bring up my slides, or do I do it? I do it. So, now I --

(Off-mic speaking)

DR. ALEX KEMPER: Okay. Well, while they're doing that, the -- Before I go through the presentation, I -- I just want to put a couple of thoughts in your mind. So, the first thing is to remember 9 months, right? So, now, under the legislation, that's how long we have to do it. So, 9 months makes me a little bit nervous, so I prefer to think of it as 23,328,000 seconds, which sounds like a Broadway song, as well. But -- but -- but, really, a lot of what

we're going to be doing is -- is -- on the talk is focusing on that, although it'll take me less than 9 months to get the slides up. So --

(Off-mic speaking)

DR. ALEX KEMPER: Okay. Here it comes. You can talk amongst yourselves. I -- I guess the other thing I want to say, while they're pulling my slides up, is that when I talk about the methods, I want everyone to remember that these methods are always a -- a work in progress. So, in -- in a sense, they're, really, never fully finalized, because we learn things each time we do a condition.

However, we're still receiving comments back on the points that I'm going to be making today. As a matter of fact, last night Annamarie sent a nice -- oh, there we go -- a -- a nice set of comments. Scott Gross, who wasn't able to be here in person but I believe is on the phone, has also given us a lot of feedback. Sylvia has, as well. So -- so, again, these are issues that we're really grappling with, and, hopefully, in

whatever period we have for questions and answers, if you have any suggestions, we're certainly happy to hear them.

So, again, this is just a list of the members of the Condition Review Workgroup. You know, of course, I'd be remiss if I didn't highlight the work that K.K. Lam has done to keep things moving, and -- and, really, her insight in the process. And then, this is the group that was specifically advising us around the cost analysis, although, as I mentioned, we've also gotten comments from a wide variety of folk.

So, this is where we're going to talk today. I'm going to begin by discussing the work that we've done around developing consumer-friendly summaries of the previous evidence reviews, and then I'm going to spend a little bit of time talking about revisions to the process, and then cone down a little bit more into the cost-assessment methods. And then, I'm going to end by bringing it back to thinking about how we do this within the 9 months that we have to do

it. And, again -- I mentioned this before, but we're continually updating this process to meet the needs of the Advisory Committee.

So, let's -- let's start with something I'm really, really proud of, of how they're coming together: these consumer-friendly summaries. So, these are summaries of the previous reviews that have been done. We're not updating the reviews, but we're really summarizing them at the point that they were finalized and tied to whatever recommendation came from the Advisory Committee. These are, really, written to be targeted to the -- to the -- to the general public. We're not having separate summaries for different groups but, really, one -- one review that we hope hits the general audience. These have all been designed to be at the eighth-grade reading level or below, which is, really, remarkably challenging given the complexity of the disorders and the nuanced decision-making that goes on.

So, they begin with an executive summary,

and then there's a -- a -- a summary of the report itself that's, you know, up to 10 pages long, and these were developed on other consumer summaries that we found, including ones that the Agency for Healthcare Research and Quality have done for other preventive service recommendations. This is the outline of how they look. I -- I won't read through the whole thing, other than to say that they -- they summarize newborn screening and then the particular condition, and they follow along the outline of the report itself.

Now, because we're doing all the reports, there are, you know, certain points where not all the reports had all these elements. So, for example, the public health impact was added later in the process. So, not all the reports are going to have the exact same pieces, but to the degree that we can make them look the same, we are.

And so, this just -- I like this slide because it just looks pretty in terms of what the report looks like. And here's the inside part.

One of the things I think is really nice is, we have -- In describing what the condition is, we have that -- that little guide there, with -- with arrows explaining how the condition affects the individual. So, you can see this the one for X-linked adrenoleukodystrophy, but the other reports look similar, like I said, and then you can see what -- what the rest of the body of the report looks like. I don't want to spend too long on it, other than to say that I'm -- I'm pleased for -- for all those members of the Condition Review Workgroup for helping with this, because I think they're really nice.

All right. So, now let's drill into where -- where we are right now in terms of methods. And, again, we've updated and are continuing to update the condition review process, both to reflect the current legislative mandates for the review process, and also, you know, ultimately, to hopefully continue to facilitate the decision-making process, which is not easy.

So, again, the work that we do is based

on the Newborn Screening Saves Lives Act, which specifically says that the Advisory Committee shall evaluate public health impact, including the cost of expanding newborn screening. So, cost is in there, right? Not just a good idea, it's the law. And then, in terms of the deadline for review that I mentioned before, for each condition nominated, the Advisory Committee shall review and vote on the nominated condition within 9 months of referring the nominated condition to the Condition Review Workgroup. So, you know, the clock has already started on SMA.

So, what I want to do now is talk about the -- the cost component. So, there's nothing really new that I'm going to be talking about here. We've discussed this in the past. But I do want to summarize, again, where we are, and then if the Advisory Committee has, you know, special requests in terms of how we do it, then, of course, you know, we'd be happy to figure out how to -- how to go about doing that.

So, our primary objective is to inform

the Advisory Committee about the cost to expand newborn screening, okay? And -- and so, we're not looking at the -- the costs to the individual or long-term cost effectiveness, but, really, what does -- what are the costs associated with expanding newborn screening? And for most of these conditions, it's going to be within the context of the public health laboratory.

But our secondary objective -- and we understand that this is important -- is to inform state newborn screening programs. But, really, our primary role in this work is to inform the Advisory Committee.

So, the framework for doing this is based on a budget impact analysis, where we're [focusing] on the fiscal impact to the payer. Now, one of the -- I think Annamarie sent this question. When she thinks payers, she thinks of a -- of a -- like, a health insurer, Aetnas (sic) or whoever. But -- but here, we're talking about the -- the -- the person that is paying for the public health system to add the intervention. And

I'm going to be talking about our -- our -- our approach in the -- in the next couple of slides here.

So, again, this table summarizes things. It's a budget impact analysis, focused on the -- the laboratory costs. Again, we're assuming here that most of the conditions are going to be laboratory based. We're looking at adding the newborn screening condition to the existing screening panel infrastructure. So, we're not starting as if, you know, there was no screening in place but to expand it. And, of course, that has particular implications if you're adding on a screening test that uses a modality that's already in the state lab.

And then, we're looking at short-term follow-up of the presumptive-positive screens. So, not including diagnosis, right? So, we're -- we're looking at the costs that are typically faced by the public health laboratories. So -- And I -- I appreciate the -- you know, the issues of short-term and long-term follow-up vary by

newborn screening program, but we're really just looking at this, sort of, constrained first couple of steps.

In terms of the time horizon, we're looking at the -- the first year of starting up screening for it, as well as the -- the longer term, and by longer term, we're only looking out to 5 years of -- of implementing it. Our data sources are going to primarily come from newborn screening laboratories, but of course, you know, we're going to look to other sources, including any pilot programs that might be in place, researchers, vendors who provide the laboratory equipment or reagents.

And in -- in terms of looking at alternatives and -- and issues of uncertainty, you know, it -- it's -- it's interesting that laboratories can go about implementing screening tests a variety of different ways, right? So, they may have a contract with a vendor to provide the equipment and the -- you know, the reagents, or they might do it themselves, in-house. There's

purchasing versus leasing; there's all sorts of different funding streams. To the degree that we can assess this variability and summarize it for the Advisory Committee we will do so.

And ultimately, what we hope to end up with is the cost per specimen to add the condition on and looking at the total cost per a hundred thousand for the startup year. We want to look at the range-of-cost estimates highlighting all the assumptions that go in, and then have a narrative that will describe these assumptions.

So, you know, we're -- we're going to do the best we can, within the limited timeframe, to give a sense of the cost of -- of implementing and -- a new condition, as well as the, sort of, you know, 5-year out period. But it's going to be -- You know, it's going to have a lot of caveats. Oops. I don't know -- Oh, there we go. Nobody wants to see a big picture of me. They want to see the slides.

So, the -- the primary costs are associated with equipment. Again, that can be a

direct purchase or a lease, or there could be a reagent rental agreement. There are other laboratory expenses that you could consider, including maintenance or repairs, expanding things, adding things on to the laboratory information management system. There could be additional employees that need to be hired, and then there are indirect costs associated with space-building utilities, that sort of thing. So, there -- there's a lot of stuff to drill into, and -- and, again, we're going to do the best that we can with the likely limited information that's available.

So, there -- there are lots of other costs that we -- we would like to be able to look at, and we -- we appreciate, too, that -- that states are variable in how these costs will play out. So, a small state, like Delaware, versus a large state, like Texas, is going to be different. And so, again, to the degree that we can describe these variations, we will.

There are other secondary costs that

would be interesting to get to, although we may not be able to get there. This includes things like confirmatory testing or the cost of referrals, the need for follow-up for genetic counseling, and then, certainly of great interest to us all is, you know, what -- what are the long-term costs, those associated with the delivering of care, for monitoring, all the other kinds of things that happen. It would be nice to get to those things, but I'm -- I'm doubtful, especially given, you know, how new the evidence is -- is for a lot of these conditions, that we'll be able to get to that level of detail.

So, I mentioned before, there are a lot of things that -- that can drive the cost, so state annual birth is highly variable. There are variations in the number of specimens that are sent for -- for babies. So, there's, you know, one-sample versus two-sample states. There's this issue of who pays for what within the newborn screening, you know, how -- how newborn screening's set up in a particular lab. There's

all sorts of issues with timing. States have a different political context in terms of how things are -- are appropriated, and there's likely going to be other sources of variation, too, in terms of if there happen to be any variations in how the algorithms for the laboratory testing are put into place, and, you know -- you know, what's done in-house versus sent out -- all sorts of things like that.

So, again, we're going to try to -- to summarize what we think is the -- the waterfront and give reasonable ranges. And I think the best thing that we can do, as well, is just be clear about the assumptions that are in place, so that it's, you know, something meaningful to the Committee.

So, this slide summarizes the -- the steps in terms of -- that -- that we're going to take in terms of first figuring out what the -- the methods are, then identifying states that could assist with a cost-estimate approach, and then we have a cost-estimate tool that will help

us gather the costs, and I'm going to show examples of this in a minute, although you've seen at least a -- a version of this before. Then, we'll summarize the information as best as we can, and then we'll obviously incorporate that into the reports that we generate that -- that are part of the condition review report. So, I won't read through each little line here, but I think this slide, just, is our, kind of, approach to moving forward.

This is the cost-estimate tool. You saw this before, with MPS 1; it's been tweaked a little bit. But it's a way for us to systematically work with newborn screening programs to collect the information. So, you know, if -- if they use a rental reagent equipment versus direct purchase, you can see how we're -- we assess equipment, consumables, laboratory expenses, and those sorts of things. And, again, I'm not going to belabor this point, because you -- you've seen this before, when we did MPS 1, but you can see that -- that,

ultimately, it gives a -- a -- a range.

And so, I'm just going to highlight some of the challenges, many of which I talked about before. But -- not to harp on it, but there is a limited time for doing this. Newborn screening programs, oftentimes, in our experience, don't have the costs available for us in the way that we need it, and it's not surprising, right? Because it's not their job, and it's a lot of information that we're asking. The estimates that we get from the states that do participate, they may not be that generalizable because they reflect early adopters. Cost variability is hard to predict. State newborn screening programs have privacy issues that might limit the information that they can share with us. So, states' contracts -- right? -- are -- are, you know -- are personal things that they may not want other states to know about, or they may be held confidential for some other reasons.

We didn't talk about point of care or other non -- non-dried blood spot specimens.

That's going to create its own pile of grief, as I like to think about it, but that's not an imminent concern of us right now.

One of the challenges that may come up is if we are asked to evaluate a condition where no state's begun screening for it yet. Again, that's not the issue for SMA.

And then, we all appreciate that these cost estimates, it's a -- you know, the -- the sands are shifting -- right? -- because prices are -- are apt to change as, you know, technology gets better; there's more competition. There's -- I don't know how much competition there is in the market, but you can imagine that there are lots of things that could change the -- the prices that we come up with when we talk to states. So, again, you know, it -- there -- there's going to -- You know, we're going to have a lot of caveats, and it'll also be good for that point in time, but recognize that things change.

So, I'm going to now -- It's kind of a, like, a bummer to talk about a lot right before

lunch, isn't it? So, I'm going to move and talk about the condition review itself, just so that you have a sense of what it is that we're doing, again. So, the -- the components include the systematic evidence review, the public health impact at the population level, that modeling, the expected number of cases and what that might mean if newborn screening were adopted for the particular condition nationally. And then, we have the public health impact assessment, where different newborn screening programs are surveyed to find out whether or not they could implement the screening.

And you can see on the right that this is -- this -- this whole process has been evolving. And I like to think that the information that we provide you is -- is more helpful as these different pieces have come into play. But there's really a lot of -- lot of pieces to the whole puzzle.

And this -- this is like -- every time I look at this slide, it's a little bit sobering.

So, it -- it goes through the conditions, in reverse order, that we've looked at: when it was nominated, when it came to the Advisory Committee for a vote, when the -- when -- when it was finally voted on, and the little checkboxes of the different components. And what you will see is that, in general, it's been over 9 months long.

And part of this is that when we've done the evidence reviews in the past, we've gone beyond, oftentimes, what's in a traditional evidence review. So, if you remember, with adrenoleukodystrophy, we actually got primary, unpublished data from a couple of centers and analyzed it ourselves, because the information that the Advisory Committee needed to move forward hadn't been published, and the people that had the data actually didn't even consider this particular analysis in the past. But that was actually a really helpful thing, but it took a long time to get to those data. So, we're going to have to be, you know, circumscribed in the

kinds of things we can do moving forward, but we -- we do have a plan, which is here, and you -- you can see the different components and then how we plan to finish this in a 9-month period.

One of the key things is going to be racing through with the systematic evidence review, because the systematic evidence review, in large part, serves as the anchor for everything else, so. You know, I was -- I was joking with K.K. that when -- when SMA got handed off to condition review yesterday, we -- we should, like, run out of the room and -- and start -- start doing the search, because we really can't afford to let those -- these deadlines slip to be able to meet the targets.

So, on the previous slide, I showed you what our -- what our -- you know, our internal time points are, and the -- the key thing is that we need to move, you know, rapidly forward with our technical expert panel, who helps guide us in terms of making sure that we're thinking about the condition correctly and then, of course,

things are anchored on when the Advisory Committee meetings occur. And, obviously, we -- we want to start as soon as we can, which was yesterday, I guess.

So, again, this is another slide; you all have it in your briefing books. I'm -- I'm not going to walk through it again, but it's just another way of thinking about how we're going to get through this in the 9-month period in terms of what components we plan to have done, when. So, I -- I -- I'm, you know, pleased with the structure, that we'll be able to get through the 9 months, but know that -- note that, you know, we're going to have to be very careful about the kinds of things that -- that we can promise, as I mentioned before.

So, you know, I -- I always like to -- to be clear about, you know, what -- what are the threats to our success. Well, you know, we're doing things a little bit new here. Some of this depends on the availability of evidence, although, certainly, Dr. Tarini, yesterday, did a

-- did a great job of setting this up and, sort of, summarizing where the -- the evidence is. Again, there's pilot data, both in the U.S., as well as on Taiwan, which is going to be helpful to us. SMA, thinking about it in particular, is complex -- right? -- because there's -- you know, because of -- it -- it can affect individuals at -- at different ages, and then there's the issue of the number of carriers, and also issues about the screening tests.

So, you know, every condition -- right? -- that -- that we're ever going to look at is going to have its own complexities, right? They're just each going to be complex in their own way. That's my shout-out to Anna Karenina. This is my, like, literary allusion for the day. That was pretty good for someone who's an engineer.

So, you know, here -- you know, the risk for delays are related to the systematic evidence review, most of which we have to have done in -- in the first 3 months of the activity, how

complex the decision analytic model needs to be, to be able to get population health-level estimates. And then, again, the -- the cost data are going to be complex to get. I -- I think, at the end of the day, we'll have a range, with a list of caveats, to help inform you in -- in that process that you have to go through.

So, we are going to be able to leverage preliminary data that comes from the nomination package. Now, we use the nomination package as, sort of, a launching point to make sure that we understand the condition, but we also don't want to be biased by those things that are in the nomination package, and we'll continue to do all the normal things that we do in terms of looking everywhere.

We're going to have to start earlier than we have in the process in terms of gathering pilot screening information. I discussed before about, you know, how we're going to have to, you know, just really focus on published and unpublished data that are already analyzed and

available to us. We're not going to be able to do that, kind of, primary analysis again. And I already talked -- I, like, then, won't repeat myself -- about the -- the cost data and -- and incorporating things into a summary that addresses the -- the decision-making that you all will have to do.

So, again, our -- our bottom line is, we need to facilitate the decision-making process of the Advisory Committee and, you know, hear the things from the matrix. In terms of how you use these components, of course, that's -- that's a -- an issue for the Advisory Committee, including how you weigh things like cost.

So, again, this is information you've seen before, about the summary of the evidence that we will be providing. We've really -- I didn't talk about this before, and I suspect this may come up as a question in terms of how we are going to grade the evidence.

So, in the past, we've had, you know, fairly long, narrative summaries of the quality

of evidence, but I know that there's interest among some members of the Advisory Committee to assign specific grades to that evidence based on the risk of bias, and so that's certainly something that we plan to do. When you assign assessments of the strength of evidence and the risk of bias, there's really -- you do that both at the individual study level as well as the -- the total strength of evidence across the -- the key question, and that's something that we can easily add in. The rest of the things that you've -- you've seen before, so I won't, in the interest of time, go through it again but open things up for questions. Thank you.

DR. JOSEPH BOCCHINI: Alex, thank you very much. I -- I want to commend you on your analytical process and how you've broken things down in such a way that it's very clear what needs to be done and when, to -- to work through a -- a condition review within the assigned timeline, and if we look at our timeline, we're looking at three meetings, and we're looking at

February of 2018 as an opportunity to make our decision for SMA if everything goes as -- as planned. And so, certainly, I appreciate all the work you've done to kind of get things prepared to make that happen. So, thank you.

DR. ALEX KEMPER: Thank you.

DR. JOSEPH BOCCHINI: In addition, I want to thank you for the other work that you've done. I think that the -- the consumer-friendly summaries are really going to be something that's going to add value to what the Committee has done and -- and -- and make the public and others more aware and able to, kind of, have a better feel for what -- what the Committee has accomplished. So, thank you for that, as well.

I want the Committee to know that draft -- the draft reports that Alex is talking about will come to the Committee shortly for review, comment, and -- and -- and suggestions in terms of providing feedback to Alex, as well. So, let's open his presentation to discussion by the Committee. First, Joan?

MS. JOAN SCOTT: Thanks, Alice, for -- Alex, for that very great overview about how to compress all this into the 9 months. Do you want to say anything about changes to the nomination package or the information that it requests to come in with nominators to help fill some of that informational gap and help move that -- start the process off faster?

DR. ALEX KEMPER: Yeah. Obviously, the more information that's in the nomination package, the -- you know, the more helpful it is. You know, we'll be able to find the published reports around the particular condition, but, you know, to the degree to which we can identify who's actively involved in the screening will short circuit the process that we have to go through to identify individuals to -- to talk to. But I -- I -- you know, and especially after hearing the nomination presentation yesterday, I think that a lot of that stuff is there, so I -- I feel good about that process.

DR. JOSEPH BOCCHINI: Jeff?

DR. JEFFREY BROSCO: Jeff Brosco. As you know, Alex, a lot of the issues that come up for the Committee are -- are in the ethics realm, so, what are the outcomes for carrier identification and things like that. Do you feel like the -- you have sufficient information from the nomination package and a procedure for including those sorts of issues?

DR. ALEX KEMPER: You know, what -- what you're really raising is -- is a broader issue related to newborn screening. So, there's the issue of carriers, and there's also the issue of secondary targets, so other things that would be picked up in the process of screening. It -- it's been my experience, when looking at other conditions when carriers are reported, that there's just a -- a -- not that lot of -- not a lot of information around outcomes for either the carriers themselves or the family or the impact it has on the family. So, we may be able to quantitate the number of carriers that would be expected to be identified, but to the degree that

which we can say anything about what that -- that means, what the -- what the impact is, we're probably not going to be able to say a lot. I think the same is true for some of the secondary conditions that are going to be identified.

So, you know, the best -- I -- I mean -- and I shouldn't say "the best." I think what's likely to happen, although we never know that until, you know, we look, is that we'll be able to quantitate things but not be able to tell you what the impact that is -- of that is, either for the good or for the bad.

DR. JOSEPH BOCCHINI: So, we have Beth.

DR. BETH TARINI: This is Beth Tarini. So, first, I want to acknowledge -- and this is, I think, fitting that much of the work on -- if I remember correctly -- on the friendly summaries comes from Don, right? And -- and he brought it up in our Education and Training Workgroup Committee. So, score for Don, score for the Workgroup. So, thank you, Don, for --

DR. ALEX KEMPER: Yes, thank you, Don,

who's also a friendly guy himself.

DR. BETH TARINI: The --

DR. DON BAILEY: Mostly because I didn't understand them.

(Laughter)

DR. BETH TARINI: So, I wanted to give Don his -- his due credit in having worked alongside him on that workgroup.

And the second -- the -- the question I have is: I'm deeply troubled that the cost analysis only has lab. And I know you and your research background, and so I know you've done cost-effectiveness analyses, and I know you've seen them in the literature.

And so, this makes me wonder if -- is -- is the problem in -- Let me pause. This data is not out there on cost. We've known it's not out there. By "this data," I mean anything that's not on a receipt that comes with the reagent. We've known it for decades. The -- they are known assumptions that are built into all the cost effectiveness on newborn screening that exists,

going back to the '90s, and we -- we are not making any progress in this realm, so it seems. So, I'm wondering if this is because we are not adequately resourcing you to do that groundbreaking work to give us some bit of estimates on this.

And my concern is that half data is treated as full data. And so, if we go forward and say, "Oh, here's the cost data, asterisk, caveat, this is actually in the labs," that it's going to be used -- if this -- if it gets anointed by this committee -- as the cost of newborn screening. And we just spent an hour discussing that the cost of CCHD screening is entirely based on the data that we collect that allows us to determine if we're actually making an impact. So, I find this troubling.

DR. ALEX KEMPER: So, I -- I agree. I mean, my -- my immediate first response was to see if we can get those pandas back up.

(Laughter)

DR. ALEX KEMPER: But -- but I -- All

right. So, I agree with you. I -- I think that, in -- in some ways, the cost data that -- that -- that you or I or most of the people in this room would be most interested in knowing is, really, unknowable to a certain degree, and part of that -- Well, I -- I think -- Well, it depends on how fine a point you want to put on it.

And the reason is, I would be most interested in understanding what the cost implications of this is at a more societal level, right? So, how much do we need to resource systems to be able to do the screening, to be able to do the follow-up, to be able to provide all the care that individuals need over their lifespan, to understand, you know, if it's something that involves a -- a -- a medical food or an expensive drug, what -- what these things are going to be like over the life of the child.

Now, the reason I say that it's unknowable is because there are not a lot of good data that are available feeding into the system, and I also suspect, based on my experience with

other preventive services, that once things roll out, the costs change.

So, you know, I wasn't involved in -- in writing the legislation that -- that mandated cost. I think that given that we have the 9 months, I think this is the best we could do. I think that if, you know -- you know, somebody came and said, you know, here's a -- here's a ton more money, now do a bigger cost-effectiveness study, I would still be skeptical about the -- about the -- the accuracy of the final number. But it would be nicer to have that stuff, and we can probably make estimates of it.

DR. BETH TARINI: But I -- I just wanted to clarify: I'm not saying we need to carry the child's quality-of-life costs out 'til they're 25, because I had this conversation, exactly, with Dr. Prosser about my timeliness RWJ grant, which was, "How can I do the cost effectiveness on a timeliness project, Lisa, if" -- she's on the grant -- I said, "If we don't have the costs?" And she said, "You're going to have to --

They -- they're knowable. They're estimatable. You know, if you do a time --" I'm not saying you should do this. As -- pushing back on this unknowable. Unknowable is, like, you know, does God exist? Like, that's the type of --

DR. ALEX KEMPER: Okay.

DR. BETH TARINI: -- level of, like, unknowable, perhaps. I'm talking about, it -- it is estimatable within a reasonable fashion of -- In that case, she was like, "You should -- You -- What you'd have to do is time track people, then know what their actual salary is. Then, you'd sort of -- Then you'd take the time tracking, then you estimate it back."

So, it's knowable, it's just that we don't have the resources or the time to know it, and -- and also to push back -- Things change, but if things change, then we change. So --

DR. ALEX KEMPER: Right.

DR. BETH TARINI: I -- I feel for you, in that in 9 months, you are not going to be able to provide, I think, the time -- the type of cost

estimates that a system -- not just a testing system, but a newborn screening system, requires for appropriate adequate assessment. That's not your fault. I'm just saying -- I just want to put it out there --

DR. ALEX KEMPER: No -- No -- No --

DR. BETH TARINI: -- and say that, hand on the Bible, it's been said.

DR. ALEX KEMPER: And I -- I would -- You know, we don't -- You know, we only have a limited time up here, but, you know, the -- the question is, how do we make sure that it's clear in the reports what a limited view of cost we really have, and how do we make sure that in the material that comes out from the Advisory Committee, it's included?

I mean, one question that's come up, too, is how the Advisory Committee's going to use these numbers, as well, but that's -- I don't have to figure that out, fortunately.

DR. JOSEPH BOCCHINI: All right. Next, we have Dr. Matern, and then Dr. Bailey.

DR. DIETRICH MATERN: Yeah. Thanks, Alex, for the -- the review of all the things you're doing. I have two questions. One is: Where are these consumer-friendly summaries placed? Where can we find them? And if they are on a website, who's going to update them to make sure they're current?

DR. ALEX KEMPER: So, the -- the first issue is that as we prepare them, we are handing them off to our HRSA colleagues, who are then going to make it available to you all to look at, to see if you have any final comments, and then they'll go up on the HRSA website, which has, you know, actually gotten much nicer recently. I don't know if anyone's had a chance to take a look at it. So, they'll be available to the public that way after you've had a chance to look at them.

We're still working on them. We're going backwards in time, from the most recent to the -- to the oldest. We just recently finished the CCHD one, and we're, you know, continuing to -- to

produce them.

Our charge was to produce a summary of the reports, which means that they're frozen in time. So, they are not continually updated. So, again, they reflect the -- the report at the time that everything was finalized and the Advisory Committee voted. So, it -- it's not within our contract to continue to update those things.

DR. DIETRICH MATERN: Okay. So, I think that just needs to be very clear on the website that these are status of 2017 or '16 or whatever it may be.

DR. ALEX KEMPER: Yeah. And they have the date emblazoned on the front.

DR. DIETRICH MATERN: Yeah. Okay. The other question or comment I have is, I'm -- I'm glad that you have to look at the cost, including care and monitoring, and when it comes to your current project, for which you have 8 months and 30 days --

(Laughter)

DR. DIETRICH MATERN: -- you -- you might

want to check with -- with -- I mean, you have to check with the physicians who are actually treating patients right now. So, in Minnesota, 2 weeks ago, at the Advisory Committee meeting, we had a very nice update on how it's going at the University of Minnesota, so they have, I think, a good amount of data of what it takes to get the approval to treat patients in terms of, how long does it take, how many phone calls do you have to make, how many letters do you have to write, all the usual stuff that physicians to do get a patient treated.

And then, when it comes to the actual procedure, since it is an intrathecal infusion of the medication, what effort has to go into this, and what does it cost in -- in time, et cetera. So, I think you should be able to get that information.

DR. ALEX KEMPER: Excellent.

DR. JOSEPH BOCCHINI: Dr. Bailey?

DR. DON BAILEY: So, thanks, again, Alex, for that great summary and all the great work

that you and your -- your group are doing. I like the -- the timeline that you put up there in terms of us adding expectations to the review over time. So, we started with the evidence review, and then we added the public health component, we added the cost component, we added the modeling component. And I think it's very clear that we're getting a -- you know, as good a picture as we can get in this short period of time.

What I -- This is more -- I don't know if it's a -- a noble or existential question, Beth, but it's a -- I brought this up with the Committee before, but I do think it's something the Committee really, at some point in a near future meeting, needs to step back and think about, which is the -- the pipeline.

So, there's a pipe -- there's a really big and rapidly growing pipeline of conditions that are just -- the advocates and researchers are just very anxious for us to -- to review them and consider them. And -- and -- and there's --

there's going to be changes coming up in the next few years, where it'll either be a technology change that will, you know, allow us to screen for a lot conditions that are treatable that the only reason we're not screening for them now is -- is that we don't have a -- a good screening test.

I was just looking at an article from -- it was just actually 3 years ago, identified 89 treatable causes of intellectual disability. Well, you know, if we could screen for those, what would we do with those? What if those 89 came to us as a bucket to be -- to be nominated for the Committee?

The same thing is around treatment. What if there was a new treatment modality that all of a sudden could help benefit many, many different conditions at one time? How are we going to deal with that as a committee?

I don't think -- I think we've -- we've taken a condition-by-condition review process as very ethical, scientific, rigorous, as all the

right things that we need to do to make good decisions at this point in our -- in the history of our committee, but I -- I don't think this is a sustainable model going forward. I think we're going to have some disruptors that are going to really challenge us and -- or challenge you.

And so, I don't have an answer for it, and it's certainly not a criticism of the process -- no, because it's a great process. But I would encourage the Committee to start actually not -- not ignoring that but have some discussions about it in the group, having different people come in and maybe do some blue-sky thinking about, what if? How would we deal with those kinds of situations? Because it -- it is going to happen.

DR. JOSEPH BOCCHINI: That's a great comment. Thank you. Questions -- Oh, let's -- Before we -- we go to the org reps, any of the Committee members on the phone have any questions or comments?

(No audible response)

DR. JOSEPH BOCCHINI: Hearing none, I

guess -- Joan?

MS. JOAN SCOTT: Well, I just wanted to follow up to what Don just said about either a technology change or a treatment change, but the other -- the other context, of course, is in the public health infrastructure, as opposed to some other health care delivery infrastructure to do that. So, it's -- it's -- Yeah, that -- that -- Yeah.

DR. JOSEPH BOCCHINI: Beth?

DR. BETH TARINI: It's a quick follow-up. So, just disorder -- I'll use your example of thinking forward with the cost. If we had two tests -- or two disorders, one was pennies and one was $10, and the one that was pennies -- the -- the one that was pennies had a million-dollar treatment and cost extensive time to work up and evaluate, and the one that was $10 did not, based on the current cost estimates, we would go with the pennies on the dollar. Assuming all things were equal. No?

DR. ALEX KEMPER: I --

DR. DON BAILEY: But we don't really consider that as a --

DR. BETH TARINI: But it -- Oh, it's not a -- Oh, it's just the costs are gathered --

DR. ALEX KEMPER: Yeah.

DR. BETH TARINI: -- but they're not --

DR. ALEX KEMPER: Right.

DR. BETH TARINI: -- they're just sitting there.

DR. DON BAILEY: Yeah.

DR. ALEX KEMPER: So -- So, this is -- These are, you know, one --

DR. BETH TARINI: This is legislation.

DR. ALEX KEMPER: -- group of data elements amongst a larger pool of data elements, so --

DR. BETH TARINI: Okay.

DR. ALEX KEMPER: I mean, that -- that's why -- You know, that's why you all are here, right? Because I think there's a lot of nuance here.

DR. BETH TARINI: Okay.

DR. JOSEPH BOCCHINI: All right. Natasha.

MS. NATASHA BONHOMME: Great. Thank you so much. I guess my first question is, do you plan on sleeping in the 9 -- next 9 months? Because I've got the answer to that.

DR. ALEX KEMPER: I -- Better -- better get --

MS. NATASHA BONHOMME: Coffee, right?

DR. ALEX KEMPER: -- a little caffeine. I will say -- and -- because you join our calls, as well -- that we have just a really crack team of people working on the project, so -- and -- and especially with K.K.'s hard work. I think that the timeline we laid out is reasonable, as long as we adhere to what our mission is and not begin to, like, pull in other things.

MS. NATASHA BONHOMME: I guess I have one comment and then a couple of questions. I -- I think this cost issue that Beth is discussing and has been discussed is really important, because it makes it really difficult to communicate and educate people about what is newborn screening

and what does it take to make a great newborn screening program, you know, great and wonderful, and -- and those are the types of questions that get asked: How much does it cost? How many -- You know, it goes back to the session before in terms of the data, as well, so, how many lives exactly, and how are they affected?

So, I know it's been brought up a number of times, and I -- I hope that we can have, in other meetings, more robust conversations of, how do we actually answer those questions, instead of just saying, "Yeah, it's rough. It's tough." Like, that doesn't mean the questions are going to go away. And that's not all on you, I don't think.

DR. ALEX KEMPER: No, no, no, but if I can -- if I can just magnify it, because truthfully, when I talk about costs in newborn screening, then, you know, somebody says, "Well, it doesn't really matter what condition you're talking about." They're always like, "It's always a dollar a test. That's all it is. We should do

this, because it's only a dollar a test."

But that really undercuts the public health --

MS. NATASHA BONHOMME: Right.

DR. ALEX KEMPER: -- aspect, because it's not a dollar a test. The -- the amount of public health infrastructure you need to be able to carry out population-level screening and the monitoring and all that kind of stuff is -- it's more than a dollar a test. And I think that that's fine, but we just -- You know, I -- I don't want to undercut the -- the message of newborn screening. I think that's -- that's really what you're saying, as well.

MS. NATASHA BONHOMME: Yeah. No, absolutely. And then, just a couple of questions. For the consumer guides, were those -- are those mainly based off of just bringing the -- and not "just," as if that's easy -- but bringing the literacy level down of the reports, or is it also about, kind of, addressing common questions that maybe consumers or families have asked in the

past? So, is it --

DR. ALEX KEMPER: Yeah. It's a little bit of both.

MS. NATASHA BONHOMME: Okay.

DR. ALEX KEMPER: So, it -- it's structured around explaining what newborn screening is and, you know, why the Advisory Committee either, you know, voted, you know, for or against adding the -- recommending to the Secretary to add it to the RUSP, that kind of thing. But it does bring the literacy level down in terms of explaining what the particular condition is.

MS. NATASHA BONHOMME: Great. And will there be -- Will either -- I guess it would be HRSA -- be able to track the usage of those, like either through downloads or anything like that, or is it just going to be embedded in the page, and that wouldn't be separated out? I think that would just be interesting to see, you know, how's it being used, who -- maybe who's going to it, again, as we're trying to engage consumers more.

DR. JOSEPH BOCCHINI: Okay. We could certainly --

DR. ALEX KEMPER: Yes.

DR. JOSEPH BOCCHINI: -- work on that, about determining whether it could be tracked.

All right. Next, Annamarie?

MS. ANNAMARIE SAARINEN: Thanks for your presentation, Alex. Good work, as always. I actually had a point about the consumer reports, as well, or a question that may be similar to hers. We had a little bit of a side discussion at the state newborn screening meeting in Minnesota about the complexity of all the information coming out on the backend, but the ability for advocates and parents to really participate in the nomination process.

Just, it's very complicated, and I think, although there a lot of families who have an interest in -- in participating and wanting to be part of a -- a -- a submission, or at least looking into whether a condition could be looked at for evidence review or putting together a

packet, but I mean, you need to have some serious time on your hands, and resources, and a nanny, and a counselor and, I don't know, maybe three husbands or something to be able to actually do that, I think, as the parent of a child who has a condition.

So, I don't -- I -- I think it's legitimate. I think it's a little exclusionary, and I -- I know we can't, sort of, be all things to all people, but I -- I feel like, at least we raised it at the state level, in Minnesota, as something to look at and try to improve accessibility. That's one point.

DR. ALEX KEMPER: So -- Well, just to address your -- your point. We -- we agree that -- that the -- understanding the process of nomination and then evidence review can be, you know, confusing for those people that aren't steeped in the arcana. But to that end, that's something that -- that I've spoken to HRSA about a lot, and certainly, Natasha and I have had a lot of conversations, and we have some ideas

about how to, you know, graphically present this information. Like, we had, like, a little image of the -- looks like a little board game, like the Game of Life, where you can, sort of, march along that explains, you know, where the different pathways are and that kind of thing.

So, I -- that's -- that's a work in progress, but I a hundred percent agree with you that it's important to be able to communicate the -- the -- you know, how a bill becomes a law, essentially, and -- and so, that's something that we're working on, outside of the material that I presented today.

MS. ANNAMARIE SAARINEN: Sure. And I -- I imagine Scott Gross might be listening in, but he and I have had a -- a few chats about some of the cost assessment of CCHD slides that, you know, this -- this information that was put out there, back in, I don't know, 2013 or something like that.

And to Beth's point, you know, half data is sort of data, and I -- I still see the same

numbers, to this day, being quoted as, like, "Yeah, but that presentation that I saw said it costs $15 to do every --" You know what I mean? Like, it's just like, once you put it out there in the universe, it's -- it's, you know, like -- Google just adopts it as real.

So, I -- I -- I don't know if there's a systematic way of saying: At a present moment, this is what we've assessed the cost around a program to be, and, oh, by the way, we're actually going to check back in on this next year, or how -- you know, how that gets updated and in -- in a way that's meaningful, to -- to -- not just to -- to programs but to policymakers and others that -- that, sort of, need that information. You can go back to the pandas, if you want. I --

DR. ALEX KEMPER: Yeah. Yeah. I always think of that. Again, I -- I agree with you about updating things, but that's out of our, you know, specific purview, but I -- I do worry -- and I think this gets back to the comment that Beth and

others were making, too, is, once you put a number out there, it becomes -- you know, people buy into it.

And there's so many caveats that go into the number, as well, that -- that -- I don't know how to make -- you know, other than putting it on each slide, how to make sure that those caveats don't get lost. But I'd be -- I mean, if you have solutions, that'd be welcome.

DR. JOSEPH BOCCHINI: Next.

DR. KATE TULLIS: Hi, Kate Tullis representing AMCHP here, but in my daily job, I'm the director of the Delaware Newborn Screening Program. So, I am a big proponent of looking at costs. And do I see here in the -- your cost estimate tool, you do list follow-up, but in the examples that were provided -- at least on my packet -- it's only laboratory.

DR. ALEX KEMPER: Yeah, so we're --

DR. KATE TULLIS: And so, if you --

DR. ALEX KEMPER: We're -- As a -- as a primary outcome, we're really going to be looking

at the laboratory costs related to follow-up, but to the degree that we're able to assess any, you know, longer term costs -- you know, if we can find those -- then we'll -- You know, that's -- that's information that we're going to provide to you all.

DR. KATE TULLIS: Mm-hmm.

DR. ALEX KEMPER: But within the -- the time window that we have, I'm not sure how much of those data that we're going to be able to get. So, the minimum is, sort of, the primary outcome. We're going to be looking at the, you know, repeat tests and that kind of thing that might be required within the lab.

DR. KATE TULLIS: Mm-hmm.

DR. ALEX KEMPER: But to the degree that we can stumble upon other good data around longer-term follow-up, we'll provide that.

DR. KATE TULLIS: I -- I hope you can stumble upon that, because that's the big component of getting the results out the door.

My second, sort of -- I don't mean to be

snide here, but there are -- Let's see, I looked, just today. There are 12 states with over 100,000 births per year, but there are 26 with less than 60. And being one of those 26, we really need something to work with, because although the Committee might not look at these cost estimates, the states really do, and our leadership really will look at it as, you know, a Google-for-real-it-exists number, and sometimes that's harder to translate for -- for our smaller states and smaller programs. Thank you.

DR. ALEX KEMPER: So, I -- I mean, and, you know, we -- we've -- I mean, by -- by issue of disclosure of conflict of interest, you know, we certainly tried to -- to include you to -- to think about the small state issue, and of course we're going to reach out broadly when we try to get these cost numbers. The reality is, though, that, oftentimes, the smaller states don't have the kind of data that could inform a cost estimate. So, you get, kind of, in this circular thing.

So, I don't want to promise that we're going to have this number that's going to be, you know -- that -- that you can, you know, like, look up the number of births you have and this and, you know, come up with a -- with a satisfactory number. We'll do the best that we can and then put the caveat out there. But I'm, like, you know, I'm a hundred percent sympathetic to these issues at the -- at the small-state level. And so, again, this will be something that we'll make painfully clear to the Advisory Committee, and you're going to have to weigh these data, you know, to the degree to which, you know, you -- you think that they're valid. Roll the pandas.

DR. JOSEPH BOCCHINI: Natasha, you had one more question. I'm going to -- and then I'll give you the last question, and then we go to break.

MS. NATASHA BONHOMME: It's more just a comment to what Annamarie was saying. I'm not happy to hear, but I did seem to hear that a lot

of the questions around getting more clarity around the nomination process is something that you're hearing, kind of, at the state level, because that's something we at the national levels of Genetic Alliance have been hearing a lot about for, I mean, really, years at this point. So, I'm happy to circle back around with you in terms of some of the conversations we've had of how we can maybe address that, like Alex was saying, with some of the different images we've come up with.

But I think as this process gets more complex, or maybe just evolves, that there's going to be -- continuing to be that need for people who are interested in nominating conditions to know how to do that, how best to do that, what were past experiences and have some guidance around that. So, I'm happy to follow up with you on that more.

DR. JOSEPH BOCCHINI: So, if you'll come up to the microphone?

MR. JOE SCHNEIDER: Sure.

DR. JOSEPH BOCCHINI: Thanks.

MR. JOE SCHNEIDER: Thanks. Joe Schneider, I'm the -- on the Long-Term Follow-Up Program. I'm from Dallas, Texas. I first want to just absolutely -- I'm thrilled that -- I'm a pediatrician, and I'm thrilled that you all are doing this, and I thank all of you for doing it.

The -- the one question that -- that I have is -- it's more in the lines of the future, as you were talking about, and then the small state is, the -- I'm new at this, I'm learning, but does the Committee feel that it has a responsibility to, if there are programmatic ways to reduce costs in the -- across the United States, does the Committee feel that that is within its charge to -- to work on cost reductions, particularly for smaller states?

I see a smile on the face, so I might be hitting something. And that's just a -- it's a -- it's a question for the Committee. Is it in your -- Do you feel it's within your purview? Thank you.

DR. JOSEPH BOCCHINI: I -- I think as cost has become part of our responsibility, certainly, thinking through ways to reduce cost -- If it -- if it's something that's an opportunity for the Committee, I think that certainly would be something that we would pursue.

MR. JOE SCHNEIDER: And in -- just as a follow-up, the -- one of the ways to reduce costs that we've learned from business and other organizations is to -- is not to do -- so, for CCHD, for example, is not to do 46 or 50 different collection -- data collection processes. It's actually to regionalize or to centralize that cost -- or that data collection process. So, I would just offer that as something for the future. And I know I'm standing between lunch, and so thank you very much.

DR. JOSEPH BOCCHINI: Thank you. All right. Alex, again, thank you --

DR. ALEX KEMPER: Thank you.

DR. JOSEPH BOCCHINI: -- very much for

your work and your presentations, and we know you'll be working a lot of weekends. So, that's good. All right.

So, I think, with that, we -- we are in line for a break, so we're going to come back promptly at 11:45 so that we can get through the workgroup reports and try and finish on time. So, any other -- Okay, so thank you. We'll be back in 10 minutes. Thanks.

(Whereupon, the above-entitled matter went off the record.)

DR. JOSEPH BOCCHINI: All right. If we can get everybody seated so we can get started? Thank you.

Okay. So, we're going to now hear from the chairs of each of the three workgroups. The -- the presenters will summarize for us where the workgroups are with the various priority projects identified by the Committee in 2016. The chairs will present a 10-minute summary, and then the Committee will have 10 minutes to discuss and provide feedback to each workgroup.

So, the first presentation is by Beth Tarini, who will report on the activities of the Education and Training Workgroup. Beth?

DR. BETH TARINI: Okay. So, my co-chair has decided to -- that it's more important to remain here than fly back to Chicago, so thank you. Thank you for your dedication to serve your country. Okay.

So, we have expanded our committee and now have a plethora of additional expertise, as listed here, and our new members have approached the job with much enthusiasm and have joined onto our projects, making significant contributions. So, yesterday, we introduced our new members, welcomed them into the fold, and then discussed relevant updates for members, which actually was quite useful because what it did was highlight some issues on the horizon.

Pam -- It was Pam Clark -- right? -- from Georgia talked about legislation in Georgia to add Krabbe as an optional newborn screen. Discussions about how it only costs $10 to screen

for it were part of the thrust of the decision-making, and in -- right now, they're in the throes of working out how one -- how that program would roll out an optional screen. We also talked about activities for newborn screening education through the AAP and through NSGC and opportunities we have to get involved and leverage education and training issues there. And we reviewed our current work projects and discussed additional project ideas.

Did I hit on most of the --

(Off-mic speaking)

DR. BETH TARINI: Go ahead.

MS. CATHERINE WICKLUND: You know, we did discuss -- because Ohio is joining us --

DR. BETH TARINI: Oh, yes.

MS. CATHERINE WICKLUND: -- with the opt-in for Krabbe, and Aaron was talking about some of the data that they're collecting about who is choosing to opt out. And so, this will also -- When Beth gets to the matrix --

DR. BETH TARINI: Oh, yeah.

MS. CATHERINE WICKLUND: -- we can talk a little bit more about that, but we felt that maybe this was a good point for us to discuss as a broader group or have some presentation from Aaron and his group, once they have more data, about people choosing to opt in or opt out of Krabbe and the reasons that they're choosing to do so, and some of the ethical issues around that for a broader Committee discussion.

DR. BETH TARINI: Mm-hmm. Thank you. So, our first project is to create a document that provides guidance to providers on how to discuss initial out-of-range newborn screening results with parents. We have discussed this project before with you. Here is our small workgroup, and they are moving it forward under Amy's fearless guidance.

And where we are with this project is that we will utilize existing resources from previous focus groups and best practices for communication. We have -- Some of the -- the time so far has been spent, sort of, figuring out the

best way to disseminate this information, as well as identifying what information pieces we can incorporate into this communication document, and so some of that has been where we've been spending our time. I think, now that a lot of those issues have been settled, we're going to make quick and brisk progress.

So, where we stand now is, once the final -- the document is finalized, we will do two things. One, we'll submit it to ACMG for their committee to review, the ACT Sheet Committee to review, and for approval to be linked to existing ACT sheets, and also identify alternative ways to disseminate this information. For instance, one way that was discussed was to integrate it into the current information packets that the states fax out to providers when an out-of-range result comes through.

So, there's been some -- Some people have had some challenges, sort of, imagining what this might look like, this document, but I -- I had done something similar with CF in Michigan, and

we -- we disseminated that amongst the group to show that we're really talking about a -- a piece of the document that's, sort of, condensed and -- and quite concise about issues to discuss best practice for communication, alternative places to go when you have concerns.

And the other point to reinforce is that this is cross-cutting. These -- this -- this communication are the types of communication you would have, whether or not it's an MCAD out -- or it's out of range suggestive of MCAD and out of range suggested of -- suggestive of another disorder. So, they're, sort of -- there -- there's no need for them to be altered, depending on the disorder type.

The second is the educational outreach project, which is the mapping that Cathy was referring to of educational resources, and this is spearheaded by Jeremy Penn and Cate Walsh Vockley. And the -- the theoretical framework for this project is based on educational curriculum development, which starts with developing a

matrix for relevant stakeholders and topics -- sort of an X-axis and a Y-axis that I'll show you here -- to identify for which stakeholders, which are the most important topics regarding newborn screening.

So, you see stakeholders on the left here. On the column and on the -- or on the rows and on the columns here, you -- to the right, you see the different topics. And so far, internally, the group has made these decisions about which topics are relevant to which stakeholders. The next step is to start to then disseminate and get feedback from stakeholders in each of these groups, solicit feedback, if you will.

And then, we talked about -- you know, this was built on the current newborn screening paradigm, the information needed, and should this be -- could there be potential movement into issues related to the age of molecular medicine? What about return of carrier results? And -- and the recognition of both of those may warrant a broader discussion with the Committee. Other

points on there? Okay.

And so, the next steps would be to continue to refine this framework, as I said, with input from the group, reaching out to the key stakeholders, and then determining how to utilize a framework. Could we apply it to existing educational resources? Could we give it to the -- the programs and other educational organizations to help guide the creation of future documents? This is where the next step will be with the brainstorm.

MS. CATHERINE WICKLUND: Do you want to just talk a little bit about utilizing the summit? Because I thought that --

DR. BETH TARINI: Oh, right.

MS. CATHERINE WICKLUND: Yeah.

DR. BETH TARINI: So, one of the places, for instance, to solicit the feedback will be the Beyond the Blood Spot Summit in early June, because a number of stakeholders, particularly around the state -- right? -- will be there. And so, we've been offered the opportunity to have a

specific breakout table -- Am I correct on that? -- that -- in which this -- would be devoted to looking at this matrix and soliciting feedback from those stakeholders.

MS. CATHERINE WICKLUND: And I would also add that one of the things that Cate added to the stakeholder list was foster parents --

DR. BETH TARINI: Oh, yes.

MS. CATHERINE WICKLUND: -- which came out of a -- direct result out of the testimony -- public --

DR. BETH TARINI: Yes.

MS. CATHERINE WICKLUND: -- comment that we heard yesterday.

DR. BETH TARINI: Excellent. And then, we discussed, within this, using Workgroup members' organizational relationships to encourage submission of educational materials to the clearinghouse. The clearinghouse is, as we know -- relies upon -- relies, to a large degree, upon submission of documents. They do create their own, but, really, the -- the goal is not to

reinvent the wheel. The goal is to sort of -- is to get very useful documents into the clearinghouse, so that the public can access them. Questions?

DR. JOSEPH BOCCHINI: Okay, this is open for questions, comments. Accepted. Well, let's -- We're going to need you to -- bring you up to the microphone. Any questions from the members of the Committee that are on the phone?

(No audible response)

DR. JOSEPH BOCCHINI: All right. K.K., I think there's a -- Yeah.

DR. BETH TARINI: Oh, here, go to mine.

DR. JOSEPH BOCCHINI: Oh, you can use one on -- whatever's closest.

(Off-mic speaking)

DR. JOSEPH BOCCHINI: Press the button.

DR. BETH TARINI: Press it.

(Off-mic speaking)

MS. K.K. LIN: Hi, K.K. Lin. Hi, I just wanted to make a suggestion that the addition of foster parents in consideration be broadened to

foster and adoptive parents.

DR. BETH TARINI: Perfect. So noted.

FEMALE SPEAKER: One of the other content areas we added to it was also the -- potentially the opt-in, because that isn't something, right now, that is really necessarily incorporated into a lot of the educational materials, so whether or not we need to consider having --

DR. BETH TARINI: For the --

FEMALE SPEAKER: -- opt-in conditions as a content area that some stakeholders might need to be aware of, we also discussed --

DR. BETH TARINI: Like Ohio.

FEMALE SPEAKER: -- that, as well.

DR. KATE TULLIS: Yeah, the -- I think, when we talked about foster parents and -- and K.K.'s comment about adoptive parents, we actually looked at the system as opposed to just the -- the foster parents, because --

DR. BETH TARINI: Mm-hmm.

DR. KATE TULLIS: -- they would be interacting with the -- in the case of foster

parents, maybe, children, youth, and families or whatever.

DR. BETH TARINI: Mm-hmm.

DR. KATE TULLIS: So -- so, we have to figure out, what's the right target --

DR. BETH TARINI: Yep.

DR. KATE TULLIS: -- in that area.

DR. JOSEPH BOCCHINI: If there are no other comments, Beth, thank you. Thank you, Cathy.

Next on the agenda is the summary of activities of the Laboratory Standards and Procedures Workgroup, and Kellie Kelm will present this update.

(Off-mic speaking)

DR. KELLIE KELM: Well, thank you very much. So, I'm here representing Susan and all the great people on the -- Do I have this right? I messed it up, didn't I? So, we had a -- a great discussion yesterday. Okay. And here is our current workgroup, although I was just updated to let us know that Dr. McCabe had retired, so we'll

remove him from our -- as an ad hoc expert from our group.

But we had a fantastic discussion yesterday, and we talked somewhat on next-generation sequencing, as well as some preliminary discussion about the data that will be -- the Committee will be hearing about in August, from NewSTEPs, about the labs and meeting the timeliness goals that we had recommended in 2015. And, lastly, we had only, unfortunately, a short period of time for new topics.

And so, just a reminder: We have two charges, and one of them is that we explore the role of next-generation sequencing in newborn screening, and the other one is that we should be reviewing data related to testing and labs meeting our timeliness goals.

So, first, we had a short presentation by Rachel Lee, and she -- her day job is that she works in Texas in the -- the state public health lab, and in her free time, she is now the chair of the APHL Molecular Subcommittee. And so, she

gave us an update on the meeting that they had in February to talk about next-generation sequencing, and once again, I believe that there is going to be a presentation to the larger Committee in August about the meeting. So, we got a little bit of a -- a taste of what's to come.

So, here are some slides, and so the purpose of the meeting was to convene stakeholders to discuss the current states of gene sequencing and newborn screening and identify barriers and solutions for the future. The meeting was in February, in Atlanta, sponsored by APHL in -- in collaboration with CDC and HRSA, and had a number of states and participants, and they -- they crammed many presentations and breakouts in the close-to-2-day meeting that they had. And the meeting had lots of objectives besides just discussing the current status. You can see here that there were a number of things that they looked at and talked about during the 2 days.

So, here are -- many of the common

barriers are identified, although there's a lot more, I believe, that were listed, but these are the main ones. So, barriers are: decision-making, the knowledge barriers and gaps. Costs are always there, and resources. Some of the questions about reporting, of course variance of unknown significance and the consistency, et cetera. IT and bioinformatics is a big barrier and issue in this space. And then, they looked at some lab and follow-up specific barriers.

So, these are some lists -- a small list of the solutions that were discussed. I know we talked about it yesterday, but there were many more potential solutions discussed. But something that I know this committee has heard before that came up again was whether or not, you know, there's a need for regional laboratories, especially for sequencing, the use of peer-to-peer training, training videos, sort of, a call site that's a resource for labs, and lastly, sort of, a clinical variant database with information relevant specifically for newborn screening. And

one of the things that actually was discussed was -- Michael Watson talked a little bit about ClinGen and a project there for one of the LSDs, I believe. Right?

DR. MICHAEL WATSON: Yeah, all the metabolic diseases. We're actually trying to prioritize the genes involved in newborn screening for variant curation so they get cleaned up before we go into pilot studies. So, we're prioritizing the pilots we're moving into.

DR. KELLIE KELM: And so, here's a list of next steps, and so -- and -- and things that -- There was some discussion about whether or not that might be something to work on, so action plans for individual states -- you know, they're hoping to get together and have an evening follow-up session at the symposium coming up in September -- working on a decision-making matrix for states to use if they're considering whether or not to bring on gene sequencing in the state is good for -- a good idea for them or not, working on some training opportunities, and, once

again, the idea about a curation -- a curated database.

So, then, we did have a discussion about -- from -- people from APHL and NewSTEPs on timeliness. So, this was more of an informal update. It wasn't a -- there was no data, no slides, but just sort of a general "Where are we now, and what are we going to be talking about in August?" And so, we had Sikha and Sarah and Careema from APHL and NewSTEPs give us this update.

And so, this is just a reminder. This is our nice slide to remind you of our timeliness goals that the Committee recommended in 2015. And so, we talked a little bit about what they plan to talk about in August, what's happened in the last year or so.

And so, APHL plans to present that timeliness data in our August meeting, and so this will be the data that they've collected from states over the period of 2012 to 2015, from 39 states, and this was the data that was given to

the GAO for them to write the report. APHL would like to give us, sort of, their analysis and their description, showing, for example, how states -- you know, what has happened in those years, that although 2015 was sort of when the recommendations were made, that a number of states were already making improvements in their timeliness.

And so, I -- I do think it's going to be a different interpretation than what the GAO report provided us. I think they're hoping to show us a little bit more recent data. I think they told us yesterday that they had not yet even really gotten into 2016, because they were just getting some of that final data from states from 2016.

So, the take-home message is that states are improving, but they are not meeting the recommendations 95% of the time, which was, sort of, the -- the goal that the Committee stated, which was that states meet the goals 95% of the time by 2017.

So, then, we did hear, also, a -- a snapshot of some of the NewSTEPs 360-funded projects and improvements that 28 states' programs are participating in. And so, it was quite an extensive list. It was -- There were quite a lot of fantastic stories, and I haven't captured them here.

But one of the things that I think we were most excited about was working with other national organizations -- for example March of Dimes, ASTHO, and AMCHP -- to develop a toolkit to help state programs that want to increase their program hours and courier service, to have something to help them, for example: advocate in -- in their state to -- to try to get those resources.

One of the other things that was a message that we heard from multiple workgroup members was that we need to do a better job sharing our success stories publicly, you know, where we're identifying babies early and -- and helping them, and that, also, this is something

to help have our staff that are working all these, you know, longer hours and doing all this work -- to -- to show that their effort is rewarding and really does help the babies in their states.

We did hear that APHL is working on a policy statement on the timeliness goals and that they're hoping to, optimally, publish that white paper in 2017.

So, we only had about 10 minutes to talk about our workgroup and what we could contribute to the cutoffs discussion that we've been having the last 2 meetings, and so this, unfortunately, wound up being a very preliminary brainstorming session, if you will. And we had a couple ideas, but, obviously, our -- our thoughts are, you know, keeping in mind: What is the ultimate goal of this discussion and this work that we can do, and how can we state -- help state programs? We heard that APHL is doing a anonymous survey of state practices in this -- in this -- sort of, the cutoffs and -- and practices, and so that is

ongoing.

So, some of the thoughts that -- that we heard was, for example, could we get data comparing, you know, if you do screening with a, basically, cutoff alone versus cutoffs using other covariates? One other suggestion is to figure out how we can normalize data between labs, and instead of using cutoffs as we do, develop a risk-assessment algorithm that uses analytes and other variables. And this would be similar to the Maternal Serum Health Screening that's -- that is what state -- is what -- not state labs, but labs do, where they use a different kind of a risk-assessment algorithm.

And, lastly, one of the suggestions was to share resources and strategies that are already available now to improve screening algorithms, that we could do a better job communicating and helping -- you know, one state helping another one and -- and sharing some of the strategies that they've used to actually improve the performance of the labs with regards

to false positive and false negatives.

So, I believe that that's it for us. Thank you.

DR. JOSEPH BOCCHINI: Thank you, Kellie. This report is open for discussion/comment. See no Committee members, so we've got Natasha and Carol Greene.

DR. CAROL GREENE: One of my hats is that I work a portion of my time with Ira Lubin in one part of the CDC, and your -- one of your projects, the project on trying to figure out how to handle molecular with networks or experts or resources, that's a larger issue. And I'm -- I don't believe there's a current project, but I know it's an area of interest for them; they're working on it. And I just want to mention that so that that could be included.

There's some significant challenges, if you really want the expertise in a particular disorder, if you want to know there's a -- you know, a new, never-seen-before mutation, so that what's already curated is not going to answer

your question, and you want to know somebody -- talk to somebody who really knows how the -- the -- the molecule works and how that relates to the gene -- Who's going to pay for that person's time? Who's going to make sure that person has a license?

So, there -- there's some interesting challenges that I know ACMG must be working on, but I -- I don't know what, you know, Mike and the team are working on. But I do want to mention that CDC has an active interest in that.

DR. KELLIE KELM: And CDC was one of the main collaborators of the February meeting, as well, so.

MS. NATASHA BONHOMME: Great, thank you. Natasha Bonhomme. Thank you so much for that presentation. I had, I think, two questions. One, like -- now I can't remember exactly how it was phrased on the slide, but when you were talking about cutoffs -- I can't remember, exactly, the language, if it was to what end or what's the goal of that discussion. Was that within the

context of this particular workgroup or within, just, the general newborn screening space in terms of what's the goal of discussing cutoffs?

DR. KELLIE KELM: So, I think -- I think what we meant by that is, we've obviously had presentations, this meeting and the last meeting, with some discussion about the Committee taking a role, and I think that was our question, is, what is the ultimate goal for what the Committee could do when we were asked to sort of think about, what can each workgroup do, you know.

And -- and so, I think -- the Committee, obviously, hasn't figured out what we might do in this space, but I think that was our thoughts. And obviously, it was with regards to what our workgroup could do, but obviously, we had a lot of people from labs. And so, I think, also, it was sort of asking them, what -- what would they want this, you know -- if -- if there is something the Committee does, you know, what could they do to help them?

MS. NATASHA BONHOMME: Okay. Great.

That's really helpful. And I think that's important just to frame, because while, obviously, cutoffs is a lab issue, the discussion is happening in the public, and to really bring that into -- into the discussion somewhere.

And then, secondly, in terms of the activities happening around timeliness, there was the piece about sharing success stories. And I couldn't tell what role the workgroup was going to take in that, but -- if -- if there was a role in that sharing of stories, but if there is -- and I'm not the co-chairs of the Education and Training Workgroup, but potentially, that could be an interesting way, where those two workgroups could partner in some way, because those sharing of stories, definitely, I would think, fall under education and awareness building. So, maybe there's some opportunity there. I don't know how, logistically, that works, but a suggestion.

DR. KELLIE KELM: Mm-hmm. Agreed.

DR. JOSEPH BOCCHINI: Thank you. Other questions? Dr. Matern?

DR. DIETRICH MATERN: Yeah, it's not a question, but something that I noticed, looking at the website, HRSA website, the Committee's website, is -- And we talk a lot, also, on NewSTEPs and everywhere about timeliness and the critical conditions, but I don't see, anywhere, spelled out which those conditions are, except in the SIMD policy statement that you have to find through some major clicking and Googling, because it's not listed in PubMed, either. So, is it something that we can include somewhere? Maybe one could have an asterisk for each of the condition that are currently on the RUSP so that people know which ones those are.

DR. JOSEPH BOCCHINI: Yeah, that's a good comment, or even, maybe, making a specific timeliness page with that information all in one spot, about the recommendations, plus which are the critical conditions.

DR. DIETRICH MATERN: And -- and some of this is actually nuanced, because, for example, Pompe disease -- I think the data from Taiwan is

represented, also, recently at the ACMG meeting, suggests that the treatment needs to start for early infantile Pompe disease within days to weeks. So, that would be a time-critical condition, whereas the later onset, apparently, you have more time. So, to be considered.

DR. KELLIE KELM: Well, and I think the -- the more -- the two recent conditions that were added were not included in that assessment by the Workgroup years ago, so we may also need to discuss how we can have that -- those assessed and if -- if a list would be posted.

DR. JOSEPH BOCCHINI: Yes. I think that's a good comment, to make sure that newly added conditions are looked at to see if they meet the critical -- critical condition criteria. So, I think that's great. So, I think that's great. So, Joan, and then Sue, if you want to come up?

MS. JOAN SCOTT: Yeah, and I'll just follow up, though, that that's a great comment, and, obviously, we don't set what are the -- you know, the critical, and so that requires, you

know, interacting with our, you know, SMID colleagues and other colleagues around what those should be.

DR. SUE BERRY: And so, I'll just comment from the public policy side on SIMD. We have a process ongoing to reassess that list. Obviously, it's a -- it was a one-time effort, but there are more things added to the RUSP, so there's a process by which we'll be annotating or rewriting or reevaluating and then republishing.

That -- I don't know that that means that this committee automatically adopts it, but of course, we see the pressure and the -- and the need to reassess that, as well. So, to let you know, we are actually undertaking that responsibility from the professional side, and we'll certainly keep the Committee updated regarding that.

DR. JOSEPH BOCCHINI: Great. Perfect. Thank you.

DR. KELLIE KELM: Well, and I -- I just wanted to add a comment that outside of the ones

that SMID weighed in on, as part of our work, when we were drafting the report, the members of the -- the group actually reached out to experts that HRSA had used previously for case definitions and other things, and so we got their input on whether or not the other non-metabolic conditions were time critical or not, and so that -- You know, we can talk to Joan about whether or not she wants to post those, since that was work of the Workgroup, on behalf of the Committee, to -- to evaluate the other ones.

DR. JOSEPH BOCCHINI: Thank you. Other comments? Catharine?

DR. CATHARINE RILEY: Just to make one comment: We're also working on updating the Committee's website in general and moving it to a new platform, so we'll see some new -- present -- So, all the information will remain. All the information will remain there, although presented in a new way. And so, this is a -- We were going to take this opportunity to actually update the -- the -- not update the RUSP but update the look

of the RUSP for how the information is presented. So, I think this is a really great time to be able to add some detail and some information, and we'd be happy to share that with the Committee before -- you know, before that goes live on the website.

DR. JOSEPH BOCCHINI: All right. Thank you very much.

FEMALE SPEAKER: All right. Thank you.

DR. JOSEPH BOCCHINI: Next is the update from the Follow-Up and Treatment Workgroup. Dr. Brosco?

DR. JEFFREY BROSCO: Great. Thank you. So, with our co-chairs, Steve McDonough and Chris Kus, who's out of town -- they asked me to do the acting chair job -- and we welcomed four new members. We have a very vibrant group. Debbie Friedenberg, Nancy Leslie, Margie Ream, and Joe Schneider all joined us, and we had a very robust discussion. It was hard to get people to stop at 5:00, but we managed to move on.

There are two main things that our

subgroup is working on: medical foods -- which we talked a lot about in our Committee meeting yesterday -- and quality measures. Just quickly follow up on medical foods: Of course, the report was affirmed yesterday by the Committee, and the workgroup -- the subworkgroup on medical foods feels strongly they want to continue meeting, because they feel like it's a unique group, this is a critical topic, and their -- their next key, concrete outcome will be to do a publication based on the report.

I'm going to talk, just, quickly about quality measures to give a little bit of background, so everyone knows where we are, and then Alan Zuckerman -- right here -- who has been doing great work with the Subworkgroup for the last year, is going to give you an update on what's happened more recently.

So, many of you remember that this has been going on for over a decade -- right? -- since long before I was part of this committee. So, the first publication from this group was led

by Alex Kemper, and the idea of long-term follow-up was based on this idea of four central components: care, coordination, evidence-based treatment, and quality improvement, and the features they identified early on were about quality chronic care disease management, both condition specific and care through the lifespan.

A slightly different cast of characters, but the group continued on with the same central components and -- and added the idea that there were different perspectives, and that there's the state and national perspective, but there's also the provider perspective and the family perspective, and that all of these were important when thinking about quality improvement and long-term follow-up.

Most recently, just this past year, Cynthia Hinton and -- and the group published a framework for assessing these outcomes, and I just want to take a minute to look at this, because it's really remarkable work and really sets the context for our subworkgroup. I'm not

going to go through the details of it, but as you can see, there are clear outcomes that are identified that are seen as critical over the last 10 years, really, and then those primary drivers fit very well into what I just was talking about, the different perspectives. And then, there's these measures and the kinds of broad categories of things we could measure.

In this same paper, the group looked at sickle cell disease and PKU and went through very detailed examples of the kinds of quality measures that could be used to make sure that we're getting appropriate to children and to their families.

So, that led to the most recent effort of our subworkgroup, and back in the spring of last year, with the help of the Committee, they identified that quality measures are still an important thing to follow up on, and here are the tasks that we asked of the Subworkgroup: so, a background document about what's known in quality measures and newborn screening, look at some case

studies, and identify other key findings. So, I'm going to turn this over to Alan to tell you what the group has found.

DR. ALAN ZUCKERMAN: Thank you for this opportunity to share some of our progress on finding a role for clinical quality measures to promote long-term follow-up in newborn screening. We're making a lot of progress in addressing the charge and have reviewed the state of the art of quality measures, which is changing rapidly because of the increased attention to support value-based reimbursement and maintenance of certification, and newborn screening needs to be a part of this.

There are also new standards that are facilitating their use and quality measures are not just the first step in quality improvement, because you can't improve what you can't measure. It's also a pathway to gain new knowledge about what's working and what isn't.

But the use of newborn screening has, really, been very limited because of the

challenges of rare conditions, but the importance of measures have really been well demonstrated in a few conditions, and, particularly, cystic fibrosis and sickle cell disease emerge clearly. Yet, we found a number of substantial gaps and barriers that we need to overcome. We've collected several examples, case studies, that do illustrate value of quality measures, but also illustrate some of the challenges in moving forward to get more people to do this.

At this meeting, in particular, we heard from the AHRQ Pediatric Quality Measures Program, presented by Kamila Mistry, and University of Maryland Study of Primary Care and Long-Term Follow-Up of Newborn Screening by Debbie Badawi, and they both strongly reinforced everything we've been seeing in our general background.

The key issue that we've been hoping to -- to move forward is to use these quality measures to make long-term follow-up of newborn screening a reality, and you've heard about some of the continuity and the definition of long-term

follow-up, and the 2008 paper remains a valid driver today.

We're also starting to learn from conditions not covered by newborn screening, such as asthma and ADHD, that illustrate the roll that measures can play in long-term follow-up of other chronic diseases. A nice feature of these measures is that they limit the asked-for data by asking specific questions. Yet, we're also reminded that long-term follow-up is not just about collecting more data; it's about providing and changing the way we provide care. And so, it's important to find measures that really matter and measures that can have reliable data, and newborn screening, clearly, is beginning to look different from many other clinical fields.

Some of the gaps that we've looked at or the concern that there may be important gaps in evidence when many of our conditions have different subtypes and the best treatment is not always clear for conditions. But we've also seen many generic consensus measures that could be

applied to any newborn screening condition. And cystic fibrosis, in particular, has taught us that measures can be a pathway to gathering evidence.

Developing measures is not easy, especially for rare disorders, for disorders that may have variable onset, and the National Quality Forum Process is extremely difficult; newborn screening validation is costly. In fact, the almost complete lack of any pediatric measures led to a mandate in the Children's Health Insurance Program Reauthorization to launch that pediatric quality measures program we heard about at this meeting.

But having measures doesn't mean much if people aren't using them, and the cost of data collection, the small numbers of patients, single locations, drive the need to integrate quality measures into routine care. Now that we have these measures for sickle cell disease, we need to see if people live up to the expectation that they will see increased use. And we've looked at

some of the models that health departments have used to do long-term follow-up, and many fear that these are going to be very difficult to replicate elsewhere.

We also see an important need to move beyond disease-specific measures and that some of the traditional approaches to quality measurement may fall short for newborn screening, because we need to look at the entire newborn screening system through public health measures, tracking what services are out there, and even extend our domain into transition into adult care. We need child-specific measures that focus on family access to medical homes, available treatment, the child's wellbeing, and the family's satisfaction with the care process. And we're also seeing that data sources often need to move beyond health care providers and typically beyond a single provider.

One approach to making this happen is to try to leverage available resources that could accelerate the use of these measures in newborn

screening, and new tools may be able to make this easier in the future if we take action now to set foundations.

In particular, ONC, CMS, and AHRQ have a very comprehensive electronic clinical quality improvement resource center -- it's on the web at ECQI dot HealthIT dot gov -- that gives access to standards for defining and reporting measures, data models, and access to all the available quality measures and incentive programs. All quality measures are, essentially, ratios, and the NewSTEPs case definitions can help us prepare meaningful denominators, and the NBSTRN LPDR Database can help us define and access data fields, including many core and public health variables.

We feel our subworkgroup has come to a crossroads, where we've completed most of the basic tasks ahead of us, though we still need to finalize a report. We have some background material, we have some important case studies to share with you, and we've developed other

findings about the contrasts between the disease-specific public health and child-specific approaches. We're hoping that we can finalize our report by August 2017, but in addition, over the next few months, we really feel we need more time to work on specific suggestions for next steps and to be able to present these possibilities to your committee. Thank you.

DR. JOSEPH BOCCHINI: Alan, thank you. This is now open for questions, comments, discussion. All right, come on forward, please.

DR. TERESE FINITZO: Terese Finitzo with OZ Systems, and I want to thank both Alan and Jeff for a great meeting yesterday. John Eichwald called getting the NQF approval for EHDI quality measures the NQF lift. When he was able to get approval for hearing screening prior to hospital discharge, a percent -- a proportion of babies who got diagnosis by 3 months and the proportion who got into intervention by 6 months --

What resulted as a result -- what happened as a result of that was that CMS picked

up 1354% of babies screened before hospital discharge, as did Joint Commission. And they used the definitions that John had proposed and that NQF had approved. CMS also picked up a diagnosis of hearing loss by 3 months as one of its child health indicators.

So, yes, I think it was challenging, but what it did was provide some standardization. And the beauty of the NQF measures is that it -- it -- it isn't a one-time thing. John had to apply, get them approved. One wasn't accepted, and he's -- and we've had to continue to show, are they collectable?

So, CDC is continually looking at this, and so it's an ideal way, I think, for us to think of broader than just EHDI into newborn blood spot screening and into CCHD screening. What are the critical questions? Because NQF supports this continuous quality improvement. And so, I think it's something that -- that the Committee could consider. Thank you.

DR. JOSEPH BOCCHINI: Thank you. Other

questions, comments?

(No audible response)

DR. JOSEPH BOCCHINI: Well, thank you for the work that you're doing. I think we're coming close to --

DR. JEFFREY BROSCO: To finishing up?

DR. JOSEPH BOCCHINI: Hopefully all --

DR. JEFFREY BROSCO: It's going to be the last, because no one has any more energy. Just two last statements. I think what you just provided is a great example, where quality measures are being implemented, and -- whether it's the plan level, Medicaid, hospital level, and it's really critical for this group to make sure that those measures include newborn screening conditions. So, it was a great example.

And secondly, I really want to thank Alan. He's done a -- a huge amount of work this past year in leading this subworkgroup. So, I wanted to make sure he's recognized for that. Thank you.

DR. JOSEPH BOCCHINI: Yes. Oh --

DR. JEFFREY BROSCO: And Steve -- Steve, you still on the phone?

(No audible response)

DR. JEFFREY BROSCO: Well, we'll thank you in absentia for -- for your work in -- in leading this workgroup for the past year. And longer, probably.

DR. STEPHEN MCDONOUGH: Yes, I'm still on the phone.

DR. JEFFREY BROSCO: Oh. Well, thank you, then, Steve.

DR. JOSEPH BOCCHINI: Yes, I don't know if you heard that comment, Steve, but, clearly, you were recognized for the work that you did to put these two tasks through the Workgroup. And so, thank you. Thank you, Alan, for all the work that you're doing. Clearly, significant amount of effort being made to -- to bring us to the conclusion and -- and -- and some very specific guidance.

Any other questions or comments?

(No audible response)

DR. JOSEPH BOCCHINI: Okay. Thank you. So, thanks for the -- the work of each of the workgroups, and I'll add my welcome to all of the new members of each of the workgroups, and look forward to your continued participation in -- in making the efforts of these workgroups successful.

The last item on the agenda is consideration of any new business that Committee members or others wish to bring forward for us to be considering in the future. I know we have the ongoing issue that we have not yet addressed of -- of conditions that are on the RUSP, to find a way for us to consider review of those conditions in case there's an issue related to removal from the RUSP, and that's something that we certainly want to plan for in the future.

Are there any other issues that Committee members or others have thought of, either through the discussions from today's meeting, yesterday's meeting, or from other sources? Kate?

DR. KATE TULLIS: During the Education

and Training Subcommittee meeting, we talked about issues related to return of results and carrier screening, and I think it would be really valuable to bring that to the group at large and -- and have some ongoing discussions.

DR. JOSEPH BOCCHINI: Thank you. Don?

DR. DON BAILEY: Thank you. I've also brought this up before, but just as -- since this is my last opportunity to say this -- So, I do hope that the Committee will continue to think broadly about the benefit of newborn screening, and especially thinking about benefit to families as something we ought to be taking into consideration.

And I think, in -- in the past, when we've talked about families, a lot of it has been about the harms, like, you know, if we're going to -- You know, is -- Are -- Are the false positives creating anxiety, or are there other harms? And -- and if we're going to talk about harms for families, we have to balance that with benefits. You can't just talk about one without

bringing in the other.

And so, my own feeling is that there are measurable, quantifiable benefits, and they go beyond reproductive risk information, which I know is important to many families but also challenging, in -- in many ways, to think about. There's lots of other benefits. And I would just like for the Committee to -- to think about how to -- whether and how to incorporate family consequences -- benefits and risks -- into the equation as we move forward.

DR. JOSEPH BOCCHINI: Thank you. Carol?

DR. CAROL GREENE: Thank you. Some time ago, there was a look at heritable conditions -- I think it was led by the Education Committee -- looking at heritable conditions that are not picked up by newborn screen, and it's -- there's so much work to do in newborn screening that some of us feel that we're -- don't spend a lot of time thinking about people with, you know, Down syndrome, neurofibromatosis, all the other heritable conditions that kids have, and -- and

really focus on newborn screening. Another one, of course, Duchenne's fragile X -- lots of work being done there, and -- and we only look at the newborn screening side of things.

And I'm just hoping that, at some point, the Committee can, you know -- recognizing that there's a great deal of work that needs to be done on newborn screening and always will be, as it's a moving target -- but there are other folks out there for whom this committee was originally designed.

DR. JOSEPH BOCCHINI: Yeah, thanks, and that actually is another thing that the Education and Training Committee did -- did look at, and -- and the issues that came up were really related to what public health role there might be for that. And -- and that certainly needs to be looked at, again, over time.

So, Natasha, and then -- Well, we'll let Natasha, and then if you'll come up and come to the microphone, please.

MS. NATASHA BONHOMME: Great. Thank you.

I think this was touched on a little bit, but just to make it more official -- I think, kind of, what's happening in Ohio and in -- was it Georgia? -- is really important in terms of thinking about conditions that are kind of being added, but not, but there, but you opt in, but -- You know, all that is not going to -- You know, I'm -- I'm very interested in seeing what is actually going to end up being on that state's brochure and how that's going to be communicated out.

And while, yes, you -- on the one hand, we could say, "Well, it's just two states," there are lots of things that start off just in one state, just in two states, and then all of a sudden, it's -- it's really happening.

So, I don't necessarily know exactly how that discussion would be structured, but I think at least starting that sooner, rather than later, would be important, because it has a lot of consequences throughout the entire system of newborn screening and beyond.

DR. JOSEPH BOCCHINI: Okay, that's a good -- good point. Thank you.

Please state your name and (off-mic speaking).

DR. MARGIE REAM: Okay. I'm Margie Ream. I'm a neurologist at Nationwide Children's in Columbus, and so I first got involved in our local screening program when Krabbe was mandated to be added to our state screen.

And so, kind of a follow-up on what she said and what the Education, kind of, Group may consider is that as states add optional screening, I think that states would benefit from clarification or guidance in what the informed consent process should look like for those diseases that can be opted out of. I know it's something we struggled with in Ohio, and I don't know that we've really arrived at a good answer to that question, but it certainly comes up.

DR. JOSEPH BOCCHINI: Thank you. That's a very important comment.

Any other issues to be brought forward?

(No audible response)

DR. JOSEPH BOCCHINI: Anybody on the phone with any -- any questions or comments?

(No audible response)

DR. JOSEPH BOCCHINI: All right. If not, I think that will conclude the business of the meeting. I think one thing that the Committee members will receive very shortly is the -- we're working on the Annual Report to Congress, which the Committee will need to review and then bring back with its feedback.

And then as you know, you'll get a draft of the medical foods white paper. That will come very shortly. That'll go to the Committee, plus the Workgroup members, and -- and -- for feedback. We'll want a quick turnaround on that so that we can move that forward as quickly as possible.

And then, look and watch -- We'll -- we'll be looking for members for the Committee for the 2018 cycle, so there -- there'll be a number of things that will be available to the

Committee to the -- and to the public related to the workings of the Committee.

So, I want to thank everybody for what I think was really a productive meeting. Thank all of you who presented. I want to thank HRSA, Catharine, for all the organization that went into making this happen, our -- our speakers, and -- and those of you who commented from the org reps and those of you who participated in the workgroup sessions. I think they've all been very helpful to the workgroup and -- to the Committee and contribute to its -- its activities.

So, thank you all very much. We'll see you in August. There any other comments?

(No audible response)

DR. JOSEPH BOCCHINI: If not, that'll conclude the meeting. Thank you all very much.

(Applause)

(Whereupon, the above-entitled matter was concluded.)