The Advisory Committee on Heritable Disorders in Newborns and Children

Day One

HRSA Meeting

Washington, D.C.

August 03, 2017

9:30 a.m. - 5:00 p.m.

OLENDER REPORTING, INC.
1100 Connecticut Avenue NW, #810, Washington, DC 20036
Washington: 202-898-1108 • Baltimore: 410-752-3376
Toll Free: 888-445-3376

A P P E A R A N C E S

COMMITTEE MEMBERS:

JOSEPH BOCCHINI, JR., MD, Committee Chair, Professor and Chairman, Department of Pediatrics, Louisiana State University

MEI WANG BAKER, MD, Professor of Pediatrics, University of Wisconsin School of Medicine and Public Health, Co-Director, Newborn Screening Laboratory, Wisconsin State Laboratory of Hygiene

JEFFREY P. BROSCO, MD, PhD, Chair, Follow-Up and Treatment Workgroup, Professor of Clinical Pediatrics, University of Miami School of Medicine

CARLA CUTHBERT, PhD, FACMG, FCCMG, Chief, Newborn Screening Molecular Biology Branch, Centers for Disease Control and Prevention

SCOTT GROSSE, PhD, Alternate, Research Economist, Office of the Director, National Center on Birth Defects and Developmental Disabilities,

CDC
KELLIE B. KELM, PhD, Food and Drug Administration, Chair, Laboratory Standards and Procedures Workgroup
FRED LOREY, PhD, Genetic Disease Screening Program, California Department of Public Health (Emeritus), International Society for Neonatal Screening, North American Council Representative
MICHAEL LU, MD, MS, MPH, Health Resources and Services Administration, Associate Administrator, Maternal and Child Health Bureau
DIETRICH MATERN, MD, PhD, Professor of Laboratory Medicine, Medical Genetics and Pediatrics, Mayo Clinic
KAMILA B. MISTRY, PhD, MPH, Agency for Healthcare Research and Quality, Senior Advisor, Child Health and Quality Improvement
MELISSA PARISI, MD, PhD, Chief, Intellectual and Developmental Disabilities Branch, NICHD, NIH
ANNAMARIE SAARINEN, Co-Founder, CEO, Newborn Foundation

JOAN SCOTT, MS, CGC, Health Resources and Services Administration, Acting Director, Maternal and Child Health Bureau
BETH TARINI, MD, MS, FAAP, Associate Professor and Division Director, General Pediatrics & Adolescent Medicine, University of Iowa Hospitals & Clinics
CATHERINE A. L. WICKLUND, MS, CGC, Chair, Education and Training Workgroup, Northwestern University

ACTING DESIGNATED FEDERAL OFFICIAL:
CATHARINE RILEY, PhD, MPH, Health Resources and Services Administration, Maternal and Child Health Bureau

ORGANIZATIONAL REPRESENTATIVES:
NATASHA BONHOMME, Chief Strategy Officer, Genetic Alliance
SIOBHAN DOLAN, MD, MPH, March of Dimes, Professor and Vice Chair for Research, Department of Obstetrics & Gynecology and Women's Health,

Albert Einstein College of Medicine
CAROL GREENE, MD, Society for Inherited Metabolic Disorders
ADAM KANIS, MD, PhD, Department of Defense
CHRISTOPHER KUS, MD, MPH, Association of State and Territorial Health Officials
ROBERT OSTRANDER, MD, American Academy of Family Physicians
BRITTON RINK, MD, American College of Obstetricians and Gynecologists
SUSAN TANKSLEY, PhD, Association of Public Health Laboratories
KATE TULLIS, PhD, Association of Maternal & Child Health Programs
CATE WALSH VOCKLEY, MS, CGCS, National Society of Genetic Counselors
MICHAEL WATSON, PhD, FACMG, American College of Medical Genetics and Genomics

OTHERS:
SABRA ANCKNER, Nurse Consultant
DON BAILEY, PhD, MD, Distinguished Fellow,

Early Childhood Development, RTI International
SUE BERRY, MD, Director, Division of Genetics and Metabolism, Department of Pediatrics, University of Minneapolis
DIANA W. BIANCHI, MD, National Institutes of Health, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development
COLLEEN A. BOYLE, PhD, MS, Agency for Healthcare Research and Quality, Director, National Center on Birth Defects and Developmental Disabilities
MICHELE CAGGANA, ScD, FACMG, Director, Newborn Screening Program, New York State Department of Health
CATHY CAMP
THOMAS CRAWFORD, MD, The Johns Hopkins Hospital
TERESE FINITZO, PhD, OZ Systems
DEBBY FREDENBERG
AMY GAVIGLIO, Follow-up Supervisor/Genetic Counselor, Minnesota Department of Health Newborn Screening Program

AARON GOLDENBERG, PhD, MPH, Institute for Computational Biology
NANCY GREEN
JOYCE HOOKER
JILL JARECKI, PhD, Chief Scientific Officer, Cure SMA
CAROL JOHNSON, Iowa Newborn Screening Program, University of Iowa, Department of Pediatrics
ALEX R. KEMPER, MD, MPH, MS, Evidence Review Workgroup, Nationwide Children's Hospital, Ohio State University College of Medicine
ANNIE KENNEDY, Parent Project Muscular Dystrophy
K.K. LAM
MEGAN LENZ, Cure SMA
MICHELE LLOYD-PURYEAR, MD, PhD, Parent Project Muscular Dystrophy
STEPHEN MCDONOUGH, MD, Retired Pediatrician
AMY MEDINA
AMELIA MULFORD
MATT OSTER, MD, MPH, Pediatric Cardiologist, Sibley Heart Center at Children's Health Care of Atlanta

JEREMY PENN
MARJORIE REAM, MD, PhD, Nationwide Children's Hospital
PIERO RINALDO, MD, PhD, Professor of Laboratory Medicine; Division of Laboratory Genetics; Director, Biochemical Genetics Laboratory, Department of Laboratory Medicine And Pathology, Mayo Clinic
JERRY ROBINSON
DEBI SARKAR
DEBRA SCHAEFER, Caregiver for child with SMA
JOE SCHNEIDER, Pediatrician
SCOTT SHONE, PhD, Program Manager, New Jersey Department of Health Newborn Screening Laboratory
TORREY SMITH, Parent of child with CHD
KRISTIN STEPHENSON, Muscular Dystrophy Association
DEAN SUHR, MLD Foundation
JOHN D. THOMPSON, PhD, MPH, MPA, Director, Washington State Newborn Screening Program
KIM TUMINELLO, Association for Creatine

Deficiencies

JESSICA WADE

HEIDI WALLS

CAREEMA YUSUF, MPH, NewSTEPs, Manager, Association of Public Health Laboratories

ALAN ZUCKERMAN, MD, Georgetown University Hospital

C O N T E N T S

DAY 1

P R O C E E D I N G S

DR. JOSEPH A. BOCCHINI, JR.: Good morning, everyone. I'd like to welcome you to the August meeting of the Advisory Committee on Heritable Disorders in Newborns and Children. So, I want to thank you all for being here.

I want to just make a couple of announcements first. Dr. Robert Saul, the organizational representative from the American Academy of Pediatrics, needed to step down from his position, so AAP will be assigning a new org rep, and so AAP does not have a representative at this meeting. But I want to thank Dr. Saul for his work on the committee and the Education -- the workgroup.

I also want to mention that the three new members of the committee have not completed their clearance at the present time, and as a result, we've asked one of the former committee members to extend his term. Dr. Fred Lorey has agreed to extend his term, so he will extend for up to 6

months while we wait for the clearance of the next members.

So, that brings us to roll call. So, first, the Agency for Health Care Research and Quality, Kamila Mistry?

DR. KAMILA MISTRY: Here.

DR. JOSEPH A. BOCCHINI, JR.: Mei Baker?

DR. MEI WANG BAKER: Here.

DR. JOSEPH A. BOCCHINI, JR.: I'm here. Jeff Brosco?

DR. JEFFREY P. BROSCO: Here.

DR. JOSEPH A. BOCCHINI, JR.: Centers for Disease Control and Prevention, Carla Cuthbert, and Scott Grosse as an alternate? Carla?

DR. CARLA CUTHBERT: Carla's here.

DR. JOSEPH A. BOCCHINI, JR.: Food and Drug Administration, Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH A. BOCCHINI, JR.: Health Resources and Services Administration, Michael Lu?

DR. MICHAEL LU: Here.

DR. JOSEPH A. BOCCHINI, JR.: And alternate Joan Scott?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Fred Lorey will be here by webcast. Fred?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Still coming to the phone. Dieter Matern?

DR. DIETRICH MATERN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Representing National Institute of Health, Melissa Parisi?

DR. MELISSA PARISI: Here.

DR. JOSEPH A. BOCCHINI, JR.: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Beth Tarini by webcast?

DR. BETH TARINI: Here.

DR. JOSEPH A. BOCCHINI, JR.: Cathy Wicklund?

DR. CATHERINE A. L. WICKLUND: Here.

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

DR. CATHARINE RILEY: Here.

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

DR. ROBERT OSTRANDER: Here.

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

DR. MIKE WATSON: Here.

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

DR. BRITTON RINK: Here.

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

DR. KATE TULLIS: Here.

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

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH A. BOCCHINI, JR.: Association of State and Territorial Health Officials, Chris Kus by webcast?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Department of Defense, Adam Kanis by webcast?

DR. ADAM KANIS: Here.

DR. JOSEPH A. BOCCHINI, JR.: Genetic Alliance, Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. JOSEPH A. BOCCHINI, JR.: March of Dimes, Siobhan Doyle?

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH A. BOCCHINI, JR.: National Society of Genetic Counselors, Cate Walsh Vockley by webcast?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: And Society for Inherited Metabolic Disorders, Carol Green?

DR. CAROL GREEN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. So, next on the agenda is the approval of the

minutes of our May meeting. The committee received a draft of the minutes prior to the meeting. Several members submitted small changes; they were word changes in the -- in the draft. The revised version was sent to the committee. We have minor edits, now, from Annamarie to add with regard to the section covering Ms. Gaviglio's presentation.

Are there any other additions or corrections to be made to the minutes?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Hearing none, I will accept a motion to approve.

FEMALE SPEAKER: Motion to approve.

DR. JOSEPH A. BOCCHINI, JR.: All right, second?

DR. DIETRICH MATERN: Second.

DR. JOSEPH A. BOCCHINI, JR.: All right. So, we will then vote on the approval of the minutes. So, Mei Baker?

DR. MEI WANG BAKER: Approve.

DR. JOSEPH A. BOCCHINI, JR.: I approve.

Carla Cuthbert?

DR. CARLA CUTHBERT: I approve.

DR. JOSEPH A. BOCCHINI, JR.: Jeff Brosco?

DR. JEFFREY P. BROSCO: Approve.

DR. JOSEPH A. BOCCHINI, JR.: Kellie Kelm?

DR. KELLIE KELM: Approve.

DR. JOSEPH A. BOCCHINI, JR.: Fred, if you've made it to the line?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Okay. Michael Lu?

DR. MICHAEL LU: Approve.

DR. JOSEPH A. BOCCHINI, JR.: Dieter Matern?

DR. DIETRICH MATERN: Approve.

DR. JOSEPH A. BOCCHINI, JR.: Kamila Mistry?

DR. KAMILA MISTRY: Approve.

DR. JOSEPH A. BOCCHINI, JR.: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Approve.

DR. JOSEPH A. BOCCHINI, JR.: Melissa Parisi?

DR. MELISSA PARISI: Approve.

DR. JOSEPH A. BOCCHINI, JR.: Beth Tarini?

DR. BETH TARINI: Approve.

DR. JOSEPH A. BOCCHINI, JR.: And Catherine Wicklund?

MS. CATHERINE A. L. WICKLUND: Approve.

DR. JOSEPH A. BOCCHINI, JR.: So, the minutes are approved, with the changes sent by members of the committee.

So, just a reminder: This is our third meeting of this year. Our last meeting of this year will be November 08th and 09th. The next two meetings, as you can see, in February and May, have been -- are listed here -- February 08 and 09, May 10 and 11, but the meeting dates have been set up through 2020 so that you can plan ahead and -- and -- on your schedules, and they can be found on the committee's website.

I wanted to provide a brief update on the medical foods whitepaper that was -- was done. The -- medical foods is not on the agenda for this meeting. We did complete the topic in the May meeting. The committee accepted the report, and we have now gone through some iterations of editing, and final edits have now -- are -- are in process of going back to the four primary authors. They should get those shortly, and once they've looked at those and approved them or made changes based on them, that will be the final copy, which will then go back to the committee and the members of the workgroup. And once approved, we will send a letter -- cover letter to the secretary in support of the -- of what is in the document, as well as, we are working to determine where to publish this -- this whitepaper.

So, next item: meeting topics. Just to give you an overview of what we're going to see at this meeting: We're going to have the first report from the Evidence Review Group on SMA, and

then we'll follow that with a report from the Follow-Up and Treatment Workgroup on what they've been working on, a significant -- a significant effort looking at quality measures in newborn screening to promote long-term follow-up. We'll then have a presentation of further information about establishing and revising newborn screening cutoffs and screening algorithms. We're going to have a report from APHL state survey and then a brief discussion on where we are and -- and next steps for that process.

On Friday, we're going to have a presentation on the overview of newborn screening technology. The workgroups, which will have met this afternoon, will then give us updates on their activities and information that they want to bring forward to the committee for input and feedback. And then, we'll hear the second part of our presentations on -- this is focused on clinical and public health implications of critical congenital heart defects newborn screening. This is the second portion of the

presentations that we started at our May meeting.

So, now I'd like to turn this over to Dr. Catharine Riley. Dr. Riley is our acting designated federal official for today's meeting. She is the lead for the Newborn Screening/Genetic Services branch at HRSA and will be -- will be serving as the designated federal official for our committee today and tomorrow. Catharine?

DR. CATHARINE RILEY: Thank you, Dr. Bocchini. Before I get started, I just want to let you know: I did receive word Fred Lorey is on the line, so do we want to add him? Fred, if you could give us confirmation?

DR. FRED LOREY: Yes, can you hear me?

DR. JOSEPH A. BOCCHINI, JR.: Yes, we can. Thank you, Fred. Welcome.

DR. FRED LOREY: Thank you.

DR. CATHARINE RILEY: Great. And Cate Walsh Vockley is also on the line but is not able to participate right now. But she is on the line, listening.

DR. JOSEPH A. BOCCHINI, JR.: Okay.

Welcome.

DR. CATHARINE RILEY: Great. Well, good morning, and -- and welcome, everyone. Just a -- a few notes: The advisory committee's legislative authority is found in the Newborn Screening Saves Lives Reauthorization Act of 2014. This legislation established the committee and provided the duties and scope of work for the committee.

However, all committee activities are governed by the Federal Advisory Committee Act, or FACA, which sets the standards for establishment, utilization, and management of all federal advisory committees. As a committee member of a federal advisory committee, you are subject to the rules and regulations for special government employees.

So, I have some standard reminders to the committee that I just wanted to go over. I wanted to remind the committee members that, as a committee, we are advisory to the Secretary of Health and Human Services, not to Congress. For

anyone associated with the committee or due to your membership on the committee, if you receive inquiries about the committee, please let Dr. Bocchini or I know prior to committing to an interview.

I also must remind committee members that you do need to 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 as soon as possible so we can make a determination.

So, according to FACA, all committee meetings are open to the public. If the public wish to participate in the discussion, the procedures for doing so are published in the

Federal Register and are announced at the opening of the meeting. For this meeting, in the Federal Register we said that there would be a public comment period, so we'll have public comment later today. Only with advanced approval of the chair or DFO, public participants may -- may ask questions or provide comments at the discretion of the chair.

Public participants may also submit written statements. Public -- they can do this through the online registration format, and all written statements are provided to the committee members ahead of time.

If -- Does anyone have any questions from the committee?

(No audible response)

DR. CATHARINE RILEY: Okay. Just some general housekeeping, then: For those in the building -- So, visitors only have access to the fifth floor of the building. That's this -- the pavilion, which is the room we're in, the cafeteria, restrooms, and meeting rooms for those

workgroups later on this afternoon. All other areas of the facility are restricted and do require an escort, which is a HRSA staff member, and there is no exceptions to this. If you do need to leave and reenter, you will be required to go through security screening again, and you'll -- you will need an escort from security to bring you back in the building.

The -- the lunchtime has changed slightly, so please refer to the final agenda for the break for lunch. But, again, you'll have access to this area. If you need -- if you're going to need to leave and reenter, please notify a HRSA staff member or someone at the registration table so we can accommodate that.

So, without further ado, I'll turn it back over to you, Dr. Bocchini.

DR. JOSEPH A. BOCCHINI, JR.: Okay. Thank you, Catharine. So, just as a reminder, when -- when you speak or make a comment, please make sure that you turn on your microphone, and then, when you're done, turn it off. And then, when you

speak, please announce your name so that it can be recorded.

So, the first item on the agenda is an update on the SMA -- SMA Evidence Review presentation -- (Microphone interference) That's not going to work.

(Laughter)

(Off-the-record discussion)

DR. JOSEPH A. BOCCHINI, JR.: I want to make everybody aware that Dr. Kemper is the -- is the lead on the Evidence Review Workgroup, and he has just changed his academic location. He has taken on the position of division chief of ambulatory pediatrics at Nationwide Children's Hospital and is serving as professor of pediatrics at the Ohio State University College of Medicine.

And without further ado, I'll turn it over to Dr. Kemper.

DR. ALEX R. KEMPER: Thank you very much. I think I'm now required, also, to say: Go, Buckeyes. So, with that out of the way --

I would like, before I launch into the presentation, also really acknowledge all the great work K.K. Lam has done on this project, especially during the chaos of my change of academic affiliation. So, I really wanted to publicly recognize that.

So, as I go through this very first presentation from our group on screening for SMA, or spinal muscular atrophy, there -- there are certain things I just want you to think about and -- and pay attention, things that we've really tried to highlight in here.

So, one of the main things is the methods, how we're going about doing this, especially within the time frame that's allotted for the work. We are going to provide just a little bit of a discussion of the condition itself and then also focus more deeply on issues related to screening. And we just recently had an expert panel call related to screening.

And so, there's not going to be much in this presentation today about treatment, and

that's because we're still going through the process of reviewing the evidence related to that, but as you will see, screening is really going to be a -- a lynchpin, an important part of the work that's going to happen as part of the evidence review. So, there we go.

I'd like to, again, acknowledge and thank members of our Evidence Review Group. I won't read through the list of names, but I'll just leave it here for a second and thank them for their contributions to the presentation today.

Okay. So, this slide just outlines how we're going to go about completing things within the 9 months allocated to the project. You'll see the -- on the right-hand side, where it says SER, that's the systematic evidence review. DA's the decision analysis; that's where we model what would be expected if -- if newborn screening were implemented. And then, the -- the third column was the public health system impact.

And then, you can see how we've broken things into phases. Again, we're in Phase 1 right

now, where we're fleshing out our methods and reviewing the data. And, again, I'm going to be talking about that, of course. And then, Phase 2 is going to be, obviously, building on top of Phase 2, and that'll be presented at the next meeting. And then, finally, at the February meeting, that's when, you know, we'll reveal the end of the movie, so to speak.

So, let's talk a little bit about SMA. As you all know and it was presented as part of the nomination process, SMA's an autosomal recessive disease affecting the motor neurons in the spinal cord and the brainstem, resulting in progressive weakness and atrophy. As with, I -- I think, all the conditions that we end up looking at, it has a -- a broad phenotypic spectrum, ranging in onset in -- at -- at, really, birth and early infancy to adulthood, and I'll talk about ways that you can separate out these different types, and as you'd expected, there's also variations in severity in clinical course.

In terms of how common the condition is,

depending upon how you like to think about denominators, it's -- it's somewhere between 1 and 6,000 to -- to 1 and 11,000, we think, based on the epidemiologic studies that have been done. Or the way I like to think about it, because I think it's easier, is, somewhere between, like, 9 and 16 per a hundred thousand newborns. Based on the literature that's out there, the carrier frequency is somewhere between 1 in 40 to 1 in 60 individuals. So, again, not unlike many of the conditions that we look at, where there's a relatively high carrier frequency relative to the incidence of the actual condition.

So, this slide outlines different -- the different nomenclature for SMA, the clinical course effective with it, and what's known about the gene that's affected. So, we're -- and I'm going to show you this on the -- on the next slide, but really going to be focusing on SMAs type 1, 2, 3, and 4. I mean, these are really the -- the kinds of things that are targeted by screening. These are -- develop as a result of

problems with the SMN1 gene. Again, I'm going to be talking about this in a little bit.

And you can see that if you look at the numbers following SMA type, they -- they're progressive in terms of the age of onset, with SMA type 0 really beginning in -- in -- you know, prenatally, with presentations at birth, to type 1 being the -- the type that we most think about when we think about newborn screening for SMA. These are the -- the newborns that are severely affected. And then, type 2 and type 3 and type 4 progressively go out in terms of older age.

There are also other conditions that are labeled with SMA that aren't really in the -- in the same category in that they're not caused by mutations in the SMN1 gene. So, these include X-linked SMA, SMA-LED, and adult-onset SMA. And I've listed out the genes that lead to these particular conditions. Again, we're going to be focusing on SMN1, and in -- in a minute, I'm going to also talk to you about how SMN2 -- the SMN2 gene plays into this whole thing.

So, just to be clear: The -- the focus of our review and the focus of our work are on the conditions that are -- are caused by problems with the SMN1 gene, because these are the things that are targeted in the newborn screening for the condition, and it's also the thing that -- that -- that the treatment targets, as well.

So, SMA, as I said, is caused by lack of the SMN1 gene product, that there -- there's typically a loss of a particular exon, so none of the -- the protein that's encoded by SMN1 gets made.

There is another gene, named SMN2, that you -- you can have a variable number of copies of the gene -- again, I'm going to be showing this in another slide -- but the -- the more functioning copies of SMN2 that you have, the more protected you are in terms of SMA and developing it late, and it's also, sort of, the hook into where the pharmacotherapy for SMN1 -- or for SMA comes into play. Okay? Everybody with me so far?

(No audible response)

DR. ALEX R. KEMPER: Yes? Okay. So, as is typical when we begin the process of evidence review, we need to develop a case definition so that we, you know, can understand what we're looking for and ask sensible questions. So, again, we're looking for the particular type of SMA that's caused by the lack of the SMN1 gene product. This is located on the long arm of the fifth chromosome. Again, I talked about Types 1 through 4.

Nearly all cases of -- of SMA are caused by a deletion or a -- a new gene conversion mutation of SMN1, the survival motor neuron 1 gene, actually. I don't think I named it before, but that's -- that's what it is before, but -- in exon 7.

Less common is, you can have point mutations in the -- the gene, and you can end up with compound heterozygotes that -- that lead to problems with the -- with SMN1, but -- And, again, I'm going to be digging into this as we go

through, but most of what we're really talking about is this loss of exon 7. And I talked to you a little bit ago about how there's a variable number of SMN2 genes, up to 8, that -- that correlates with phenotype.

So, the -- the typical way that newborn screening is done is, it's looking for a homozygous deletion of this exon 7 in the SMN1 gene, and the main way to do this is through quantitative real-time PCR off of, you know, our good friend, the dried blood spot. And you can confirm this by looking for an exon 7 deletion.

Now, tied directly to this, and, sort of, depending upon where you do it in the -- in the newborn screening process might vary from state to state, but it's looking at the number of copies of the SMN2 gene you have, because the more copies of that you have, the -- you know, the later the onset of the condition.

So, we're fortunate, in this case, that there are data from two pilot evaluations of newborn screening for SMA, so in New York State -

- and we had a call with the New York State folk -- I would say it was last week. Everything's, like, sort of blurring together with me because of my move, but it was very recently. And I'm going to dig through how their pilot study works, but they've screened over 6,000 newborns, and they have already identified 1 case. And there's also a newborn screening program in Taiwan that's screened a substantially larger number of newborns, a little over 120,000. Again, I'm going to be talking about that -- their experience in a little bit.

Diagnosis -- I sort of alluded to this before, but it's basically looking for exon 7 deletions, looking at the SMN2 copy number, and, of course, correlating that with the clinical exam.

The treatment for it, nusinersen, was FDA approved in December of 2016. There's some other therapies that are, you know, in development, but -- but as of today, nusinersen is really the -- the -- the treatment, and it's delivered

intrathecally. We can talk a little bit more about that, but again, we haven't dug into treatment effectiveness yet.

And of course, as with any other complex chronic disease, there's -- you know, supportive therapies are -- are important. So, I don't want to overlook that, but for the sake of, I think, what the advisory committee is going to decide at the end of the day, it's going to be around how well early administration of nusinersen works. Okay, everybody with me?

(No audible response)

DR. ALEX R. KEMPER: Okay. So, we are well into the systematic evidence review process. There's really nothing different that -- that we're doing here than -- than what we've done in previous reviews. We're looking at PubMed, EMBASE, CINAHL, and Cochrane. We cast a wide net -- you can see keywords that we've used there -- and we're in the process of figuring out, you know, which -- which articles are in and which articles are out for data abstraction. I think --

and I'm going to look at K.K. to see if she agrees with me. She's nodding her head, and I haven't even said it yet, but a thousand or so articles, I think, are going to move up to the full text review process. Does that sound good?

(Off-mic speaking)

DR. ALEX R. KEMPER: Twelve oh two, okay.

(Off-mic speaking)

DR. ALEX R. KEMPER: A little more than a thousand.

This is the conceptual framework that we used when we put together the report and think about the key questions that we're going to use. We -- we've just -- when I say "we," again, I have to really thank K.K., who has a much better eye for this kind of stuff than I do, but we -- we've redone the conceptual framework in a way that, I think, sort of telegraphs better what we're trying to do, which is compare what would happen under usual clinical case detection, usual clinical care, to newborn screening.

And you can see that there is a time

shaded in -- in the pink -- I think that's what would call that, pink -- whatever that light color is, before symptom onset with clinical detection/usual care. Diagnosis doesn't really even begin until after symptoms have developed. Of course, with newborn screening, you can begin to do the diagnostic and confirmation process before the development of symptom onset and perhaps, with treatment, even delay symptom onset, which is why the -- you know, there's that asymmetry in -- in the -- in the pink.

And of course, we're going to be looking at things like the accuracy of screening, the process of diagnostic and confirmation, the -- the harms associated with all those things, what goes on with treatment and follow-up and how those modify outcomes, and then the, sort of, outer blue thing shows that all this exists within the health care system, and we're going to be looking primarily through the Public Health Systems Impact Assessment about that sort of wraparound piece. Any questions about that before

I move on?

(No audible response)

DR. ALEX R. KEMPER: Does look kind of pretty, don't you think? So, again, this is no different than what we've done before with the key topic areas that are guiding the evidence review, so looking at the epidemiology of the condition and what -- what's happening now in terms of how affected individuals are identified, looking at screening, process of short-term follow-up, the benefits and harms of screening and diagnosis separate from what happens with treatment, looking at treatments and long-term follow-up care, the outcomes, the benefits and harms of treatment and long-term follow-up care under newborn screening so we can, you know, contrast those things, and then look at the public health and health care systems' impacts.

So, you can see that this is, really, just repeats of what we were able to show with the figure before. Again, this is really the same kind of stuff that we usually look at, but I just

wanted to be clear about the direction that we're going.

So, let's switch gears again and talk about what's going on with SMA newborn screening. So, as I mentioned, New York has been offering SMA screening, but it's -- it's interesting because it's done within the context of -- of a research study, in -- in that parents have to consent for their children to be tested. Missouri has legislative approval, but they've not begun doing that yet, and then there are states that are kind of circling around and considering SMA screening: Massachusetts, North Carolina, and Wisconsin. Of course, there may be other states that are considering this that we just don't know about, but -- but these are the ones that -- that we've heard about thus far.

And then, the CDC is developing material for states to be able to test how well their screening test works and, you know, all the usual, sort of, proficiency materials for the SMA, which is, you know, really important as

other states -- if they decide to adopt screening.

So, I'm going to drill down a little bit more into what's happened into -- in -- in New York. So, the New York screening's happening in three hospitals. This is a project that's funded by Biogen, with the PI being Dr. Wendy Chung. I -- you know, because of this, you know, potential conflict of interest with -- you know, since Biogen also makes nusinersen -- asked very specifically about whether or not they were able to fully share their data, and the -- and the answer to that was, yes.

The -- the project now funds a technician to do the screening, consumables, coordinators to help with recruitment and that sort of thing, and the time spent by a genetic counselor. As I mentioned before, there's a recruitment process that involves electronic consent, and interesting: Nearly all the -- all the -- the parents -- 93% of the mothers approached have agreed to participate across the 3 sites.

Now, before I start showing you more data, there is a publication that's in press right now with Genetics in Medicine, so the people in New York were -- were very open about allowing us to share these data. But to the degree that, you know, you can, you know, be respectful of the fact that they're sharing their data with us before the publication comes out, I -- I think, would be appreciated by everyone.

I'm very sensitive to this, because in terms of our evidence review process, it would really put a crimp on things if people weren't -- didn't -- didn't feel comfortable about sharing their data with us before it appeared in the peer review literature. So, again, to all those people in New York, thank you very much for doing that, and -- and, again, be -- be respectful of the data that I'm about to show you.

So, the goal of the pilot study was, really, to demonstrate whether or not parents would accept the screening and the feasibility of screening for SMA. But fortunately for all of us

-- or, perhaps, unfortunately, I guess, for -- for the child -- they did identify one baby with SMA. They used dried blood spots with DNA amplification, again, looking for SMN1.

Before beginning this, they went through a validation process with de-identified blood spots. I -- I've listed here -- before -- again, I want to make sure that it looped back with the -- in the -- the New York program to make sure that -- that I've outlined it. You know, we -- typically, we talk about Tier 1 and Tier 2 screening -- so, you know, the initial screening and then, sort of, more confirmatory or, you know, kind of trying to, you know, separate out the -- the false positives from the -- from the true positives -- but this kind of tier nomenclature is -- is somewhat artificial.

But they -- they begin with looking for a homozygous SMN1 exon deletion with real-time quantitative PCR with a TaqMan probe. Don't ask me anything too technical about that. I'll have to defer to someone else. And then, as a -- as a

second tier, they look at SMN2 copy numbers. So, the copy number is important, as I mentioned before, for issues related to the phenotype, and then they do some more work around the -- making sure that -- that there is, you know, this missing exon 7. And all this work happens within a laboratory that -- that New York has designated for -- for this.

So, this is kind of a busy slide, so I apologize in advance, but really just goes through what I talked about before in terms of the Tier 1, Tier 2, and then issues of short-term follow-up. So, again, with SMA, you're going to have zero copies of the SMN1 gene, where you're missing that exon 7.

And then, you can go and look at how much of the SMN2 gene you have. So, if you have two copies of it, you're likely to go on to have type 1 SMA. If you have 3 to 4, then you're going to be type 2 or type 3 SMA. Again, remember, later onset, slightly different severity. And then, if you have between 4 and 8 copies, then you're

going to have type 4 SMA. It's funny, I lean on this podium, and it moves around a little bit.

And you can see that, you know, based on that, they either, you know, continue with confirmatory testing and referral to a neuromuscular specialty treatment center or, you know, in the case of carriers, with follow-up for genetic counselors. Again, this issue of what to do about carriers that are identified through newborn screening is not unique to SMA but does create challenges, because there are a lot of carriers out there.

So, I presented before about how most of the parents agreed to participate. Of the about 6,200 newborns screened, there was one affected child who did have 2 copies of SMN2 so likely has SMA type 1 and has gone on with treatment with nusinersen, and then they've identified 92 carriers. There have been no false positives.

Now, in terms of false negatives -- and this goes back to the -- the publication that's in press, as well -- you'd expect that there'd be

some false negatives just because, again, the -- the testing is really looking for this missing exon 7. If you have some other, you know, like, compound heterozygous for certain point mutations that could lead to problems with the production of the SMN1 gene product, then -- then you might go on to develop SMA.

So, we're -- right now, I don't want to comment more on how many false negatives might actually occur, because that's really something that we're going to dig out of the evidence review process. So, you know, this was mentioned in the paper. Other people have said that the false negative rate is likely to be lower. Again, this is just something that we're going to have to sort out as we go through the evidence.

Now, in terms of that one baby that was identified with SMA, that child, remarkably, was -- was followed back up at the clinic at 7 days of life and began treatment at 15 days. That baby, at least by report, is now 12 months old and is asymptomatic and is meeting developmental

milestones appropriately. Again, this is what we were told during the call, and we'll dig into other publications about outcomes of treatment later. But at least based on that one baby, it's -- it's certainly different than what you'd expect with the natural history of SMA type 1.

So, you know, there -- I'm sensitive to time, as well, now that I look up. But there -- there have been lots of lessons around the pilot test, so low false-positive rates. They're able to do this with -- in a high through-put method. We have questions that I'd mentioned to you before, about sensitivity, you know, that we're going to dig into in terms of figuring out how many babies might be missed. The carrier rate is, you know, potentially going to represent a problem.

The testing can be multiplexed with SCID screening. We were told that it's a relatively straightforward procedure, at least in theory, and they're in the process of validating that now. And so, clearly, if this can be multiplexed

with the SCID screening that's already going on, that really lowers the potential, you know, amount of work that is put on the newborn screening programs.

And so, the -- the thinking is that if you already have SCID -- if you already have SCID screening -- that's a hard one to say -- that -- that this should be a -- a highly scalable thing. And, again, we're going to dig more into literature and find out, you know, more specific details about this, but at least based on the interview we had with the New York screening program, they -- they felt very comfortable with that.

So, again, in the interest of time, I'm just going to highlight the fact that -- that in addition to the New York State pilot, there's also the work that's going on in Taiwan, which is, you know, fairly similar in terms of using real-time PCR, and then there's another test, developed by PerkinElmer, that's in development.

So, one of the questions that -- that,

you know, I know comes up when we talk to -- to newborn screening programs is whether or not, you know, it's -- it's considered to be a laboratory-developed test, because that has certain implications for their ability to -- to implement it, and it does seem that -- that across the board, it is. And so, there -- there's a lot of similarity across these three different approaches. So, again, the key thing is detecting the -- the exon 7 in SMN1, and then looking at the SMN2 copy number, which is predictive of phenotype.

You know, again, there are going to be issues -- and we're going to dig through this as we talk with our technical expert panel and look at the literature that's out there -- but in terms of exactly how you do things in terms of a single-tier screen, where you just look at -- at that missing SMN1 gene versus, you know, the degree that the newborn screening programs involved in looking at SMN2. I think it's going to be variable, and we need to learn more about,

you know, how much is involved with that process. And, again, I mentioned problems with carrier status detection.

So, again, I'm just going to hold on this slide so you can look at it, comparing the New York State pilot to the work that's done in Taiwan to the PerkinElmer test that's in development. Again, the -- the number is between -- again, the New York State pilot project, the numbers were small, but, you know, they -- they did identify one case, and as with the -- the Taiwan program, they, you know, demonstrate that you -- you do end up picking a lot of carriers.

There is an algorithm for the diagnosis of SMA. This was a consensus statement out from 2007, and it really just follows along with what I've said before, so. I'm happy to answer questions if -- Dr. Riley?

DR. CATHARINE RILEY: I just want to let you know, we have some extra time, so if you, you know --

DR. ALEX R. KEMPER: Oh.

DR. CATHARINE RILEY: Yeah.

DR. ALEX R. KEMPER: Yeah. Never tell me we have extra time. Then I'll feel like the --

(Laughter)

DR. CATHARINE RILEY: So, no, yeah, please --

DR. ALEX R. KEMPER: Yeah. Okay. So -- Thank you, though. If that's the case, too, let me just pause for a second, because I've gone through a lot of stuff. Does the committee have any particular questions as I move along, or -- or does this make sense?

DR. MELISSA PARISI: Alex, this is Melissa Parisi. I -- maybe I missed your comments about this -- this, but did the Taiwan pilot identify carriers, or did they deliberately choose not to identify them?

DR. ALEX R. KEMPER: Yeah. You know, I'm -- That's a really good question. The -- I think that the way they did it, they just didn't -- as -- as long as you had any -- and I'm going to look at K.K., who's going to, like, rescue me, as

well, but I think as long as you had any functioning SMN1, that they didn't identify -- they didn't report out carriers. Is that -- Am I saying that right?

(Off-mic speaking)

DR. ALEX R. KEMPER: Yeah.

(Off-mic speaking)

DR. ALEX R. KEMPER: Yeah. And my --

(Off-mic speaking)

DR. CATHARINE RILEY: Dr. Kemper, can you repeat that for those that --

DR. ALEX R. KEMPER: Yeah, yeah, yeah. So -- Let me just say that. So, the -- the -- the paper describing the Taiwan pilot study literally just came out, like, a week ago. It was my read of it -- and, again, we haven't spoken to anybody there, but that will be in our process -- is that they had a method where they didn't report out carriers, so as long as you had -- again, I'm, you know, not a lab person, but as long as you had SMN1, that they were considered not to be affected, and so that wasn't reported out. That

was, probably, like, poorly technically said, but that was, like, my reading of it.

(Off-mic speaking)

DR. ALEX R. KEMPER: Yeah, come up -- come up and join me at the -- the podium. Just don't lean on it. It moves around. And then, while -- while she's coming up, there was another question, as well. Yeah.

MS. CATHERINE A. L. WICKLUND: Mine's quick, I think. Do you have any idea, like, in the state of New York, how many women are getting offered SMA carrier testing from a prenatal standpoint?

DR. ALEX R. KEMPER: Oh, I have no idea, no idea.

MS. CATHERINE A. L. WICKLUND: Okay.

DR. MEI WANG BAKER: Also, I have a question regarding the Taiwan data. So, seven -- did you know what type all of them? Because --

DR. ALEX R. KEMPER: I'm sorry --

DR. MEI WANG BAKER: The type. So, you have a 7 out of a 120,000, so they're type 1, 2,

3, or 4?

DR. ALEX R. KEMPER: Oh, oh. You know, I don't actually --

DR. K.K. LAM: There -- there's more information in the paper. Again, we just didn't -- we didn't include it here because this was jammed, but it's in the Jan et al 2017. It just came out this month -- or, well, July. I can follow back up. I have it, actually, sitting right on my computer.

And just a quick update: I was just informed by someone, I'm sure, much more knowledgeable that the Taiwan study -- The screening method, apparently, did detect carrier status, but they -- like, it was not -- the method itself was not blinded to carrier status, but they chose not to report, so.

DR. MEI WANG BAKER: So, the reason I ask: I think it's very relevant to newborn screening, because I think type 4 still debate in terms of that whatever come to the clinic attention, so I think we need to know that.

And second part, for the technical part, in terms of carrier risk status, actually, quite a bit of discussion in our state. I think when you do the real-time PCR, if you choose -- like, you just quiet. If for SMN1, no signal unless it's a homozygous. Now, you don't to assess how much there that you were in the position. You really don't know it's the carrier or not. This what are we, perhaps, likely choose to do is different than a hemoglobin, because human pattern, you know, in front of you. You know exactly what it is. But for the SMA, you can trust not to know.

DR. ALEX R. KEMPER: Anything else?

DR. JOSEPH A. BOCCHINI, JR.: So, Carol?

DR. CAROL GREEN: Carol Green, SIMD. I'm thinking, if I'm not being naive, that the false negative rate is also going to change depending upon whether you report heterozygous, because from your very nice description, some of the other variant forms have one mutation in SMN -- or -- or have one deleted and some other

mutation, and --

DR. ALEX R. KEMPER: Correct.

DR. CAROL GREEN: -- if those go to neurologic evaluation, they could be picked up. So, I think that method affects not just the genetic counseling downstream but also the false negative rate.

DR. ALEX R. KEMPER: That -- that's exactly my understanding, and we really need to -- we just haven't been able to dig into that part yet, but I -- I think that, you know, given that there's probably, like, 5% or -- of -- or so of individuals with SMA that fall into that group, that's something that we're going to have to sort out.

Okay. So, again, I'm -- I'm not going to repeat that because we just did that. So, treatment is with -- This -- For whoever goes next, be careful when you lean against this thing, because it goes up and down. But nusinersen was FDA approved in December of 2016. This is the first disease-modifying therapy for

SMA. It's an antisense oligonucleotide drug which alters SMN2, allowing more SMN protein to be produced.

And the thinking -- and again, we while we haven't gotten there yet on -- on therapy, is that -- that the earlier intervention, the -- the better, because once you've lost the -- the neurons, you've lost the neurons. So, that's the argument for early intervention with therapies like nusinersen.

And again, we talked before about the clinical care, and I won't go through there. I do want to say that there are other therapies that are in development, including gene replacement therapy and some other targeted therapy that alter SMN2. So, lots of really very interesting things that are out there.

One of the things we're going to be doing shortly is holding our first technical expert panel call. So, we've already had one call related to screening. Again, how well screening works really dictates so much of the work that we

do. We wanted to really frontload things with screening instead of what we've done in the past by, you know, just sort of marching through the epidemiology first.

So, these are the individuals that have agreed to participate in our technical expert panel. So, it includes a wide array of experts in the condition. We also have Dr. Jarecki, who is the chief scientific officer for Cure SMA and also helped put together the nomination package, and then others. I -- I won't read their names.

One of the things that -- that I think is very important, as well, is that we have a -- a mother of a child affected with SMA who will be participating in the technical expert panel call. I think that's -- that's important to make sure that we really, you know, have a holistic sense of the condition to guide our review process.

So, our next steps are going to be convening the technical expert panel, marching through with our systematic evidence review, working on the decision analysis and the Public

Health System Impact Assessment. Again, these are things that we've done in the past, and I won't review the -- the details unless you want to discuss them more.

This, again, is just our -- our -- our -- our timing, and you can see where we've moved into -- and my guess is, you all probably don't care too much about the particular timeline as long as we actually get it done, so I won't belabor that point and just open things up to any other questions you might have.

You know, I should have mentioned earlier, as well, that we have two liaisons from the advisory committee who will be helping us out. They include Dr. Matern and Dr. Tarini. I'm putting it up in the air because she's on the -- the webinar, I believe. So, with that, I'd like to open things up to any other questions.

DR. JOSEPH A. BOCCHINI, JR.: Thank you, Alex. I think for the committee -- (Audio interference) This is going to be -- this is going to be a problem, or maybe this will work.

So, for the committee, this is an opportunity to give feedback to Alex about where they are and whether there are any issues or thoughts that anybody on the committee has in terms of areas that they need to be considering that are not being considered at the present time or other feedback for Alex and the workgroup at this point. Dieter and then Cathy.

DR. DIETRICH MATERN: Alex, I'm glad that you've got so much done already in such short time and -- given your move. My biggest concern at this point is really the carrier rate, as I indicated before. With New York, I guess it's not such a big problem because everyone has been consented, so they knew this might be a possible outcome. So, I think it will be important to find some evidence how -- how this is being received by families right now with -- when they are consented, whether there are any concerns with some of those that are still surprised or how this could be addressed.

I'm not so concerned about the potential

false negative rate, even if it's 5%. I know we don't like, in newborn screening, anything that is not a hundred percent, but on the other hand, if you're transparent and make it public that you will miss cases, I think that it's something we will have to live with if we decided to screen for it.

DR. JOSEPH A. BOCCHINI, JR.: Cathy and then Jeff.

DR. JEFFREY P. BROSCO: Oh, I was going to ask if I could ask if I could follow up on what -- what Dieter just said.

DR. JOSEPH A. BOCCHINI, JR.: Okay.

DR. JEFFREY P. BROSCO: So, in -- in particular -- it may not be in this particular group when they looked at carriers, but how did carriers respond to the information would be helpful. So, I don't know if it's asking too much to look beyond SMA, but to the degree that there's evidence out there about how carriers in general respond to the information, that would be really helpful in this case, because I'm not sure

that in the New York study, they specifically followed up on carriers and how they received the news.

DR. ALEX R. KEMPER: Yeah. I mean, that's certainly something that we can ask the New York folk. I want to be careful, just because we have such a constricted timeline, of promising a bigger report on carriers, but I mean, you all are experts in this, as well, so hopefully you'll be able to bring some of that to bear.

MS. CATHERINE A. L. WICKLUND: Cathy Wicklund, and I -- this, I know, is probably outside the scope, but I guess one of my concerns is, again, the repetitive nature of prenatal screening for something like this. You know, SMA is -- I'd be interested to know, again, like, how many people are really getting offered SMA carrier screening. It's one of the ones that is more typically offered in a prenatal setting.

And then, also, we're, like, now potentially adding it to the newborn screen, which is not unusual. Sickle-cell, it's the same

way. CF is the same way. And it's happening a lot. So, I -- I'm just wanting to, like, I guess, make a comment on the repetitiveness of what we're doing and the cost involved in multiple --

DR. ALEX R. KEMPER: Yeah.

MS. CATHERINE A. L. WICKLUND: -- you know --

DR. ALEX R. KEMPER: I mean, you -- you bring up -- I mean, I'm -- I'm sensitive to this in our -- in our evaluation side of things, because the yields of newborn screening is going to be strongly affected by prenatal detection.

I mean, certainly, Scott Grosse has done a lot of work on what happens in communities where, you know, babies are picked up, while they're, you know, in -- in utero, with a congenital heart defect on, you know, what happens with newborn screening for congenital heart disease. So, beyond -- beyond the, sort of, you know -- you know, potential duplication of effort and that kind of thing, the expected outcomes are going to vary based on whether or

not fetuses are identified ahead of time or parents know about their carrier status.

So, I -- I -- I think you're exactly on target. I think that that question is really important in terms of understanding the benefit of the screening. That being said, I -- we can look and see what we can find, but I doubt we're going to find anything.

MS. CATHERINE A. L. WICKLUND: I agree. I think it's -- it's just something that, especially when you're, kind of, talking about carriers, we could be already identifying a lot of people who know they're a carrier --

DR. ALEX R. KEMPER: Right. And those are, like --

MS. CATHERINE A. L. WICKLUND: -- or -- or there's not --

DR. ALEX R. KEMPER: Yeah.

MS. CATHERINE A. L. WICKLUND: -- or they don't choose to actually, you know, test their partner; some don't. And then, we're -- Like, how do we deal with that -- that -- and, again, in

the newborn screening phase.

DR. ALEX R. KEMPER: Yeah. I'm -- I'm with you.

DR. K.K. LAM: And -- and just to comment, anecdotally, at least, just purely anecdotally. We don't know the numbers at this point, but some of the comments back from the New York folks said that -- that their -- the folks who were identified as carriers were -- many of them -- many were aware. Yes. And --

DR. ALEX R. KEMPER: I forgot that they said that, yeah.

DR. K.K. LAM: Yes.

DR. ALEX R. KEMPER: They did mention that.

FEMALE SPEAKER: That's K.K. Lam talking, so.

DR. ALEX R. KEMPER: Yeah, that is the world-famous K.K. Lam.

FEMALE SPEAKER: Yeah.

DR. ALEX R. KEMPER: We want to make sure that's in the minutes.

(Laughter)

DR. JOSEPH A. BOCCHINI, JR.: Okay. So, first we have Dr. Baker, and then we have Beth Tarini on the line, and then Carol Green. And --

DR. MEI WANG BAKER: I just want to emphasize --

DR. JOSEPH A. BOCCHINI, JR.: -- Siobhan, Mike.

DR. MEI WANG BAKER: Oh, sorry. I just want to emphasize: When you do the evidence review, I think it's terribly important, the type. You -- you -- we need that, because this is the first time we're able to, from a screening point of view -- The reason is, type 4, if we use clinical phase -- because this is not a very common, but because you don't genetic testing, if they're not have symptom, they'll never come to the clinical attention. I think it's very important for the program to prepare. And especially the newborn screening program, if we choose only to report SMN1, then the family need to know. I think it's terribly important.

And also, in terms of carrier -- And look the -- the errors when you provide. Sounds like some program mentioned -- in New York, after SMN1, quote, unquote, carrier, they will do the sequencing. If that sequencing at their -- Can they be in a position to do more beyond this deletion?

So, this -- I feel, in that group, the chance have a heterozygous -- another mutate, because 5% is one deletion, and a heterozygous would another one could be potentially another thing. It's like Carol was talking about a carrier. The -- the sensitivity can change. If you only report genetic counseling without a clinical assessment, I'm not so sure you can change the sensitive range.

DR. JOSEPH A. BOCCHINI, JR.: Beth, on the phone?

DR. BETH TARINI: Yes. Beth Tarini. So, I just wanted to comment on the false negatives. I also had a question. My first -- Two questions. The first was, what's the comparative rate for

other disorders, and the second was a follow-up on Dieter's comment that this is something that we're going to have to live with, which may very well be possible outcome.

But I want to put forth the consideration that the goal of screening is always, primarily, to minimize missed cases. That's why the sensitivity is always given special emphasis. And if we are going to, as a group, accept 10%, then we may be -- and I don't know the answer, because I need the answer to the first question -- we may be changing our standards. And if we are going to accept a higher false negative rate, the question I have is: for what gain?

And I think this is something that we need to explicitly discuss at the next meeting, because this can become a slippery slope. If we accept 10, do we accept 15? Do we accept 20? And if -- if this matters, then we need the false negative rate for everyone, all the disorders pending and all the disorders existing.

DR. ALEX R. KEMPER: So, can -- can I

just comment on that? So, Beth, I -- I -- I understand your anxiety about missing cases, as well, but I think back --

DR. BETH TARINI: Well, I don't have anxiety; it's not personal.

DR. ALEX R. KEMPER: Well, I -- no, no, no, no. Well --

DR. BETH TARINI: (Off-mic speaking).

DR. ALEX R. KEMPER: -- intellectual -- How about intellectual anxiety? Well, I mean, none of us want to miss cases, right?

DR. BETH TARINI: (Off-mic speaking)

DR. ALEX R. KEMPER: I think all of us have anxiety about missing cases, but -- but -- but that being said, you know, there's some conditions where you -- I -- I -- I think, again, back to CCHD newborn screening, where, you know, not every affected baby is going to be picked up. So, I think that there's, you know, this issue of balance of overall benefit and harm. So, if it turns out that you can pick up most cases, and by early identification, you lead to, you know,

significant benefit for those babies that are detected, then even if you're missing some cases, then -- then maybe that's okay.

So, I -- I mean, I certainly can't compare, especially within the constrained time frame that we have, the false negative rate for SMA against a bunch of other conditions, but -- and I -- I may be stepping outside of what we're allowed to do in terms of evidence review, but one of the things that we will be able to produce for you is expected number of cases picked up, and then, from that, you can estimate what the overall net benefit would be. So, I -- I -- Hopefully, that'll help.

DR. BETH TARINI: No, I think that you are correct in showing the balance of benefits versus harm, and I think that is the next step. Do we expect a benefit balance to outweigh the missed, and what do we get for the risk of the missed?

I also want to clarify that I'm not anxious; it's not a personal issue. Simply asking

a question is raising a point of question. It's not a point of personal anxiety.

DR. JOSEPH A. BOCCHINI, JR.: Mei?

DR. MEI WANG BAKER: Okay. Yeah, I want to make some comments on that, too. So, I think -- I would think this -- this issue is the screening sensitivity, because the -- in term, you cannot detect all the case, and not because the assay problem. It's because you choose the deletion of a type if you not choose.

So, I think -- My opinion is, it's acceptable. You just need to settle the expectation at the beginning. Understand that the limitation. If we talk about a CF, the sensitivity is at 96% overall experience. The reasoning is, these RT. If the mutation doesn't affect your pancreas function and you will not use RT, no matter what you do.

So, I think -- CF -- Well, everybody accept this sensitivity. That's -- I don't think it's because the assay perform. Then we have to be very careful in term slow, slow. That's my 2

cents.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. Next, we have Carol Green, then Dr. Doyle, Dr. Watson.

DR. CAROL GREEN: Carol Green, SIMD. The discussion of the false negative is going to be fascinating, and it needs to be -- I -- I would like just to add to what Dr. Baker said. It needs to be looked at in context, and it has to do with the disease definition. We've never picked up all the homocystinurias. We pick up homocystinuria due to cystathionine synthase deficiency, because the other ones have low methionine, and our method is looking for high methionine.

And it has implications for what the neurologist and the pediatrician and everybody understands. The -- if we decided that we needed to pick up every heart defect, and screening for cyanotic heart defect picks up those which are cyanotic, we might not be picking up babies who need help now if we decided that we couldn't screen for cyanotic heart defect because we

weren't going to pick up coarced.

So, if you set your definition and then you pick up the cases so you can have an argument about whether you only look for deletions or whether you have to be able to sequence the whole gene, but if what you're looking for is SMA due to the deletions, then you have to just go with your definitions.

We've always -- we've never picked up all the hemoglobinopathies. We're -- we're looking for specific hemoglobins. And the reason I originally raised my hand is, on the issue of carriers, there's lots and lots and lots and lots in the context of newborn screening because of the hemoglobinopathies. And there are -- there's a lot written on it, and there are states that have decided not to disclose carrier status, and there are states that do disclose. And so, I think there's a lot already on that, and I have a feeling that's when you raised your hand, as well.

DR. SIOBHAN DOLAN: This is Siobhan

Dolan. I just wanted to comment on the prenatal aspect. So, spinal muscular atrophy has a sort of interesting history, because for several years, there were conflicting guidelines for obstetricians. The American College of OB/GYN said that it was really rather complicated and challenging for obstetricians to screen routinely, so unless they had a setting where they could provide the post-test counseling, it wasn't, sort of, required, or it wasn't considered in the standard versus American College of Medical Genetics, who said, based on carrier frequency, we should be screening for it. So, this has been several years in the -- in the practice setting, and so obstetricians had to figure out how to deal with it.

Most recently, in March 2017, just several months ago, new guidelines came out suggesting that -- this is from the American College of OB/GYN -- suggesting that spinal muscular atrophy, along with cystic fibrosis, fragile X, and the hemoglobinopathies, should be

offered to every pregnant woman. It's incredibly challenging for the general obstetrician to do that with the attendant counseling required for the different inheritance patterns of those conditions and the requirement for partners and so forth.

At the same time, and specifically in the New York area, the whole idea of panethnic or expanded carrier screening panels has really risen dramatically. It's accessible; the insurers are paying now. So, a lot of obstetricians have just said: This is really complicated. I'm just going to go to expanded carrier screening. When I find something, I'll refer to genetics. So, you have, sort of, a bunch of different, conflicting things happening at once.

What I'll tell you from the patient perspective is, when we start these long discussions -- because I do see the patients in genetics -- the carrier issue, basically what they want to know is kind of a -- what pregnant women and couples want to know is like a

dichotomous outcome: Do I need to worry or not? And all our discussion about copy number and all this stuff, like, really just goes right, sort of, over -- around people's heads. Despite their effort to try to understand it, it's just overwhelming.

So, I think what happens, or the risk I see, potentially, is, when we do all this prenatal counseling, get the partner in, assess the risk for particular diseases, and end up saying, bottom line: Don't need to worry. Not a -- I mean, we'll give a residual risk, but it's going to be low, and we'll try to reassure the -- the patient and the couple.

Now when it comes back up in newborn screening, is it something to worry about or not? Did we have the right father of the baby? Is the, you know, testing -- was it actually accurate? Did all this happen?

So, we have a risk of both patients being overly concerned, again, in the newborn screening period about something that they already thought

they dealt with or ignoring what happens in the newborn screening period because they feel like, "I already dealt with this."

So, it's pretty tricky terrain, and SMA has been a really conflicted issue for years. Hopefully we're moving in the right direction, but patients are going to come into newborn screening with a lot of history potentially.

DR. ALEX R. KEMPER: Can I ask you a odd question, Dr. Dolan? Are there any data -- I know you where it says -- Are there any data about the percentage of pregnant women that are getting screened for SMA, getting carrier screening?

DR. SIOBHAN DOLAN: I'm not aware of any data, but it's -- it's been a place where conflicting guidelines were noted, and that has changed in March, and it takes a while to change practice patterns. So, I'd say, it's a moving target right now, and we -- we -- you know, we really don't know. So, even if one were to collect data right now, I think it -- it would be changing.

And like I said, this, sort of, sense of overwhelmed for the obstetricians to be able to do all this counseling is really opening the door for the expanded carrier screening panels, which there's -- there's some interest there in looking at the utility of that and the cost effectiveness of that. But I'll tell you, as a solution to a logistical issue, it's really gaining a lot of traction. So, I think -- I think, but I don't have data on this, we'll see that be the solution.

DR. JOSEPH A. BOCCHINI, JR.: So, we have Mike and then Carol Green again.

DR. MICHAEL WATSON: So, I would -- This is not my question, but I bet it'll end up around 30% will have carrier screening, because that's, sort of, where CF seems to have leveled off and as they go to expand it, it'll probably be similar.

But my question is about, when you get to your step 8 on evaluating the public health care system and the -- and the other health -- the --

the other health care, quote, system, how do you -- what do you look at in the health care system itself? And we have huge capacity problems now for just running newborn screening pilots first.

And then, X-ALD, in the state of California -- The providers there are saying, "We just can't absorb another screening test," because the X-ALD carriers are burying the -- the -- the workforce.

So, when you look at the health care system part of the problem, I know most of what you -- you've talked about in the past has been, sort of, public health system capacity, which not always has the health care system piece. I mean, it sort of says, yes, there is a system, and we can get people into it, but then do you look at the capacity of that side of the system for these kind of things?

DR. ALEX R. KEMPER: Yeah, you're -- you're -- you're talking right in terms of this limitation of the scope of the work that we have. We certainly -- We -- we simply, within the --

the time period allotted to do these reviews, we can't look at, you know, what the system that's in place outside of newborn screening to provide the care --

I mean, we can -- You know, we're going to look at the, you know, case reports and those kinds of things about, you know, children with SMA who are diagnosed and, you know, like, you know, they're -- obviously, they're getting diagnosed and treating that kind of thing. But we simply don't have the resources, nor the time, to be able to drill into what the availability is in the -- on the clinical side outside of the newborn screening programs. So, that's something that, I mean, you all are just going to have to use your expertise to -- to fill in that gap.

DR. JOSEPH A. BOCCHINI, JR.: Carol, I'm going to give you last question or comment.

DR. CAROL GREEN: Just putting together what Dr. Watson said and what Dr. Dolan said, and the -- and also knowledge that even with CF screening, we have experienced finding babies

with CF on the newborn screen where the family says, "But I was screened, and I'm not a carrier."

So, it -- it -- it's painful, and if you've only got 30% being screened, even if it goes up as people get more and more coverage and -- and, you know, screening just -- carrier screening becomes more common, and the paternity, I -- I think that the understanding of the prenatal screening is going to impact our understanding of the economics of the newborn screening, but it shouldn't change the fact that we would need newborn screening to find the affected babies.

DR. JOSEPH A. BOCCHINI, JR.: Before we close this session, are there any questions or comments from the individuals who are on the phone?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Hearing none, thank you, Alex, for bringing us up to date. I will echo Dieter's initial comment about

how much has been done in a short period of time, so thank you. As everyone knows, this is the first condition that we are looking at within the -- the -- our -- our requirement to look at each new condition in a 9-month time frame once it's accepted by the committee and goes to the Evidence Review Workgroup. So, thank you for keeping us on track.

DR. ALEX R. KEMPER: Thank you, and, again, thank you to -- to Dr. Lin for keeping the trains moving.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. So, next on the agenda is a presentation on the quality measures project. This is in the Follow-Up and Treatment Workgroup. Dr. Brosco is serving as chair of that workgroup, and Dr. Alan Zuckerman, who has been heading this effort and has been the -- the lead on putting together the data and working through the issues with the workgroup and then with feedback from the committee.

As the colleagues present -- as our

colleagues present this report, I'd like the committee to be thinking about what we've learned through this effort and what the committee would think, going forward, the workgroup and the committee might take from this, and then plan to address relative to the findings. So, with that, I'll turn it over to Jeff.

DR. JEFFREY P. BROSCO: Thank you, Dr. Bocchini. So, as you just heard, we're going to spend, maybe, 15 minutes or so letting you know what our workgroup has done and then having, we hope, an extended discussion to get some ideas of where to move next, and then this afternoon, we'll -- we'll dig into your suggestions.

So, this is the clinical quality measures part of things. So, why are quality measures so important? Why does this matter? So, one of the first things is understanding that quality measures are understood as a very technical term. They're standardized, quantitative assessment tools, and there's an evidence base that suggests that if you give penicillin to a child with

sickle-cell disease, they have better long -- out-term -- long-term outcomes. And so, there's a reason why we want to follow it. It's typically a ratio, and you can track this progress over time: How well are we doing?

You can also look at health outcomes. You can also look at attitudes. There are lots of different measures that you can look at when you're talking about quality measures. And they're becoming a critical part of a learning health care system. So, almost all of us are involved in quality improvement, quality assurance activities.

It's also being built into clinical decision-making. It's part of our EMRs. It's part of maintenance and certification for professionals at all levels, and it's really becoming a critical part of how people get paid at the individual provider level and even at the managed-care organization level.

And -- Well, the key point I want everyone to understand here is, if you have the

wrong measures, it can really be bad. And right now, there are a lot of measures that are out there that don't necessarily reflect what families care about, what patients care about, what we as providers do, and just because they're available, sometimes we use them. So, this is really a critical topic for how our kids do in the long term.

Just to remind everyone: This is something, the long-term follow-up, that we as a committee have been interested in for -- for years, and it goes back to the original paper that -- that Alex Kemper did, when we first started talking about, what are the things we need to look at in long-term follow-up. And you can see here the essential components and the key -- the key features. And they're, sort of, the core of what we want to look at for how the children identified in newborn screening do in the long run.

This was followed up by the next part of what this committee has been doing over the last

decade, and that is looking at what specific questions should we ask about long-term follow-up. And, again, the idea of care coordination, evidence-based treatment, and quality improvement are central to this in looking at different levels. And what this group did, led by Cynthia Hinton, was look at the different levels at which long-term follow-up makes sense, the different perspectives.

And then, most recently, out of our advisory committee came a framework for assessing these outcomes, again, led by Cynthia Hinton. And this is the framework that I presented back in May, for those of you who were here, and if you look, it really lays out a -- a very nice structure for understanding what we want to look at for long-term outcomes.

So, on the far left, you can see that there are things like mortality, complications, function, growth, patient/family experience, and disparities. So, this is what we're -- the big stuff that we're looking at.

And then, you can see in the central part of this, there are different drivers that can help us understand: Well, how do we get to those outcomes?

And then, finally, on the far right, you start to see some of the measures, some of the things we can look at to see how well we're doing with long-term follow-up. And it's this far right-hand column that was, sort of, the -- the -- what we're working on now as a workgroup.

I guess it was almost 15 months ago when the secretary's advisory committee asked the Long-Term Follow-up and Treatment Workgroup to have a sub-workgroup look at quality measures, and the key thing, really, is to say, well, what is the role of quality measures in promoting long-term follow-ups? That's the focus, and in a minute, Alan's going to tell you about all the work that the -- the group has done.

And the big idea is, we're going to focus on, how -- what's the state of the art, what are we doing in quality measures, how is clinical

quality measures, what are they related to newborn screening in particular, because they really are obiquitous (sic) in the medical care system now. And then, lastly, they looked at some case studies to see, how is this really working out.

And we've had regular meetings over the last 15 months. We've had a -- we have a background document that's in the -- the dossier for all of you to look at, and we have some case studies that suggest what we can do in the future.

And with that, I'm going to turn it over to Alan so he can lay out some of the details of what the -- the group has found.

DR. ALAN ZUCKERMAN: Most of the work with quality measures for newborn screening have focused on two kinds of questions: Who's been screened for what conditions, and what happens after someone has a positive screen. We're now going to shift gears and look at what happens in long-term follow-up of children whose conditions

were diagnosed through newborn screening.

There hasn't been a lot of child health quality measures, and that was one of the reasons that AHRQ and CMS had a partnership mandated by the Children's Health Insurance Reauthorization Act in 2009 to address this lack of child measures and meet a desire to improve quality of care for all children, not just those in Medicaid and CHIP. The first phase that started in 2011 funded 7 centers of excellence to increase this portfolio of evidence-based child health quality measures, and one of those sites developed several measures for sickle-cell.

Phase 2 that began last year is supporting 6 sites to -- to study the feasibility of implementing these measures in the real world, and there are 2 sites that are looking at different measures for sickle-cell. And these sickle-cell measures that are developed are now being tested and will be available for use in the future.

What we've learned from this experience

is that evidence-based measures are difficult and expensive to develop, validate, and implement, even for a common condition that's well understood, such as sickle-cell disease. Sickle-cell disease is also an excellent example of efforts to use quality measures to track proven therapies in use.

As was shown by an HQ report to Congress in 2014, there are indeed real deficiencies in care through quality measures for immunizations, for phylactic antibiotics, and particularly ultrasonography screening. But individual intervention programs using iterative cycles have indeed documented improvements in outcomes and decrease in emergency room use.

But it also emerged that it's very important to encourage cooperation and engagement of primary care specialists and emergency physicians if we're going to optimize care for children identified through newborn screening. Indeed, there are gaps in delivering services to children that can be addressed by quality

measures that help to improve the long-term outcome.

We've also been able to demonstrate that optimal care in a condition like sickle-cell disease, starting the right treatment at the right time, does indeed make a difference for outcome.

A very interesting study at the University of Maryland looked at the ability to do long-term follow-up and primary care, and they were successful in getting data collected in three different large, primary care practices. Their targets were sickle-cell disease and hearing loss, and the total number of cases, as one might expect, was relatively small. They also demonstrated that they could use NCQA tools to evaluate medical home capabilities, the capacity to care for children with special needs and their families.

But, again, improving communication emerged as a key to address the incomplete information that primary care providers are

dealing when they're attempting to follow-up newborn screening. We learned that primary care can participate and measure medical homes, and sometimes even track children who are not identified by newborn screening.

For many decades, the Cystic Fibrosis Foundation has been funding a nationwide network of centers of excellence that are required to report and share their outcome measures. Over the years, this work has led to significant new knowledge discovery about which treatments, such as missed tests or various forms of antibiotics, are most effective, and this has led to important improvement in care and long-term outcomes.

What we learned are, the quality measures can indeed be an important tool for new knowledge discovery and closing gaps in evidence, and they were successful because of the privacy protections that were such an important part of building cooperative data sharing but also limit the outside access to that data by others. And yet, they yield important findings that have been

shared. National networks are indeed a valuable and productive resource to compare different sites.

The Mountain States Regional Genetics Collaborative developed an MCAD checklist that was integrated into their Epic EHR to collect data on several measures. They identified deficiencies both in care and documentation and addressed improving the communication at each visit. The tool was particularly helpful as a reminder to new providers who'd never seen a patient with this disorder and when patients showed up in the emergency department.

What we learned are that integrating quality measures into routine care is an excellent strategy for continuous quality improvement and eliminates the need to fund additional data collection through redundant databases.

A number of years ago, with the dawn of the meaningful use EHR incentive program that was created by the HITECH Act, I had a chance to

address this committee about the list of certified quality measures that was going to be required for reporting, and in the efforts that followed, the CDC became the custodian for early hearing detection intervention measures that were certified by the National Quality Forum, a requirement in the early phases of meaningful use. Having these certified measures has helped to improve data reporting from the states, and among things that were done is, large numbers of infants, some screened before hospital discharge and some after discharge, could be compared for time to audiological testing.

What we learned is that the NQF process of developing electronic measure formats and gaining certification is very time-consuming to get through the ballots, and it's difficult but feasible for some conditions. But at the same time, having these standardized measures can help to improve the completeness of data reporting. These measures never made it into the meaningful use list because they've been used primarily by

health departments rather than hospital EHRs.

One of the best examples of public health efforts in this area is the work of the California Department of Health on long-term follow-up that has been made possible by including in the California newborn screening fee funding for both long-term follow-up and for data collection. We looked at studies of congenital hypothyroidism and cystic fibrosis that are excellent examples of what health compartments -- health departments can do when they have access to data.

We've also learned that while many health departments have huge respect for what California has done, they feel that they do not have the resources or a mission to replicate these methods. California also ends their follow-up, typically, at age 5, which is not going to be adequate for some of the new conditions. And often, long-term follow-up in other states may take place in other divisions of the health department rather than as part of the mission of

the newborn screening program.

The National Survey of Children's Health provides us with an interesting window into the consumer side of quality, and in 2016, this survey merged with the former National Survey of Children with Special Health Care Needs conducted annually by HRSA. The questions cover a range of consumer satisfaction issues and access to services that are incredibly well aligned with those key questions that our workgroup had developed previously. But, currently, there's no way to identify children who are identified through newborn screening, but they're beginning to ask about whether a child's conditions are heritable.

We've learned that these surveys provide important data on access to medical homes, adequacy of insurance, even access to clinical trials, and certainly, availability of services in the real world. Some health departments, in fact, such as Hawaii, have used some of these questions when their own newborn screening

families survey so they can compare things to national norms and deal with standardized questions.

The Organic Acidemia Association is an example of a disease advocacy organization that collects data directly from its member families that can provide key insights into the natural history of disease and the availability of services and support. But we also learned that it's -- while it's important and feasible to collect data directly from consumers, the self-selected nature of the sample may not be representative of the entire population living with a condition.

Several trends emerge from looking at these case histories and help us begin to identify the types of gaps and barriers that we're facing in applying quality measures to newborn screening. There clearly are -- are gaps in evidence that must be bridged before we can create measures. Many of these conditions have subtypes that can present with a range of

severity. Best treatment options are not always clear, posing a challenge for developing condition-specific measures. But we also have a number of cross-cutting generic measures that apply across all newborn screening conditions and are worth using in those situations.

Cystic fibrosis has also taught us that quality measures can be a way to close gaps in evidence on emerging conditions. There are indeed gaps in developing measures because it's such a challenge for rare disorders with late onset and where evidence may be limited.

The NQF certification process is difficult for newborn screening, and validating measures is costly. They've recently added a requirement for a thousand test cases for a measure to pass through, and we often struggle to find a single case identified by newborn screening in early phases of evidence review.

The lack of pediatric quality measures in general led to the CMS-AHRQ Pediatric Quality Measure product. But even after we have measures,

if they're not adopted and used, they generate no data, and this is where we need to attack the cost of data collection and the small number of patients in a single practice that become disincentives to starting programs.

If we can integrate quality measures into routine care, this may help deal with a range of conditions. The measures for sickle-cell now give us a good portfolio that are expected to increase in use. Some of the models used by health departments clearly are going to be difficult to replicate, as health departments vary so much in their mission, funding, and the communities that they serve.

We also see that we need to move beyond disease-specific measures, both those limited to one disease or outcomes that use a single lab test or other measure as a proxy measure of true outcomes. Traditional approaches to quality measure may indeed fall short for newborn screening. We need to include public health or system measures. We need to track that services

are available and that individuals are not lost to fault, and also that they transition successfully into adult care. We need child-specific measures that focus on access to medical homes, available treatment, child wellbeing, and parent satisfaction with the care process. Our data sources will probably need to move well beyond just health care providers alone.

And, finally, we need to also include the consumer perspective on quality measures, because patients and families have their own definition of quality. We need to listen to them, identify needs and gaps that providers and the system may be missing, including not only patient care but the ability to participate in research studies, access to specialists, and insurance coverage for many of the expensive treatments for these conditions. Several disease advocacy organizations have successfully collected important disease-specific data directly from patients and families using general surveys and patient natural history registries.

Quality measures are hard to do, but new tools are likely to make it easier in the future. The Office of National Coordinator for HIT, CMS, and AHRQ have an electronic clinical quality improvement resource center at ECQI dot HealthIT dot gov, and this includes access to new health IT standards for quality measure, definition, and reporting, and even a quality data model for extracting data from EHRs. But if the data isn't in the EHR, it's never going to support the measures. And we're still a long way from a goal of having automatically portable measures that will work in any EHR.

Access to available quality measures and incentive programs is important as value-based care becomes more available. The APHL NewSTEPs program has created case definitions and case reporting databases that can really help define the denominator for newborn screening quality measures, and the Newborn Screening Translational Research Network has a Longitudinal Pediatric Data Resource that has definitions of data

fields, including some of these core measures and public health measures, that essentially are a pathway to the -- to the numerator.

And at this time, Dr. Brosco's going to come back and summarize our findings, as well as point out some of the opportunities to take potential next steps.

DR. JEFFREY P. BROSCO: Don't go far, Alan. Before we go on, I want to publicly thank Alan for -- and you can see, an incredible amount of work has gone into this over the last 15 months. There's a whole workgroup involved, but Alan personally has done a huge amount of work, so thank you. We really appreciate it.

DR. ALAN ZUCKERMAN: And so have many others.

DR. JEFFREY P. BROSCO: Many others have, as well, and in fact, I want to also recognize that Kamila Mistry has lent her expertise in -- in this, particularly over the last few months.

So, yesterday, not entirely by coincidence, I was speaking to a state health

officer about some of the challenges with long-term follow-up in our newborn screening program, one of the newborn screening programs. She said, "You know, we're still having trouble getting PKU formula for babies in the first few months right after diagnosis," and we talked about some of the issues there. And then, she wanted to say, "All these new conditions coming on that we have to deal with, and we can't get PKU right yet."

And I think this really points out something that this committee has felt for a while, which is, we really need to make sure we're doing a good job. If we can identify children, there's some responsibility to make sure they're getting the care that they need.

So, I've listed here, sort of, the summary of what Alan has just presented and what our workgroup has done, and I'll go through a couple things. And then, I'm going to stop, and you have a chance for some discussion.

And then, the next two slides are about potential next steps, and we really need help

from the committee to set priorities, because as you've heard -- Let's face it. Quality measures are a crucial part of the health care system nowadays, so they are everywhere. And our children in newborn screening are pretty much everywhere in the health care system, too. So, while this is valuable, you know, and there's ways we can do this with research and clinical outcomes, we really do need to figure out what our priorities will be.

You can see here that I pointed out, yes, they're a part of our health care system, that there are different types of quality measures. And maybe this is one of the things for us to think about, right? So, what do we want to do next? What are those key things that we think we can influence as an advisory committee?

It may be that the sorts of things with sickle-cell disease, where we're trying to improve quality of care for specific diseases -- That may not be something that we can do, but that may be one area, looking at particular

diseases and those quality measures.

But it may also be at the level of the children's health surveys and how children fit in and other children with special health care needs, because that's where a lot of the money is going to be. That's where a lot of the financial incentives are.

But perhaps most pertinently might be at the level of the -- the state newborn screening programs. All these different times of -- types of quality measures depend, in part, on who you are and what it is that you're trying to accomplish.

I think I'm going to stop there, because I really want to hear questions and comments about where we are and what's next, or the things that don't make sense or that we need to clarify. And, Alan, you have to come a lot closer, because you're going to help answer these questions.

DR. JOSEPH A. BOCCHINI, JR.: So, thank you, both, very much. I -- I, too, want to publicly thank Alan. I think his expertise,

informatics, and clinical information systems and his knowledge of the subject have been really important in pulling together what was needed to go forward.

So, let's open this for discussion, but I think that one question is, given the state of -- of -- of where we are and -- and the findings so far: Is -- is this ready for the fourth publication in our series of long-term screening outcomes and -- and now the -- the use of quality measures to help answer some of the questions that have been raised? And then some other things related to the -- the potential gaps and -- and -- and -- and -- and how to go forward. So, let's open this for discussion from the committee.

DR. JEFFREY P. BROSCO: And -- and just one comment about the report itself, because --

DR. JOSEPH A. BOCCHINI, JR.: Yeah.

DR. JEFFREY P. BROSCO: -- you do have a copy of the preliminary report, which really represents Alan's work; he's the -- the primary author on that. And what we have there is,

basically, what we talked about now: What do the case studies show? What are the big ideas? But framing it, what's important and what we want to do next, we're waiting for this discussion before we do that part of it.

DR. JOSEPH A. BOCCHINI, JR.: Cathy.

MS. CATHERINE A. L. WICKLUND: Yeah, Cathy Wicklund. Thank you, guys, so much. That -- you've clearly done a ton of work on this, and I have a question more about the implementation.

And did you guys get an idea, when you were either talking to these groups or researching it, how much they actually use, like, implementation science and the -- thinking about how you want to try to move this into practice and get this data? You know, we can develop a lot of tools and do a lot of things, but, ultimately, there's a lot of things that actually have to happen for people to adopt the tool and actually put in the data.

So, was there any kind of formality when it came to how people were trying to implement

this, looking at the different factors that play a role in the implementation, and making sure those things were actually, you know, addressed and you had all those components?

DR. ALAN ZUCKERMAN: I think one of the things that's emerged is that there is a contrast between research efforts that collect comprehensive data and very focused cycles of improvement that are part of routine care. Many of the larger long-term follow-up studies require consent, collect a great deal of data, involve duplicate entry, even people doing chart abstracting.

If we can identify a few key indicator measures, it takes us into a different place, and the groups that are looking at a few indicators and they'd intend to do it until they achieve a particular target level of success and come back periodically to see it's being maintained are functioning differently. And I think it's only beginning to enter newborn screening that we're approaching that -- that method of going from the

comprehensive research approach to the targeted indicator and improvement approach.

DR. JEFFREY P. BROSCO: And -- and another way of thinking about this, Catherine, is that we saw that whole range, from zero to a hundred -- right? So, you have some people just saying, "Well, I wonder how PKU kids are doing. Let's -- let's call up a few of them and see how they're doing" -- right? -- on one end, to, sort of, things that California's doing, and others, that's a very rigorous implementation public health science approach and everything in between. But this reflects quality improvement across the board in our health care system. It's not specific to newborn screening.

DR. JOSEPH A. BOCCHINI, JR.: Kamila?

DR. KAMILA MISTRY: So, part of the Pediatric Quality Measures program, where we focus on sickle-cell -- But in any case, the second phase of it is really focused on implementation science. And so, it's exactly what you're saying, Cathy, which is that we have

measures, measures everywhere, but we really don't have a great understanding of, what does uptake look like, what are the challenges that we face around uptake in terms of moving from measurement to improvement, and improvement at different levels, right?

And so, I hope that -- You know, there's actually two groups, as Alan mentioned, that are working on this: Michael Cabana and -- at UCSF and then Gary Freed, who's at University of Michigan. And I think that we'll continue to learn lessons around that.

But it's really, I think, the interest of -- You know, our focus on -- in implementation science is really to understand usability, feasibility, boots-on-the-ground kind of issues that occur. I mean, you can measure something, but how does that information really improve care?

And so, I think we're going to learn a lot about that. And, you know -- And some of those measures are related to follow-up, so

hopefully we'll be able to bring that back.

DR. FRED LOREY: This is Fred. I have a comment. Can you hear me?

DR. JOSEPH A. BOCCHINI, JR.: Yes, Fred, go right ahead, and then we'll follow that with Dieter. Go ahead, Fred.

DR. FRED LOREY: Alan, thanks. That was really incredible and thorough. I appreciate it very much.

Just a quick comment on the California long-term follow-up program: That 5-year cutoff is, like, an arbitrary cutoff, and it dates back to before I was even director, to George Cunningham, and he felt like under the newborn screening regulations under program evaluation, we had the authority to follow for 5 years without consent, but if we continued beyond that, we probably would be getting into a consent situation, which might be costly and bring the numbers down, et cetera.

So, that's all that was, but I agree, it would be better if we could go longer. Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. Dieter?

DR. DIETRICH MATERN: Yeah, thank you. I -- I wonder -- I mean, at this point, it seems to be all about data gathering, but it seems you already have some interesting findings from, for example, the mountain region, with the MCAD project, and as more and more hospitals and clinics use the electronic medical record, and Epic in particular, why can't we take some of the information already implemented, and how can we push that forward?

So, for example, if a baby is picked up with MCAD or any other condition, how could Epic help you by immediately raising the -- the question: Okay, this is -- comes in as MCAD. Now you have to do this, this, and that based on the ACMG algorithms, for example, and then also, when it comes to follow-up, put in, at specific times, flags that the physician knows, "Okay, kid has to come in for a follow-up, or I have to explain this and that." How can we push that forward, or

should we not?

DR. JEFFREY P. BROSCO: I -- You start.

DR. ALAN ZUCKERMAN: I think one of the problems is that each of the Epic systems or NEHR system are different from each other, and what ONC is trying hard to do in funding demonstrations is to build application programming interfaces into all EHRs that would allow a single plug-in for a condition to be added to many different EHRs. That's the nice advantage to what they did in MCAD, that a care plan and a data collection form popped up, but they had to do it themselves. It was custom development.

We are moving towards this Fast Health Interoperability Resource. We are now in the early phase of Nationwide Interoperability 10-Year Roadmap that will hopefully open the door to these plug-in tools with application programming interfaces to EHRs. But if the data isn't in the EHR, or if it isn't coded properly, we won't get to use it, and that's why the redundant data

entry of things like the LPDR has been so important in the past.

DR. JEFFREY P. BROSCO: And to, sort of, emphasize that -- So, our EHR is Epic, right? And I use it all the time. It took us years to get vaccines as a quality improvement thing, where it would just pop up and say, "This is the vaccine that you need."

And you have to remember that newborn screening conditions are in the context of a health care system, and in the adult health care system, pediatrics is tiny. And then, if you start talking about specific newborn screening conditions, they are so rare that they don't even show up.

So, it took a long time for us to do vaccines for all children in our EHR, so as Alan's pointing out, it -- we're -- we're -- there is a roadmap to it, but there's still a long way to go.

It might be good to do the last couple of slides, and then, just so we have a sense --

because I think that's one of the kinds of things that we can move forward on is the -- the EHR, but I just wanted to give what our process is and a couple more examples.

So, we think that we're mostly done with our task. As I said, the draft report's done. We just need to make sure it's framed properly. But we really need input from you about next steps, and we're going to spend a fair amount of time this afternoon taking your recommendations and trying to figure out. And we just put down a couple of possible next steps.

So, one of them, as Dieter pointed out, is, you know, we can't do everything, but maybe we can push a little harder on the EHR and, you know, the sort of plug-in that Alan was explaining. And that sort of fits into these strategies to encourage development and validation of quality measures for long-term follow-up with newborn screening.

It may also be that we want to focus more of our attention with helping state newborn

screening programs get to some level of organization for follow-up and maybe building on the NewSTEPs. And so, are there certain measures we'd want all state programs to look at, or is this something -- the next discussion point.

We could also look at gaps in -- related to newborn -- quality measures for newborn screening, so looking at particular conditions, and as new conditions come on to the newborn screening panel, should we include quality measures? So, that'd be one of the things we'd ask from the nominating groups.

And then, there's always the education possibility, but if we're going to educate, whom should we be spending our time trying to do, because all across the health care system, we can do this.

And then, lastly, as I mentioned a little bit before, are there ways to make sure that children with newborn screening conditions are not lost? And so, if we include them as a part of the Children with Special Health Care Needs and

the broader measures -- And just to give you an example on that: Right now, general pediatricians like me are being asked, "Well, did you do a lead level? Did you vaccinate all the children at the right ages? Did you have a follow-up visit every year?" And that's basically it. There aren't a lot more things than that.

And yet, clearly, children with special health care needs have many more needs and conditions and things we should be measuring. So, do we want to, sort of, join forces with that much larger group, that's 15% of children, and maybe work with them on making sure that there are quality measures that would improve the outcomes for children with newborn screening conditions?

So, we think these are some of them, and there are many others that we could move next on, so we really need some help trying to set priorities about what, if anything, this workgroup can look at next.

DR. ALAN ZUCKERMAN: Yeah. But I -- I

think what we clearly know is that without priorities to drive things above decision points in hospitals, things will get lost. Jaco's (phonetic) been incredibly successful in getting people to pay attention. What may be needed is a way to decrease the cost of implementation and to identify a limited priority ask, whether it's for the hospitals, for the health departments, or for the specialists, or even for accessing consumers.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. I have Melissa and then Dr. Ostrander and then Carol and then Annamarie. Melissa.

DR. MELISSA PARISI: So, I just wanted to comment on some of the challenges of extracting from the EHR. I mean, this has obviously been an ongoing issue and something that I know, Alan, you've been working on for quite a while.

So, in the absence of being able to have systems that really work uniformly and reproducibly in this domain -- You know, obviously, there are some resources that have been developed, including the Longitudinal

Pediatric Data Resource for the NBSTRN and some of the APHL measures. And, you know, one of the challenges that I think we face, given that long-term follow-up is, in some ways, the holy grail for what we're trying to accomplish in newborn screening as a public health initiative anyway, is this issue of, do you focus on the more common conditions as, sort of, a -- a starting point for, if we can succeed here, we may be able to expand to rare conditions, in which case things like hearing loss or hearing screening programs and sickle-cell disease are likely to be the -- the first programs that have a possible implementation.

First is this idea of using a core set of long-term follow-up quality measures, as you've indicated here, so that you would have the potential of gathering data across all of the different newborn screening conditions, realizing that it's going to be less granular, but at least you would start to have some sort of baseline of some standard measures that could be utilized

across all of the different conditions. I don't have any answer, I'm just throwing that out there for your comments.

DR. JEFFREY P. BROSCO: We -- we actually want the answer to that.

(Laughter)

DR. JEFFREY P. BROSCO: I mean, seriously, the -- the group could go in different ways, and so we would like to get some direction as the comments go on from, should we say, "Okay, here are some general measures that pretty much cover the waterfront," or should we put our time and effort into specific disease outcomes and -- and prove that things can work at a wider level? So, you laid it out perfectly, and we're -- we -- we want to know which way to go.

DR. JOSEPH A. BOCCHINI, JR.: Dr. Ostrander.

DR. ROBERT OSTRANDER: So, a couple things. I sit on -- Oh, sorry, Bob Ostrander, American Academy of Family Physicians. A couple of things.

One, I sit on this workgroup, and I think, partly, we're looking to the committee to help us focus our role, because, you know, we keep coming up against, in this workgroup, all sorts of things we would like to be doing, but we don't have the resources to do them. And so, we hope others are going to do what we think is a good idea.

And I think it would be very helpful for us to specifically define our role as a workgroup, where things stop and start, and whether we're simply going to publish this, sort of, analysis of things, with a description of why quality's important, or whether we're going to make this, kind of, soft recommendation that others pursue quality measures that conform to these things, whether we should list some of the criteria of a good quality measure.

You know, for instance, at the very beginning, we talked about the fact that we had -- quality measures aren't good just because they're easy to glean the number, but they

matter. And, you know, should we list the -- just like we did with the other framework paper, should we have a list of criteria of which quality measures we should not pursue? Because that's something we see in medicine all the time.

So I -- I just -- I -- I -- I feel like we're still a little weedy in -- in terms of how directive or not directive we're going to be, and I think we should make up our minds with that.

The other comment is a -- really, a secondary issue, and that is the difference between doing rigorous data analysis like you do for global assessments of the effectiveness of a program, and the less-rigorous data analysis that goes with the cycles -- short cycles of change in implementation science. And I don't know that we've distinguished among those two things.

I think that's actually quite important, because if you only do the slow thinking, big-data analysis of where your gaps are, you end up not using that short-cycle-of-change implementation science. You know, you say: Oh,

there's this big gap. We need to fix the system. It's slow. You get off to false starts. You do things with unintended effects, where if you use the short-cycle-of-change model, things happen sooner; they happen more incrementally. But by nature, you're using data that you're not quite as comfortable with.

I mean, I teach a course in the city, University of Rochester folks, about the -- the differences between short-cycle-change qualitative measures and rigorous scientific qualitative measures. And so, those are some of the ideas I -- I think it would be nice to -- to firm up a bit and make more concrete in the paper.

DR. JOSEPH A. BOCCHINI, JR.: Thank you.

DR. CHRIS KUS: This is Chris Kus. If there's time, I'd like to make a comment.

DR. JOSEPH A. BOCCHINI, JR.: Yeah, Chris, go right ahead.

DR. CHRIS KUS: Yeah, I think one of the big issues here, in order to really move along

with long-term follow-up, is the financial support of long-term follow-up. Some states, like New York, doesn't have a fee, and I think it would be good to get some sense, maybe from California, what does the long-term follow-up program cost and discuss strategies of where that should come from, where that funding comes from. Is it Title V, with state funding, or other -- other ideas.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. Carol?

(Off-mic speaking)

DR. JOSEPH A. BOCCHINI, JR.: Okay. Annamarie?

MS. ANNAMARIE SAARINEN: Thanks, Carol. I don't care about order, but -- So, thank you so much, to both of you. It's so much work.

For those who don't know -- and Alan maybe even forgot -- we -- we met each other in 2009 at the ONC's Health IT Standards Workgroup meeting for the first time, at which time we had hoped newborn screening would be part of Stage 2

meaningful use. So, this conversation's been happening for way longer than any of us want it to. And I remember talking to the CEO of Epic about, how do you make exactly what was on 4 of your slides happen now -- not 6 years from now, now.

And I -- I -- I don't know, outside of the hurdles of, again, them taking EHR -- vendors taking it up as something like: Wow, that'd be a great thing to do, but we have to bear the cost of it, and who's going to provide the direction about how this data can systematically flow between health care providers and public health departments, which is not an easy thing to do.

But back to Dr. Ostrander's point about, what is the, sort of, reach of our committee and what -- what would you like to see happen coming off of a report like this. I don't know -- I imagine this committee has explored where the crossover is, like, what other FACAs or other groups are already trying to support long-term follow-up of children with special health care

needs, whether that be birth defects or other rare diseases.

There -- there must be more than one that are doing that sort of work already, so where does our job, sort of -- I don't want to say, sort of, end, but where can it hand off from the newborn screening world in terms of follow-up with these kids, so that there aren't duplicated efforts but that the efforts to make sure children will have access to the care they need and that we are getting the data to know whether screening made an impact on where they are today, much beyond knowing whether they die within 5 years of being screened.

To the -- to the point of -- Where I sat in a meeting this week, because I'm moving my child from one school to another school, thinking that the IEP team that's been following her for 3 years now was going to be there for her at the new school -- because it's all part of the school district's program, right? And I find out that I'm moving my child over to this new school just

for special care services or special needs services, but none of that IEP team is coming with her. Her entire case load, 3 years of data -- clinical data, data from her teachers, data from us as her parents -- will have to be somehow transferred over to an entirely new team of 6 people plus teachers. And I went home and cried for an hour.

DR. JEFFREY P. BROSCO: You said two critical things, I think. One is that the kinds of things we typically measure in quality measures don't get to the real point you just made, which is: How is my child doing in school? Is my child being included in community activities? Is he or she really beginning to do things that -- that they should be able to do? And so, that's one of the critical ones is, how do we make sure that doesn't get lost in the quality measures?

And what, in particular, is the special responsibility of this committee? Because there is a lot of improvement happening in many

different ways, so is there some special thing that we as a group can do?

I see that the time is pretty far along, so I'm not sure if we want to, maybe, come up with specific things this afternoon and bring them back tomorrow or --

DR. JOSEPH A. BOCCHINI, JR.: Well, we're going to give you an additional 5 minutes. We have one public comment, so we can give you an additional 5 minutes. And I do have Beth on the phone, who wants to make a comment, and then we'll go to Carol.

DR. BETH TARINI: Hi, this is Beth. I -- I want to say, I think that long-term follow-up is vital, because you don't know how your investment is paying off unless you measure the long-term outcomes of your screening.

That being said, I want to echo Chris's question, which is, is the committee considering putting this as a sort of unfunded mandate on the states? And I want to caution us if we lean that way in terms of the operationalization of this,

because when this committee speaks, it has -- and writes things down, and the secretary approves it, or it is published in the literature, it has great power. And I am hesitant to put this on the states given their increasing burden of adding new disorders.

So, I wanted to just get a sense of, is that what we are thinking, or it's just one of many possibilities.

DR. JOSEPH A. BOCCHINI, JR.: Well, I -- I think it's one of many possibilities, and I think that's where we are with the workgroup presenting today, is to determine how the committee feels we need to move forward. And I think we've had some really good, insightful comments from Bob and Annamarie, amongst others, about what the key issues may be. And -- and I think that that's -- really, the committee needs to kind of think about, what are the -- what are the best approaches, now that we have this database, in terms of moving forward?

And -- and -- and so, I think that's

where we are, Beth, but I don't think that this would be put together in such a way that it would require states to do specific things but just to make people aware of the potential for quality measures that might be useful in application to newborn screening. And so, I think that's sort of the framework that we're working in, and so.

DR. JEFFREY P. BROSCO: Yeah, and I -- I would add to that, that this is certainly not where we're thinking about making a specific recommendation right away, but we're looking for more direction. So, it might be something like: Work with APHL and state newborn screening programs and other stakeholders to figure out what a minimum set of reportable conditions and measures might be. So, that next step might be, this is where you'd like us to focus, but it wouldn't be to make recommendations about that focus; it's where we would look next to sort of fine-tune things.

DR. ALAN ZUCKERMAN: Yeah. We also, I think, need to look at the consumer pathway, and

I haven't heard much response from the committee about going directly to consumers for data. Should that be a focus?

DR. JOSEPH A. BOCCHINI, JR.: Yes. Carol?

DR. CAROL GREEN: Carol Green, SIMD. One specific question that was asked, and I would just offer, asking about specific diseases and -- versus looking at more broadly. I personally think that given the complexity of all the quality measures, we're going to get a lot more value if we try to focus on quality measures that look at multiple disease, because otherwise, we're just going to be looking at small subsets of individuals and have difficulty getting data.

The other thing I wanted to say is, I've been part of this work, and it's just amazing what Alan's doing, and all the other folks, and I'm learning things about quality measures. I had no idea how hard it -- actually, a little idea, but now I really have a better idea how hard it is to get a quality measure approved and then they get used nationally and broadly.

And I think we're, sometimes in our discussion, going back and forth between quality measures, which are these complicated things that you have to get validated and have to be used nationally and take years to bring on board and then you can use them, and quality improvement, which is what Colorado did, which is, I'd love to implement it, and it's -- it's in -- it's program by program, and we can use models, but when we discuss this as a committee, I think we have to -- Sometimes we go back and forth, and we're not distinguishing between them.

The other thing I wanted to say is, in the -- in the EHRs in the pediatric world, I can't close a chart without answering the question: Do you use smokeless tobacco? He's 8 months old.

(Laughter)

DR. CAROL GREEN: Okay? So, there's -- we -- the -- the quality measures have been decided, and -- and -- and I -- I can't overemphasize: Pediatrics has no role in any of this, and so

newborn screening has seriously no role in any of this.

And with that said, another thing about the EHR is, when you extract information from an EHR, all of this is only going to apply to the long-term data collection follow-up -- data collection, not to the long-term follow up, but -- to see how the outcomes are, if you've got the right diagnosis. And I have a kid with polymicrogyria, but somebody took that off his list of diagnoses, so it's not going to appear on his problem list.

So, your outcomes are only as good as the input, so we still have a lot to work on in the EHR. And the EHR will never capture what Annamarie Saarinen was just talking about, because that's the schools, and outcomes that are incredibly important are not in the health record at all.

So, I think there's a sense of some discussion saying, if we get it into the EHR, then we don't have to pay money to do the long-

term follow-up, because we all have to use the EHR; we'll just extract it out. But the EHR has -- there's a lot of work to go on there. Not all the data we want's in the EHR. It can't always be put together. The EHR is where we can look, I think, for the quality improvement locally, but that's really different than quality measures. Sorry.

DR. JOSEPH A. BOCCHINI, JR.: So, Dieter and then Natasha.

DR. DIETRICH MATERN: Coming back to the electronic medical record but also to the question whether the patient advocacy groups should be asked. I think asking them about data will give you -- give you something, but I don't know if every patient is part of those, and it's going to be very subjective, and getting good data out of it might be a problem.

On the other hand, to, again, get -- get some -- something into the system and making sure that patients identified through newborn screening get the benefit of it, and given the

fact that Epic is not as -- I mean, it's -- it's apparently a custom-based thing, so it takes forever. But maybe the advocacy groups can build their own apps or things like that, where they can incorporate all of the things that a patient should go through, and the patients get alerts that are customized to them based on their -- their age and just get a reminder: Okay, it's time to get a vaccination or whatever.

(Off-mic speaking)

DR. KAMILA MISTRY: Just a quick follow-up to what Carol was saying, which is just that, you know, measures are developed for a particular use, and so it is important to really distinguish between, you know, are these measures that were intended for accountability, in which case, we would care a lot about the scientific evidence that underlies them, as well as their reliability and the validity and how they've been tested. And so, there's, sort of, that level.

There are other measures that were not developed for that, and they were intended to be

used for quality improvement. So, I think just as we move forward, we should just be clear on what we're sort of -- what the goal is for what we're doing and make sure that the science sort of backs up the goal in terms of the measures.

DR. JOSEPH A. BOCCHINI, JR.: So, Natasha and then Bob.

MS. NATASHA BONHOMME: Natasha Bonhomme, Genetic Alliance. To go to your question about the consumer perspective -- You know, I think -- I'm happy to see this slide here and the -- You know, it isn't just the fact that parents and families have their own definition of quality. They are the end user. This whole system is supposed to be for them.

And so, I think really making sure that they are central and finding ways of not just their perspectives and experiences but ideas can be incorporated in this will be really important. And we've seen a number of other areas where there are processes in place to at least starting to do that, you look at PCORI and PCORnet and,

you know, engagement, assessments being created through that, which Genetic Alliance is involved in, that there are these processes.

And I -- I do think that it's important to note that it's not just about: Oh, that's one category, the parent and family perspective, but it isn't about creating things that we think they should want or need. It's about going to them and asking them what will be useful, and then building it based off of that. So, I'm happy to see at least the beginning frameworks of that in this, and I think that's really critical, especially as we are in an age of, ideally, more patient- and consumer-centric health care.

DR. JOSEPH A. BOCCHINI, JR.: Bob?

DR. ROBERT OSTRANDER: I'll be short. I mean, basically, my first comment was to echo what Natasha said. We're -- we're not looking to the families and the groups to tell us how many kids are getting penicillin. What we're looking to the families and the groups is, is to say: How user friendly was this system? Did you feel

informed? Did you feel safe? Did you feel hassled? Did you feel respected?

I mean, there are quality measures around that stuff. I mean, how to get a representative -- I -- I don't think the quality measures around that, those issues, are -- It's hard to figure out what measures to use as to how to get a good, representative sample. And I mean, Alan pointed that out.

And -- and obviously, there are also some true mechanical things, but we don't -- we've been doing this for a long time, and that's -- we're all -- That's how I got myself into this is talking about the interface between primary care, families, and the, sort of, higher level subspecialty and scientific community.

And over and over and over again, our parent partners got from the NICHCU (phonetic) Learning About Children with Special Needs say, "What I want to feel is like I'm a partner in my kid's care, I'm the expert in my child, I know who to call, and I'm not being hassled and

burdened by having to go 10 different directions." And those are questions we can get the answers to.

And, again, I -- I mean, I'm not parent of a child with a heritable disease or -- or special needs, but -- if I'm not -- and if I'm not echoing that right, I wish someone would chime in -- but I think those are the methods that we're talking about with them, but they're hugely important, because that is what makes people's life high quality.

The second quick thing: I -- I'm going to suggest that we don't put too much stock in using the EMRs for this, for the reason you guys said. I mean, it's just -- First of all, the EMRs -- the -- the people that are working with them have priorities different from ours, and that's never going to change. It's a -- we're still in a pair-centered medical home world, and it's going to be about chronic, expensive, middle-aged diseases that cost the system money, and, you know, little bits of too much money, lots of times, that have

lots of bits of money, like spirenza (phonetic) once or twice.

I -- I would -- I think we're barking up the wrong tree with the EMRs. I think, honestly, these sort of unusual things, the old -- the old-school way of using registries but using good information technology in the registries is probably more likely to produce a result.

And I am, by no means, an expert in that; Alan is, but just -- I am a user of an EMR all the time, and I'm involved in lots of systems that deal with population management of the whole population, and I cannot imagine anybody spending the time on people's EMRs to get it right for newborn screening. So, I think it's going to have to be a registry approach myself.

DR. JOSEPH A. BOCCHINI, JR.: So, that's a good point. So, you're saying if Carol can get that 8-month-old to quit smoking, we'd be much better off. Yeah.

(Laughter)

DR. ROBERT OSTRANDER: Chewing tobacco.

DR. JOSEPH A. BOCCHINI, JR.: Yeah. Okay.

DR. ROBERT OSTRANDER: That's their programmer. That doesn't happen --

DR. JOSEPH A. BOCCHINI, JR.: No, I -- I understand that. Yes, Carol.

DR. ROBERT OSTRANDER: That's the programmer.

DR. CAROL GREEN: I -- I -- I really, really want to reinforce and echo that, because I'm -- I'm another one of the people who's in the EMR every day, and the inaccuracy in there, the difficulty to get anything adopted into it, and the inaccuracy in the diagnostic information is just really going to take a long time to solve. And that means that we've got to solve the funding problem, because registries is the right way to get the information, but then somebody's going to have to pay for it.

(Off-mic speaking)

DR. JOSEPH A. BOCCHINI, JR.: Are there any questions or comments on the telephone?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: If not, we need to close this session, but it seems like we still need some discussion. But I think you've gotten some feedback that -- that's helpful, but I -- I think the committee probably needs to discuss this further to give you more insight and help.

DR. JEFFREY P. BROSCO: And that's great. We have time this afternoon in our workgroup, and I think we can come up -- We -- we've heard a lot of good things. We can come up with some specific suggestions for tomorrow.

DR. JOSEPH A. BOCCHINI, JR.: Okay, thank you very much. And, again, thank you both for the work that you're doing on this project. Thank you.

(Applause)

DR. JOSEPH A. BOCCHINI, JR.: So, the one public comment that we have here is Ms. Megan Lenz. Ms. Lenz is from Cure SMA and will be discussing SMA newborn screening. Thank you for coming to the microphone. Good morning.

MS. MEGAN LENZ: Good morning. Good morning, Dr. Bocchini, members of the committee. Thank you so much for letting me come and speak today. Again, my name is Megan Lenz. I'm the director of communications for Cure SMA. I'm also here on behalf of our partners at Muscular Dystrophy Association, who worked with us on the nomination and submission.

So, I am testifying on behalf of the spinal muscular atrophy patient community regarding the nomination of SMA to the Recommended Uniform Screening Panel. As you know and as we've already heard, this nomination is currently in evidence review.

Currently, SMA is the leading genetic cause of death for children under age 2. We know that newborn screening, combined with early therapy, is the best chance that we have to change this for the next generation and beyond. On December 23, 2016, the FDA approved Spinraza, also known as nusinersen, the first-ever FDA-approved therapy for SMA.

Results from Biogen's open-label study of presymptomatic infants, called NURTURE, demonstrate that infants receiving treatment presymptomatically obtain more motor milestones when compared with infants in the ENDEAR study, who received their treatment after the onset of symptoms. As of October 31, 2016, no presymptomatic SMA infant treated with Spinraza has died or required permanent respiratory support. In fact, 39% of the infants in the treatment group for ENDEAR, which was the post-symptomatic trial, have died or required permanent respiratory support. Furthermore, 89% of treated infants in the NURTURE trial have gained motor milestones, such as the ability to sit, stand, and walk, and 39% are achieving normal, age-related motor milestones, growth, and development.

In addition to this clinical data, we know that natural history data indicates there's just a small window for optimal intervention in SMA. Dr. Kathryn Swoboda has shown that type 1

infants suffer rapid and severe loss of motor units in the first 3 months of life and that within 6 months of age, oftentimes, 90% of the motor neuron units have died.

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 outcomes. The evidence to support this, many of which we've already heard about today, includes the two ongoing newborn screening pilots in New York State and Taiwan, very sensitive and specific diagnostic tests and screening assays, good understanding of SMA natural history, including genotype-phenotype correlations, and a life-saving treatment for SMA that has been shown to have more impact when delivered presymptomatically.

In addition to my work with Cure SMA, I also have personal experience with the disease. Years ago, my cousin passed away from SMA type 1 just a week after his fourth birthday. His diagnosis took us by surprise, and we had no

treatments, no hope and opportunities available to us.

Along with thousands of families affected by SMA, my family looks forward to celebrating the day when newborn screening, timely treatment, and supportive care can change the course of this disease. I thank you, again, for the opportunity to address you today and for your consideration of our nomination.

DR. JOSEPH A. BOCCHINI, JR.: Thank you very much. Thank you for being here.

So, that was our only public comment for this morning, so we are ready to break for lunch. We have a 1-hour lunch break, and I'm going to turn it over to Catharine for some additional announcements.

DR. CATHARINE RILEY: Great. Thank you all for a great morning session. Just -- just a reminder for those who are visitors to remain in the -- on the fifth-floor pavilion area. There is a cafeteria across the way here. There's also a little snack shop for those that are interested.

And we will -- we'll break for 1 hour, and we're going to start up again at 12:50, and I also want to know, for the committee members, if all the committee members could stay -- stick around for a few minutes. We're going to get a picture. So. Stick around, and then we'll see everyone back here in 1 hour. Thank you so much.

(Whereupon, the above-entitled matter went off the record and then came back on.)

DR. JOSEPH A. BOCCHINI, JR.: All right, let's go ahead and call the afternoon session to order. First item is the -- the roll call. Kamila Mistry?

DR. KAMILA MISTRY: Here.

DR. JOSEPH A. BOCCHINI, JR.: Mei Baker?

DR. MEI WANG BAKER: Here. Here.

DR. JOSEPH A. BOCCHINI, JR.: Jeff Brosco?

DR. JEFFREY P. BROSCO: Here.

DR. JOSEPH A. BOCCHINI, JR.: Carla Cuthbert?

DR. CARLA CUTHBERT: Here.

DR. JOSEPH A. BOCCHINI, JR.: Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH A. BOCCHINI, JR.: (Off-mic speaking)?

FEMALE SPEAKER: Here.

DR. JOSEPH A. BOCCHINI, JR.: Fred Lorey?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Dieter Matern?

DR. DIETRICH MATERN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Melissa Parisi?

DR. MELISSA PARISI: Here.

DR. JOSEPH A. BOCCHINI, JR.: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Beth Tarini?

DR. BETH TARINI: (Off-mic speaking).

DR. JOSEPH A. BOCCHINI, JR.: Thank you, Beth. Catherine -- Catherine Wicklund?

DR. CATHERINE A. L. WICKLUND: Here.

DR. JOSEPH A. BOCCHINI, JR.: And Catharine Riley?

DR. CATHARINE RILEY: Here.

DR. JOSEPH A. BOCCHINI, JR.: Go back to Fred Lorey?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: And Beth Tarini?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Now for organizational representatives. Bob Ostrander?

DR. ROBERT OSTRANDER: Present.

DR. JOSEPH A. BOCCHINI, JR.: Michael Watson?

DR. MIKE WATSON: Here.

DR. JOSEPH A. BOCCHINI, JR.: Britton Rink by webcast?

DR. BRITTON RINK: Here. Here.

DR. JOSEPH A. BOCCHINI, JR.: Kate Tullis by webcast?

DR. KATE TULLIS: Here.

DR. JOSEPH A. BOCCHINI, JR.: Susan Tanksley --

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH A. BOCCHINI, JR.: -- at the podium. Chris Kus, webcast?

DR. CHRIS KUS: Here.

DR. JOSEPH A. BOCCHINI, JR.: Adam Kanis, webcast?

DR. ADAM KANIS: Here.

DR. JOSEPH A. BOCCHINI, JR.: Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. JOSEPH A. BOCCHINI, JR.: Siobhan Doyle?

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Cate Walsh Vockley?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Carol Green?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Okay.

DR. BETH TARINI: Beth Tarini, I'm here.

DR. JOSEPH A. BOCCHINI, JR.: Okay, thank you, Beth.

DR. CATHARINE RILEY: Dr. Lorey, are you on the line yet?

(No audible response)

DR. CATHARINE RILEY: Okay.

DR. JOSEPH A. BOCCHINI, JR.: Okay, the first item for this afternoon's agenda is a report from APHL related to establishing and revising newborn screening cutoffs, entitled "Lessons Learned from States." This is the result of the APHL survey that they conducted with newborn screening programs, and after Dr. -- Dr. Tanksley's presentation, our goal is to then kind of summarize what we've done over the last few meetings and then begin to frame the steps we need to do to go forward.

And just as a reminder, Dr. Tanksley is currently manager of Laboratory Operations Unit, the Texas Department of State Health Services. She's been actively involved in -- at a national

level, working as co-chair of the Mountain States Genetics Regional Center Newborn Screening Workgroup since 2009 and as co-chair or chair of the Association of Public Health Laboratories Newborn Screening and Genetics and Public Health Committee since 2010. She is a member of the APHL NewSTEPs steering committee and has been representing APHL at our committee meetings and is a member of the Condition Review Workgroup for Secretary's Advisory Committee. So, Susan, thank you.

DR. SUSAN TANKSLEY: All right. Thank you to the committee for allowing us to present this survey report to you today, and thank you to all the states who contributed to the survey. We really appreciate your time, your efforts, and your -- your very thoughtful input for this survey.

So, just to remind you of the -- the timeline that we've been working in -- So, earlier this year, there were media stories that came out related to missed cases in newborn

screening and -- and questions about how cutoffs -- or why are cutoffs variable in different states. And -- and the APHL Newborn Screening and Genetics and Public Health Committee, we decided that we really wanted to gather input from the states and determine, how do states actually set cutoffs and determine which results are going to be reported out or not, and what tools do they use. And that was really the purpose of the survey that -- that we developed. We wanted to be able to provide that information to you and then also to have it for our use.

So, the survey was developed by the committee, fielded by -- as a pilot by a few states just to try to determine -- to make sure we could get the information that we really wanted, and then was put out for states to respond to for about a 2-month period, which ended about 2 weeks ago. So, we haven't had a huge amount of time to pore through the data, but what -- what I'll present today is a summary of that data for you.

Our audience for the survey was newborn screening lab directors, follow-up managers, clinicians, and any other personnel who were involved in newborn screening who might use the analytical tools. So, we fielded it to 53 newborn screening programs and received 38 responses back.

The first nine -- There are nine multiple-part questions to the survey, so it ends up being over 30 questions if every -- every question's answered, but in general, the first part was about how states determine when a result's not normal. And then, the second part is about the use of R4S and CLIR tools, specifically because those have been a topic of -- of discussion over the last few months.

So, the -- the -- the first question was really about, how does a state establish their cutoffs. And so, this was a free-text answer, so we received very -- very long responses in this, and we tried to boil this down to general -- general methods.

So, some utilize vendor recommendations, so something that's within the kit insert that provides a reference range to start with. Many states use population data from -- from screening dried blood spots, utilizing their normal population as well as trying to incorporate affected babies whenever residual newborn screening specimens are available from affected babies. There were some that mentioned considerations, so establishing age- or weight-specific cutoffs based on that data, as well. Many mentioned consulting others -- so consultants, clinical specialists, the Newborn Screening Advisory Committee within the state for input on those cutoffs, as well -- utilizing published literature, and then also talking to other state programs.

And there were many -- there was mention of different tools and how those cutoffs are actually established within each state. So, Excel was mentioned, R4S, SAS, and then also utilizing the cutoff analyzer that's available within the

Specimen Gate LIMS that many states use.

So, we also asked, how often does a program evaluate cutoff values, so, basically, once it's established, how often do you look back. The -- the most common response was, when it was triggered by -- by certain events, but multiple responses were allowed here, so a state could have responded multiple times to this question.

So, what would qualify as -- as one of these certain events that's triggered? So, an example listed as a missed case are too many false positives, but also things like when there are new kit lots, if you have a change in instrumentation, and then some even mentioned that they really do it on a continuous basis -- annually, monthly, quarterly. We received, you know, input -- basically, everybody is looking at cutoffs on a -- on -- on some sort of basis. It's not something that's set and never looked at again.

So, when changes are made to reference

ranges or a referral protocol, we asked: Does your state have a process to communicate this? And, primarily, the response was, yes, with only two programs responding that they didn't have a process for communicating that information, and one state did not know.

We also asked, does your results report -- so, this is the report that would go to the physician -- include a risk assessment? So, does it -- does it provide the results, or does it provide something that says it's normal or abnormal or elevated or a possible heterozygote?

And 86.8% of the states indicated that their results report does include a risk assessment, and for those that said no, we asked: So, what challenges are encountered to incorporate the risk into a report? And one state responded that their LIMS -- lab information management system -- is set up to report out abnormal analyte ranges, not disorders, and that that sort of change would require reworking of the -- of the LIMS, which would require time,

personnel, and money, which are all factors.

So, then we asked specific questions about R4S and CLIR, and we wanted to -- to first know about awareness, so are states actually aware of these tools and their availability. And there were 4 states that responded, from the 38, that said they were not aware of the tools; 89.5% of the states were aware.

And then, of those that answered yes, the -- the -- So, the remainder of the questions are basically for those who answered yes. So, do you have access to CLIR? And 67.6%, which equates to 23 states, have access to both R4S and CLIR, 29.4% had access to R4S only, and then one state did not have access to either of them.

So, then we asked about actual usage, so how often are the tools used by newborn screening programs and -- and other staff who, maybe, staff different parts of the newborn screening system. So, within the lab, about a third of the states use the tool at least monthly. Follow-up staff, about 8 of the 34 states responded that they use

the tools at least monthly. Some medical consultants stated that they use the system, and then "other" could have been anybody else in there, so it could have been newborn screening advisory committee members, biochemical consultants, scientists, and there -- there was, I think, one that responded -- must have been more than one. I don't have a percentage there, but. So, there are a lot of staff within newborn screening programs who are accessing the system and utilizing it on a -- a frequent basis.

We asked about training. So, of the 33 responses to this question, 25 of -- of them responded -- of the states responded that they had been trained on how to use R4S or CLIR, while 8 states responded that they had not received training.

And then, we wanted to know, how does a program use the R4S or CLIR tools. So, 22% said that they use it to determine which disorder the analytes markers ratios to include in the risk, so in assigning -- in -- in, basically,

determining whether a child is at risk for a disorder or not. Nineteen point two percent said that they use it for managing cutoffs, eighteen point two for determining risk for very select diseases. Setting cutoffs -- so similar to managing but actually setting the cutoffs -- They use it -- 12.1% of the programs use it. Determining the normal or abnormal status -- so that's a patient-by-patient look, so 7.1%, and determining risk for all diseases was 5.1, and then 1% said that they didn't use it.

So, then we asked, if your program doesn't use it to -- doesn't use R4S or CLIR to determine risk or normal/abnormal status, why not? So, kind of trying to look into barriers and -- and what are reasons that a program may choose not to use R4S or CLIR.

So, we have a -- a quote here. So, R4S has not been subjected to peer review with published results clearly supporting the use for risk determination. In addition, the algorithms have not been validated and are subject to

change, which does impose a risk on a clinician.

A second program responded that there's not enough evidence that the tools work better than cutoffs to convince us to do so. For R4S, the tool risk determination continuously evolves every time someone is adding data. You never know how well the tools were performing in the past, and there's not good integration with the state LIMS -- the lab information management system resources. There's a lack of normalization.

So, we asked specifically -- because there -- there were questions -- You know, the issue in the media was that there were false negatives, and if -- if there are different cutoffs in different states, then could they have been caught in one state versus another. And because R4S came up as an example where some cases could be detected with that versus using the normal cutoff that would have been in that state, we just asked: Do you have examples where using R4S or CLIR resulted in either false negatives or false positives? So, 32 states

responded. Forty percent said that no, there were no examples, 34.4% said they did have examples, and then some of them listed some examples.

So, in one case, there was a false positive for maple syrup urine disease, CPT1; there was a false negative using both the state's cutoffs as well as CLIR of beta-ketothiolase. Another one, there were two false negatives. So, there have been two known cases of babies diagnosed with maple syrup urine disease through our program that would not have been reported out for follow-up using the tool, and then, finally, the CPT2 and maple syrup urine disease concern was some disorders for positives that do not overlap the positive range significantly enough to get a positive score. As more data is added to the tool, we observe, significant change can occur.

And so -- and the point here is really that there -- these are extremely rare disorders, and there's nothing that's perfect and is going to pick up every case every single time. We had

some discussion about -- about that this morning, and the fact that this is a screening -- Newborn screening is a screening; it's not a -- it's not a diagnosis, and so the awareness that even though -- if you have a negative, as a physician, you see a negative result, a normal result, that if the baby seems to have symptoms of a particular thing, you need to go to diagnostic testing and -- and not rely -- not rule out based on the newborn screen alone.

So, we asked, also: Does your program use R4S or CLIR for every abnormal result? And 12.5% of the states responding said that they did, and then for those states that responded that they do use it -- and they could respond in multiple ways, it's that when using data from R4S/CLIR to determine risk or normality status, where are those determinations made? So, 21.1% said that it was made in the clinical setting by specialists, 15.8% said it was in the lab and results are reported on the newborn screening reports, and then another 15.8% said in follow-up, and results

are used to determine which follow-up algorithm to use.

So, when using R4S/CLIR -- and this was back to all 32 -- or 32 that responded. When using R4S/CLIR data to determine risk, has your program rerun values to obtain a new risk assessment on previously reported cases? Twenty-one point nine percent of the states responded that they had, which equates to seven states, and in one case, there was an example where the risk changed over time. So, I think that was mentioned in a previous -- previous slide where, as -- as more and more data are entered into the system that the risk itself may change.

Oops. Sorry. So, we asked states, what are the strengths -- what do they feel the strengths are of R4S/CLIR, and here, the larger font and the darker -- The -- the color indicates that that was mentioned more times, and obviously, it's a very large data set, and that was mentioned as a definite strength of the system. It can be compared -- You can use it to

compare to other states, validates newborn screening findings, it's helpful for rare disorders, supports risk assessments, and can help you rank the urgency of cases. Also mentioned multiple times was the choice of the modules and -- and that it's easy to use.

So, one quote from a state was: There's a lot of information about disorders and primary markers and also the ability to make sure the cutoffs are set appropriately. There are also ways of comparing results and cutoffs with other programs that use the system. So, that's helpful, as well.

We also asked, what are the perceived weaknesses of R4S and CLIR to try to get a feel for why states would choose not to use the system. And so, the responses -- the most common responses received were that the algorithm's not validated, need to customize the algorithm for each state, the lack of transparency, better integration is needed with the LIMS, data and tools are not method- or instrument-specific, the

tool changes as more data is entered, there's a concern about variability in the case definitions, and the training is lacking or not accessible when it's needed.

So, one of the quotes from a state was that there's no clinical data available about false positives, referring to specificity of positive predictive value. The tools give very likely, likely, possibly, and not informative. These are very subjective interpretations. If the system were tied to results from false positives, more information could be provided to clinicians when diagnostic testing is recommended for babies with positive screening results.

And then, we asked about data submission, so do states participate by submitting data to R4S or CLIR. So, when asked about submitting normal population data to R4S/CLIR, 34.4% stated that they do actively submit data, 31.3% noted that they used to submit but they do not submit data anymore, and then 34.4% responded that they did not submit normal population data results to

R4S/CLIR.

We asked about the frequency of submission of that data, and so, overwhelmingly, most did not submit quarterly or annually or monthly. The lack of staff time was the most common reason given for not submitting data, and then in regards to frequency, some submit upon request, some submit biannually, and others intermittently, as time allows.

And then, in regards -- So, the previous slide was for population data, and in regards to case data, 53.1% of the states responded that they do submit case data to R4S or CLIR, 28.1% said that they used to submit but do not anymore, and 18.8 -- 18.8% responded that they do not submit case data. And the frequency, again, is very similar, with only 5.9% submitting either annually or monthly and the remainder submitting other. And again, the same sort of time frames, so either biannually, intermittently as time allows, or upon request when confirmed cases have been identified.

So, we asked: Why did your program stop submitting data, and again, lack of staff time, difficulty collating data from the LIMS, so actually getting the data from the LIMS to add to the system. In one case, it mentioned that the department of health was concerned about potential data security issues. There was a concern expressed with managing, storing, and sharing newborn screening data without a parental consent structure within the program's newborn screening process, and then legal concerns were also expressed.

In reference to the concern about uniform definitions about, you know, the cases that are entered into CLIR, we asked what benchmarks are used to define a case before adding it to R4S or CLIR, and typically, it was a positive diagnosis that was confirmed either by a clinical specialist, the follow-up program, or a genetic referral center.

So, in conclusion, we did have limitations. First of all, we -- we only received

38 responses, so we didn't receive responses from all states. We did ask some additional questions to some of the states for clarification on the responses that were provided, but we didn't receive that information back in time to include it in this presentation.

In addition, there -- even though we piloted the -- the survey and -- to see if we would get the answers we wanted, we noted that there were -- there were not always -- the answer we were given was not always to the question we were asking, and so interpretation of -- of the questions was a limitation of the survey, as well.

So, in regards to use of R4S or CLIR, approximately 97% of the states that -- that completed the survey do have access to the system, and -- and many of those programs do use it on some sort of basis. States have varied processes in determining what their cutoffs are going to be. That involves analyzing state population data derived from screening of normal

and affected infants, incorporating feedback from the specialists within their state, consulting published literature and/or R4S or CLIR, consulting other state newborn screening programs. And we did note from the survey that states have mechanisms in place to reevaluate cutoffs and -- and do that on a regular basis.

We -- So, APHL has a QA/QC Subcommittee, and that subcommittee has been working on a document that would be basically a guidance document for states on ways -- not, like, one way to set a cutoff, but basically gathering guidance from different regulations and -- and other guidance documents to basically come up with something that newborn screening programs could refer to when setting cutoffs, and that's going to be discussed -- We'll get an overview of that at the Lab Workgroup meeting this afternoon.

I think it'll be good to be able to provide the results of the survey to the QA/QC Subcommittee, and I think that -- that they'll be able to glean some additional information from it

and perhaps determine where some additional gaps may be or where additional guidance may be needed.

So, if anyone has any questions or comments?

DR. JOSEPH A. BOCCHINI, JR.: Susan, thank you very much. This is open for questions, comments. Dieter?

DR. DIETRICH MATERN: I have a few comments, but I guess I first have to disclose that I'm an employee at Mayo Clinic, where Dr. Rinaldo works in close proximity to my office. He's the inventor of R4S and then CLIR. This is a free product that anyone can have access to, free meaning it doesn't cost you money, but it does cost you time, and you have to submit data. Does -- if that doesn't represent a conflict of interest, then I will make my comments.

(No audible response)

DR. DIETRICH MATERN: Okay. This survey -- The survey was put together, apparently, by some people who don't really know R4S or CLIR.

R4S/CLIR is not the same, so they're very different, as Piero, based on the minutes, informed everyone here at the last meeting.

So, most of the questions, I think, are misleading or getting you answers that you might want to have. The audience, as you indicated, were newborn screening programs or those related with newborn screening. I don't believe we received the survey at Mayo, which would have probably helped to kind of provide you some input as to how those questions should have been asked.

The weaknesses of CLIR being not validated, not peer reviewed, I think are wrong, because there are multiple papers out there that are all peer reviewed. If a state wants to check whether the system works or not, it is very simple. You use the paper written by Hall et al in Genetics in Medicine and basically do what California did. They took the data for whatever, 200,000 babies, and ran them through CLIR and could show that they would have reduced the false positive rate by 90%. Every state can do that

with their own data.

Training -- many states have been trained. They went back and just forgot about it, or the people who were trained were told, "Don't do that." You can actually save time by using CLIR, and that can free you up doing other things that you should be doing.

I think I'll stop here for now.

DR. SUSAN TANKSLEY: And there is training available; it's online, and this is a representation from the results that we were given back. So, thank you.

DR. JOSEPH A. BOCCHINI, JR.: Joan?

MS. JOAN SCOTT: Thank you. I just have one quick question. On the states that responded -- I think the total number was 38 -- was there any analysis done on respondents versus non-respondents that should be taken into account, also, when looking at the responses?

DR. SUSAN TANKSLEY: No, that hasn't been done yet, but we can certainly look into that.

DR. JOSEPH A. BOCCHINI, JR.: Kamila?

DR. KAMILA MISTRY: I think the other concern is, really -- You know, the comment that you made about people interpreted the questions differently, so that just gets to the heart of, you know, just survey methods in terms of validity of the results. And so, I -- I mean, is there -- do you have specific questions that you're concerned about, or do you feel like that was a concern overall?

And, you know, I think Dieter also pointed out some specific questions around, you know, the way that the terms were sort of, you know, combined. And I mean, in some ways, it's a double-barrel question because if it's -- if they're different, then, you know, you could have asked that question about one and then the other. I think that --

So, there's a number of those kind of concerns which then makes me wonder about the results, and -- Are there specific questions that you're more concerned about or overall --

DR. SUSAN TANKSLEY: Well, so, the very

first question about just describing your process used to establish which infants, essentially, are going to need referral after screening. So, we were trying to not say, how do you establish cutoffs, because we didn't want to presuppose that they use a cutoff, because they could have used CLIR, which is looking at multiple analytes as well as the data at the same time. So, we were trying to ask that question without giving a response and trying to actually determine what is your method for developing the cutoff or -- or how -- whatever you use.

And we got some responses that started with: Based on the cutoff, we do this. So, it was after cutoff, how does the referral happen versus how is -- what sort of data is used, or what do you -- what do you utilize to determine what you would actually consider to be normal versus abnormal. So, that's -- that's one example.

And then, in regards to R4S/CLIR, that was meant as, do you use either system. We know that they're very different.

DR. JOSEPH A. BOCCHINI, JR.: Jeff.

DR. JEFFREY P. BROSCO: I -- I have two questions. Thank you for -- for bringing this to us.

How -- how does APHL -- how do you see this survey fitting into a bigger, sort of, project -- I mean, I presume that you did it with a particular idea in mind -- and how do you think that you use the data, or is it not as useful as you had hoped? Because you sort of said that yourself. And then --

DR. SUSAN TANKSLEY: Well, I --

DR. JEFFREY P. BROSCO: I'll let you answer --

DR. SUSAN TANKSLEY: I'm sorry.

DR. JEFFREY P. BROSCO: -- that and then I'll ask another one.

DR. SUSAN TANKSLEY: I'm sorry.

DR. JEFFREY P. BROSCO: Go ahead.

DR. SUSAN TANKSLEY: So, we received -- we -- we boiled down responses to have something that's presentable, but I literally have four-

and-a-half pages of small font just from the first question.

DR. JEFFREY P. BROSCO: Wow.

DR. SUSAN TANKSLEY: So, you can take that information, and then that can be used by -- like I said, I think we need -- we now need to hand this off to our QA/QC Subcommittee so that they can look at the information and try to determine: Are there -- what -- what are the gaps here, what are the issues being faced, and is there a -- a tool -- is there something else that needs to be addressed in the guidance document, specifically based on the responses that are received in this survey? So, I think -- I think there's a use for the information.

DR. JEFFREY P. BROSCO: Right.

DR. SUSAN TANKSLEY: No, it's not a perfect survey, fully --

DR. JEFFREY P. BROSCO: So --

DR. SUSAN TANKSLEY: -- fully acknowledged.

DR. JEFFREY P. BROSCO: You know, I think

that makes a lot of sense. This isn't so much a research study on whether CLIR works or not or should work or not; this seems more like a -- sort of a quick survey to find out, where are we in --

DR. SUSAN TANKSLEY: Right.

DR. JEFFREY P. BROSCO: -- the field. It's an assessment before you start doing teaching. So, it's a very common, kind of, pre-diagnostic thing. So, that makes sense from that point of view, and so we can all take a deep breath.

All right. The second question is more about the fundamental issue about false negatives. And I -- I think we might have talked about this in one of our workgroup calls. And is there a sense that we have an understanding of how many false negatives there really are? And I know there are media stories about it, so it's always hard to know if you've got a lot of traction because of media stories, or do we see this as a widespread problem that deserves a huge

amount of attention -- because we don't want to miss cases -- or is it that there are going to be some small misses here and there, and that's just the way things are? I mean, how do you -- What's your sense of that?

DR. SUSAN TANKSLEY: Well, so in regards -- in regards to false negatives -- and I know this was discussed at the last meeting, as well, as I was reviewing the minutes -- You know, these are extremely rare disorders, and so when there are false negatives, when we miss something, when there's something that's out of range, below the cutoff, above the cutoff, whatever it is, we have to have feedback from -- from the medical community in order to even know those cases exist, first of all.

So, when there is a false negative, when a newborn screening program is made aware of that, they go back through -- They take that very seriously. They look at -- They reanalyze the specimen, if they still have the specimen, and try to determine, should this have been caught by

our existing system? Why was it not caught? What went wrong that caused this issue? They may go back in and -- and put the data in -- into R4S and -- or CLIR and -- depending on which disorder -- and say, "Okay, would we have caught this?" But there's an analysis that's done to determine that, but without the feedback, without knowing -- without knowing that there is a false negative, you can't do any of that.

You know, there's -- States try -- When -- So, let's say there -- there's a new disorder that's added or a change in technology, going back -- the ability to be able to go back to residual specimens from a case, a diagnosed case, and to be able to analyze that and determine, where should I set my cutoff or -- or how can I actually detect these children -- You know, that's -- that's -- it's an analysis that's done. It's taken very seriously. The more information you have, the better.

DR. JOSEPH A. BOCCHINI, JR.: Carla?

DR. CARLA CUTHBERT: Susan, thank you for

-- for your presentation. It's very, very informative, and I -- we really appreciate what you guys have done.

At CDC, we've been trying to think of ways that we can, perhaps, help. I know that as part of our process as a -- as an agency, we do not set cutoffs. This is something that -- that every state and every program has to determine for themselves.

And in -- in a discussion about how we might help, we were wondering whether it would be beneficial for us to be able to get borderline positive cases or even borderline -- borderline cases at all from state programs, have it be tested at CDC, and recreate some of those materials and redistribute them to programs, so that at least there -- there would be some level of -- of samples available to states so that they could know what samples might have given a positive result. Is that something that would be helpful at all, do you think?

DR. SUSAN TANKSLEY: I think that would

be incredibly valuable in order to -- to have samples that would actually simulate positive, real cases, simulate real cases that might or might not be caught if they're really in that -- in that borderline range.

DR. CARLA CUTHBERT: Right.

DR. SUSAN TANKSLEY: You know, there are -- there are some disorders where we know -- and this was talked about this morning -- where -- where we know that we're going to miss some cases. Cystic fibrosis is one of them. We know for a fact we're not going to catch every one, otherwise we'd be sending half of the population for sweat testing. And so, to have -- to have a resource like that, I think, would help states.

DR. CARLA CUTHBERT: Sure. And that's something that we can certainly do, and I -- And again, for the very, very early states and programs that actually do this, you have no sense, because these are rare -- rare specimens and rare cases. I know that you guys set very conservative cutoffs to be able to try to capture

as many cases as you possibly could, so I know it's sometimes hit and miss, and these patients do teach you a lot about where to set some of these -- these -- these cutoffs.

DR. JOSEPH A. BOCCHINI, JR.: Dieter?

(Off-mic speaking)

DR. DIETRICH MATERN: Dieter Matern. About the false negatives -- The beta-ketothiolase case and the MSUD cases that were brought up through the survey may have been one beta-ketothiolase case from Minnesota that was published, and I don't think that any change -- any reasonable change in cutoff would have made that a positive. Unfortunately, thanks to the Minnesota laws where we had to destroy everything, we cannot go back and see if CLIR would pick that up today.

The MSUD cases -- MSUD is, as most of the conditions, has variable phenotypes, and thiamine response of MSUD is probably not detected in most cases. And that is also published. And maybe those two cases are the ones from California,

where even the second-tier test looking at alloisoleucine was negative.

So, that is just a fact. There are some cases you will not pick up. But, again, not having seen the data, I don't know if CLIR, today, would really miss them or would pick up more than we have in the past.

DR. JOSEPH A. BOCCHINI, JR.: Mei?

DR. MEI WANG BAKER: I just have a couple of comments. A comment to the false negative -- I feel, when things happen, indeed, that we need to check our system and look at that, but I think we also keep in mind the specific case is what kind of circumstance we need assess it. Is it really -- Is it because the system failed or because this case has special situation? And we experience with that.

And the babies with mild MCAD because have some sickness or have sugar, you know, loaded -- You -- you just cannot -- I -- I think it's very important, because if you just because of miss this, then you change everything, you may

not solve the problem you --

MALE SPEAKER: Right.

DR. MEI WANG BAKER: -- intended to. So, I think we need to keep this in mind.

And also, I want to echo about MSUD. So, when you mentioned the case, I immediately in my head is, you mention one type. But also -- MSUD also have called a intermittent type, and you -- you can -- you can -- because they were not sick, each don't have that, is why people start look at -- analyzing those things.

So, I think we need be careful. The things that we -- we haven't picked up, is it really everything's contribute to cutoff, so we need to be very, very careful to -- to look at this.

DR. SUSAN TANKSLEY: I -- I agree. I mean, definitely, investigating false negatives, you have to take everything into consideration, not just the cutoff, and try to learn more about the case.

And I think both you and -- and Dieter

have referenced definitions, and, you know, we -- we talk about case definitions all the time, and we have for years, and how do you define a case, and what are you screening for. And it's really hard to answer that question, and each -- within each program, there may be a different definition for what you're actually screening for. And when we get reports sometimes, we ourselves have to ask, what are we really -- are we trying to catch that particular case? We were set up to screen for the classical type, and this may be three types down from that.

And so, it -- it really is a question I don't have the answer for, but what -- what are we specifically screening for when we say we're screening for a particular disorder? And that's one of -- one of the concerns, was the cases that are within R4S and CLIR as -- as diagnosed cases. That's as a case -- as a state defines them. And so, each state having different definitions, there is different types of a disorder, perhaps, that's -- that's for -- that's -- that's within

the database.

And so, I don't know -- I don't know how we solve those problems, but case definitions seem to be something that continue to come up. I know it comes up within -- within our own program in Texas: What are we screening for?

DR. JOSEPH A. BOCCHINI, JR.: So, I have Mike Watson and then Carol Green.

DR. MICHAEL WATSON: So, it sounds like the -- I mean, the -- the best way to get to the resolution is the comparative analysis of the cutoff systems being used and the CLIR tool or the R4S tool. How many -- Is California and Georgia the only two states that have really done that comparison, or are there other states that have actually run the comparison of the tools?

DR. DIETRICH MATERN: Dieter Matern. Piero is working with several states currently, primarily focused on congenital hypothyroidism and looking, also, at the one-screen versus two-screen option. Again, I think every state can do that. It's really not that hard. As long as you

have your own data, you can just run them through CLIR and see what you get and compare it to what you got through the prospective screening.

DR. MICHAEL WATSON: Certainly, the false positive rate -- We talk more about missing people in the negatives, but the false positives are enormously expensive on the workforce and the health care system. I mean, when you have -- we -- I know tandem mass spec was running at a level of 2% positive predictive value all the way up to 60% across different states, and the implications are enormous amounts of money.

DR. MEI WANG BAKER: Just to follow with Mike's comments -- Actually, Wisconsin, right now, we are parallel. We are doing -- we just start a couple of weeks ago for Pompe, so what we are doing now is parallel running to traditional cutoff. We have the -- 30 the medium percentile cutoff. Also, at the same time, we use the CLIR tool.

So, the -- our -- we want to do a prospective comparison, and our idea is, from

either system, indicate positive or go through more -- even second-tier or confirmatory, and in and we hope about a year or so time, we'll have data. And I can tell you right now, we getting to more -- close to 4,000. Everything has been agreeable, so we are continuing doing that.

DR. JOSEPH A. BOCCHINI, JR.: Carol?

DR. CAROL GREEN: So, I have two very short things and one major philosophical question that I think is underlying all of this. One is, there was a great discussion about the physiologic differences that, you know, not all false negatives are equal, but coming back to the slide -- and -- and I'm hearing lots of people talking about MSUD cases, and I'm noticing, on that slide, a very big difference between the second bullet and the third bullet.

The first one, false positive for MSUD and CPT1 -- if that's one case each, you know, that's one case; that's not a big -- The second bullet's really clear. The third bullet, would not diagnosis with MSUD through our program that

would not have been reported -- that's not reaching the level of clarity of the second bullet. Diagnosis through our program because the kid showed up clinically and would have been missed by the state's tool --

So, I think going back to find out, was that missed by -- was that picked up by the state screening but missed by CLIR and RL4 -- that would be not physiological. So, that just needs to be clarified. And the people who know the case may know the answer, but it isn't clear to me from the slide.

The second thing is, is when the states -- the lovely quotes about the states, why they're not using RL4, the third point is -- is the one about the -- the reason the -- the philosophy, the validation, the whatever. But when they say that cutoffs changes (sic), well, states change their cutoffs all the time. The only difference there, at least, is, the state knows when they changed them.

But I've been working with state newborn

training labs forever and ever and ever, and the whole point of all of them reevaluating their cutoffs is, when you have too many false positives or something's changed, you go back and you change the cutoff. So, the fact that RL4 and CLIR changed their cutoffs over time, it's a moving target. That's what the states do. So, it may be something that could be negotiable.

But I think the basic philosophy is, we're right here at the margin between medicine and public health, and do you require -- I mean, the federal government cannot require any doctor to come up with the same answer as another doctor. And this is a lab, this is medicine, but it's also screening, and to what extent can anybody compel a state to use something if they feel that they're not protected legally?

And I think we're talking a lot about which is more accurate, but I don't think that's the question. I think the question is a fundamental point of, can you control what people use? Is there any reason people can't use both?

Can they refer to it? You know, I think -- But I -- I think there's a lot of talk about which is better, but it's not better. I think it's, which is going to be acceptable to -- to the states' attorneys.

DR. DIETRICH MATERN: When it comes to the attorneys, I mean -- or states feeling that they cannot use it, I really don't care what they feel about. I mean, ask your attorneys whether you are at risk, which means that the attorneys need to understand how the system works, what is known about it, and what is transparent about the limitations of the system. I think as long as one is honest about the tools that one uses and points out potential limitations --

Again, I think there were many more limitations mentioned through the survey than there should be, because that -- that's just not true. I think one can move on. But based on feelings is just not getting us anywhere. Where's the Evidence Review Group?

DR. SUSAN TANKSLEY: So, I -- I want to

make one comment in response to -- to Carol's point about the -- the -- the validation. So, I've -- I've been in many conversations about this, and so a concern that I've heard expressed -- So, any time, in a newborn screening lab, that we make a change, we have to revalidate. So, we go back through and revalidate it or reverify it and make sure that we're still going to have accurate results. The concern is that as more data are put into the system, it's not revalidated. That's the concern.

DR. CAROL GREEN: And -- and I -- it's -- I'm thinking that I probably was not entirely clear for both sides, is that I'm not sure that a federal -- Well, I think it's an incredibly complicated discussion. I don't -- I think our state -- I don't know if Lisa (phonetic) is here -- I think our state -- I know we set cutoffs, and I know we use CLIR. And we go back and forth, and, you know, we use our -- we use CLIR to look at our cutoffs, and we use our cutoffs and we go back and look at each case.

And I think there are multiple ways to do it. I'm just wanting to put on the table that I think it would be very hard for a federal committee to mandate how state labs practice their interpretation.

DR. JOSEPH A. BOCCHINI, JR.: Natasha?

MS. NATASHA BONHOMME: Thanks. I have two questions and then a comment.

For -- Going to the survey: Are there plans to do anymore data collection or -- you know, understanding that this was kind of a snapshot and a very general collection of data from states, but is there any plan to do this any further, particularly around getting more specifics around the plans or the process to communicate reference ranges and protocols back or more details around how the risk assessments are reported back?

DR. SUSAN TANKSLEY: So, as I said, data collection ended 2 weeks ago, so we haven't yet thought -- and I think there's a lot of ideas being generated in this conversation today that

could lead to us going back and asking for further clarification, either specifically from states based on how they responded or to come up with an -- with new questions to dig deeper.

And so, at this point, we don't have -- we don't have a planned next survey. As I -- as I mentioned, I really think the QA/QC Subcommittee would be a good place to send this information and let them -- let them dig further. But, I mean, some of the places that have specifically been pointed out, we can -- we can dig a little deeper in those, as well.

MS. NATASHA BONHOMME: Okay. And do you know of -- I think the way you laid out, you know, what happens when -- and the program finds out that there's a missed case and, kind of, the process along that was really wonderful, and I was wondering if there -- if that is laid out anywhere in terms of what happens if there's a missed case or a -- a suspicion of a missed case.

And I guess I'll just jump into my comment. I think it's important -- I know that

we've gotten really specific into R4S and CLIR and the data, but what kicked all of this off was a media report, which really means that someone either found something out or didn't understand what was going on. And so, there needs to -- I would say, there needs to be a communications education perspective on this and not to think we're covering that with the information that is being gathered and mainly discussed today.

And so, one, kind of, thought of that -- and I am sure there are liability issues and all of that, but I don't know if you know of any states or any public anything that actually lays out, well, what happens when there's a missed case, or even before that, what are cutoffs? Why are there different --

You know, there's a lot of this discussion that it was clearly triggered because people don't know and think that, oh, maybe labs aren't thinking about it. But there just seems to be a really big communication education component here, and I'm just wondering how -- are there

examples of that need being met, and if not, from your perspective, do you think that also needs to be part of this discussion? Not this one particularly, today, but the broader discussion of cutoffs.

DR. SUSAN TANKSLEY: Well, I think -- I think there needs to be a better understanding of newborn screening in general. We've addressed -- we've addressed that issue -- not addressed, we've discussed that issue on a -- on a public level and the understanding of newborn screening, and even not just public, but even parents. And, you know, the -- the clearinghouse has done a great job at -- at bringing that information into one location so that -- that -- that parents can go to that information and obtain that information.

I think there's a huge opportunity here to also think about reeducating primary care physicians about what newborn screening is and what it means, what those results mean, and -- and the whole -- You know, in the -- in the media

articles that came out, the -- there seemed to be instances where the physician ruled out a disease, a -- a particular disorder, because the newborn screen was normal.

And, again, if -- Newborn screening is a point in time. It's -- it's -- so, it's a snapshot depending upon when that -- that blood spot is collected. We've talked about variable expression of -- of the -- the condition itself. And so, it may not -- Whenever the blood spot was collected, that analyte may not have been elevated or low, depending on the condition. And so, if it looks like something's wrong, it shouldn't -- you shouldn't rule out based on a newborn screen.

And I think that that's a message that needs to be given to health care providers so that, yes, the newborn screen was done -- check -- but it -- but more than that. If it still looks like cystic fibrosis, get the baby sweat tested. Don't just assume it's not cystic fibrosis, because the baby -- baby's newborn screen was

normal for that.

So, yes, we -- we do need to do a better job, and -- and I know we -- we've talked about putting information on -- on the clearinghouse about cutoffs and trying to come up with language about why they are variable in different states and that sort of thing, so that we can try to get to that more parent-type education, but I think there's a role, also, here for opportunity to educate the health care providers, as well.

DR. MEI WANG BAKER: I just wanted to make additional comments. I think Natasha is kind of concerned, like, to medium find out what's really going on if they don't, right?

I think I can speak from our -- you know, our state experience. So, actually, we take false negative very, very serious -- seriously. Every single time when they become too -- when we're aware of that, we do thorough investigation, again, take all these into consideration, then take to our advisory board. So, that's a situation. Then we understand what can we do in

future trying to avoid it.

And I can give you example. The news media talk about a Wisconsin case that -- propionic acidemia , and we -- after, we did a investigation. We really feel we need to change our cutoff. But also, we recognize, changing cutoff alone will cause another side problem: too many false positive. What we did is, we changed cutoff lower, and we waiting on the second-tier testing. So, that's why you -- this -- I think that's the process.

And also, we learned, special community like Amish, their history is very low. We -- even we cut it low, we still may not be able to get information. For that community -- community, now we encourage them, in the newborn screen cards, indicate they come from this community. We just do the second-tier directly, and we do medical testing directly.

So, I -- I just want you to know, like, program does -- I mean, programs do have this kind of in place, and everybody pay attention to

false negative very, very seriously. Just -- if it never come to our attention, then we don't know. Yeah.

MS. NATASHA BONHOMME: I just want to say, I wasn't implying that I thought programs didn't. I think it's more so, we who are in these meetings and speak to each other, we know all the effort that goes into it, but we can't -- If we're not communicating that out beyond the newborn screening chorus, or choir, you can't expect someone on the outside to really understand that and to know that and to appreciate the effort and the time that all of that analysis and investigation takes.

DR. CATHARINE RILEY: Hi, this is Catharine Riley. Just a reminder for the transcripts and for those on the webcast: If people could state both their first and last name before comments, just helps for the documentation and for those on the webcast to -- to know who's speaking. Thank you so much.

DR. JOSEPH A. BOCCHINI, JR.: Yeah.

Melissa and then Annamarie.

DR. MELISSA PARISI: I just mostly wanted to make a comment and -- and an experience that recently happened with one of our groups -- Sorry, this is Melissa Parisi. I just disobeyed your --

(Laughter)

DR. MELISSA PARISI: -- your guidance, Catharine. Sorry.

So, a comment -- a -- a real world example, too. I mean, I know we -- we all have examples, those of you in the laboratory setting, in particular, but we had been -- We've been funding two states to do pilot screening for MPS I, as you know, which was added to the RUSP not so long ago, about a year ago, and North Carolina was having a problem with a really high false positive rate.

And based on talking with another state and hearing that, I think, Kentucky had had success using the CLIR tool, was actually able to incorporate that into their algorithm during the

development of the screening protocol and was able to reduce their false positive rate by 80%, thereby saving our investment -- the government's investment -- in their screening, allowing them to screen more newborns and to reduce the number that required secondary evaluation and, potentially, those who got called back and the stress on families.

So, I do think that there's value in using some of these analytic tools, particularly during the process of protocol development, when new conditions are rolled out by states and to think about incorporating them earlier rather than later, because I think once a -- a given program has experience in using the tools and feels confident that the -- the cutoffs that they are able to garner by using these tools are effective, then it becomes a really valuable part of their screening process.

MS. ANNAMARIE SAARINEN: Hi, Annamarie Saarinen, Newborn Foundation. I really, really don't mean to oversimplify this, but to Mei's

point: If you took a problem in your state and you've systematically solved it, and you now have the data to show that that's happened -- And it sounds like, from Dieter's experience, many of the states that have been able to run against the -- the algorithm basically can, sort of, do the same.

I -- I'm trying to figure out how there isn't just a best practice that can support standardization, because until that happens, I don't see a day when we don't have families coming in front of this committee and saying, like, "Well, if my baby had been born across the border in this state, this -- X, Y, or Z would not have happened." And I'm -- you know, I'm -- I'm all about, you know, states being able to adapt their programs for their needs, and so not, sort of, homogenizing everything, but in this case, there is, I think, a desperate need for standardization.

And maybe we were lucky enough with CCHD screening, when that came down the pike, to have

that sort of expert workgroup forum that Dr. Puryear and others here helped pull together after the committee sent its letter to the secretary, but the output of that was a -- and I know Alex hates it, but it's like the -- the Kemper protocol, right? The output of that was something that has been almost universally adopted by every state in this country.

And I'm not saying that it won't change or be optimized, because it almost certainly will, but at least in -- in most cases, there's very little variance between how that test is done and how it's measured by the newborn screening departments. So, for the blood spot screenings, I assume it's probably far more complicated, but what, truly, is the barrier right now to having standardized cutoffs from state to state?

Sorry, you did a great job in your presentation, by the way. Thank you for sharing the survey results.

DR. JOSEPH A. BOCCHINI, JR.: First

Carla, and then if you want to come up, Michael.

DR. CARLA CUTHBERT: This is not the first time I've heard a comment like that before, so, Annamarie, thank you for bringing that up again. And I know that we've had several conversations about the fact that different states do different things, so I know that at -- at one level, it would be really nice to be able to have a single cutoff and have every state, sort of, conform to the -- if it's above, you're good; if it's below, you know, you're highly at risk.

That's just not how it happens in practice and laboratories. Laboratories have different platforms, which means that they do not always get the same absolute values.

Another project that we're thinking about adopting at CDC, as well, is doing a level of harmonization. One of the things that the states do receive is that they receive all of our quality materials. So, we're -- we're actually looking into taking a look at the cutoffs that

they share with us and then normalizing against QC materials that we give them to sort of see if we can actually have a -- a standardized or a harmonized way of looking at cutoffs of tests.

But -- but that only gives a part of the story, as well, because you -- there are some states that modify their cutoffs because they're able to run second- and third-tier tests. So, you can't have one -- one cutoff that works entirely.

One of the things that we need --

(Off-mic speaking)

DR. CARLA CUTHBERT: -- to pay attention to, though -- Pardon me?

(Off-mic speaking)

DR. CARLA CUTHBERT: Yeah, and -- and that's --

FEMALE SPEAKER: Like -- like, so that you can provide that information so that --

DR. CARLA CUTHBERT: Mm-hmm.

FEMALE SPEAKER: -- states can strive for getting to that.

DR. CARLA CUTHBERT: Correct, and that's

actually what the Quality Assurance/Quality Control Subcommittee is actually going to be working on. So -- so, they are absolutely looking at the practices that occur around the country. They're going to incorporate the use of -- of the CLIR tools and -- and R4S, and I know that R4S is sort of on the side now, and CLIR is what Mayo's moving with, right? Is that correct, Dieter?

(No audible response)

DR. CARLA CUTHBERT: So -- so, there are users of these tools. And so, in terms of how you do what you do, those -- that guidance is going to be developed, and they're -- they're in the process of actually doing that right now.

Again, we are a -- a federal -- a federal entity, and we cannot tell the states what to do. As much as we would like, in our -- on our pulpit, to say, "This is right; you know, you should do it the way I -- I -- I think is right," we can't do that, but we can offer good guidance. They can come up with -- with a sense of, these are the ways that it's worked for us, and -- and

-- and that's how you go -- go forward with it.

So, I hear what you say, and I know that there's a desperate need to -- to simplify it in that way; that's just not how -- that's not how it can be done in practice, so.

DR. JOSEPH A. BOCCHINI, JR.: So, Dieter and then --

DR. DIETRICH MATERN: Dieter Matern. So, there is a best practice, and the best practice is to use CLIR. I think, again, the data that are published suggest that, and the data apparently out of North Carolina would suggest that. And our data from Kentucky suggests that, where we have screened, now, probably, 70,000 babies for 3 lysosomal storage disorders, where we found 3 kids with Pompe disease, all late onset, 1 with MPS 1, 1 with Krabbe disease, and we had 1 false positive because I overrode the CLIR result, which I shouldn't have done in retrospect. So, that's the best practice right now.

(Off-mic speaking)

DR. JOSEPH A. BOCCHINI, JR.: Committee

goes first.

DR. JEFFREY P. BROSCO: Okay. But it was a slight change in topic, which was to really push Annamarie's suggestion and say: This isn't just about cutoffs, right? This is about, as lab practices get more and more complex -- and I'm sure this committee's been through it before, so I'm ignorant of the answer -- why not have -- move it towards more regional sort of labs? I mean, it's clear that for follow-up and local, sorts of, issues they're critical, but for testing specimens, it would make sense to not have to have 50 states, or however many there are programs doing this, each do it themselves.

DR. CARLA CUTHBERT: Again, regionalization is something that -- that a state lab has to determine that they want to do, and there are -- there are instances of -- of that happening. Not every state's going to want to do their -- their testing, and they will contract with another state to do that. That's currently in practice now. But that's something that they'd

have to choose to do. And, again, as resources get tighter, maybe that will be a solution that they will actually come -- take advantage of more so.

DR. JOSEPH A. BOCCHINI, JR.: Okay. Dr. Schneider, if you'll just state your name and affiliation?

DR. JOE SCHNEIDER: Absolutely. Joe Schneider, pediatrician. I'm clinically with UT Southwestern in Dallas, and I'm a pediatric informaticist who's retired at this point.

I just want to say plus one to -- "Plus one" is that I agree strongly with the concept of the -- not doing things 53 different ways, because the -- the -- the points that are being made about trying to get to use the committee's voice to say: There is a best practice -- And -- and when Dieter says it, it comes out with a little bit of potential bias, but at the same time, I think there are better ways to do this rather than to have 53 different ways.

And -- and frankly, I would say, please,

would you all speak with a single voice to the -- to -- so that we who have to suffer on the outside -- because I take care of these -- these babies. I get the calls on Saturdays and Sundays. The -- Can -- can we speak with that single voice to say: Let's get to more national best practices? And states, while we culturally really want to respect your authority, there -- the -- there are scientific things that sort of cross borders, and we need to respect those and -- and -- and really push those.

One other quick comment, if I could. I mean, I really -- So, emphasis on standardization. The other thing to think, there -- there are cultural issues. I used to be an anthropologist, so everything's culture in my life. The -- and that is the -- when you say the words "positive" and "negative," it is incredibly difficult for me as a pediatrician, when I'm faced with a child who has a problem, to overcome the word "negative" on that screen. And -- and I know and I was trained not -- you know, that it's

just a screen, but those words say "negative" to me, okay?

And so thinking about how -- we -- we can certainly try and retrain the world. That's -- that's -- that's usually not a very practical thing to do. But finding different ways to communicate the results so that it's not so -- you know, not positive and negative, because negative, it puts -- it -- it puts it into a level of my differential that I'm -- it's really going to be hard for me to retrieve it and make it something that I'll consider.

So, I -- I just wanted to -- those two different points. Thank you very much for the time and all the things you do.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. Other comments?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Okay. We'll take one more from the floor.

(Off-mic speaking)

DR. JOSEPH A. BOCCHINI, JR.: You're

going to need to come to the microphone.

MS. SABRA ANCKNER: My name is Sabra Anckner. I'm a nurse consultant with the state of Alaska, and just along this conversation just wanted to throw in that there are differences in states. So, when you look at things like the Alaskan native population and the CPT-1A arctic variant, if we were using a single cutoff for the C0/C16+C18 ratio, it would not work for other states, the cutoff that we use, because of the incredibly high prevalence that we have.

Additionally, we have different cutoffs for 17OHP for Alaska native kids than we do for other kids because of the incredibly high rates of salt-wasting CAH that we see in kiddos who sometimes do seem to express that -- at birth a little bit lower levels than kids of other ethnicities.

So, just throwing that out there from our experiences, which is that, for us, in some circumstances -- and I imagine that's true for other places with -- with diverse populations,

that that is not always realistic to have a single cutoff, so.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. So, are there any questions or comments from the people on the telephone?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: If not, then, Susan, I want to thank you. I -- I want to thank APHL for providing this. I think this -- as Jeff said earlier, this is a -- sort of a map of what's going on in the country right now. It's -- it's sort of a scan, and it gives us an -- an -- an opportunity to decide where intervention might take place.

And to Dieter's comments, I think when -- if there are people who responded with things that are felt to be incorrect based on the available evidence, then that's, again, evidence that we need to educate. And -- and so, I think that -- it -- it also fits around providing guidance, providing, within that guidance, what would be termed best practices, and then have

them applied, as needed, to individual states.

So, I think that -- that -- that the discussion was really an important one, and I -- I think it helped frame some of the discussion that needs to be going on, going forward.

So, I had put together a couple of slides that kind of reviewed some of the -- the main topics that we've covered in the last couple of months, but I decided I'd skip that, because I think the majority of them came out in this discussion, and I just have the summary slide here.

So, what -- what do we think needs to happen moving forward? And -- and I think that after May's meeting, we asked, on a couple of phone calls, for -- for the presenters to discuss with us, the leadership of the committee and -- and heads of some of the workgroups, what -- the -- the potential role of the committee and -- and how we might help make things work going forward.

And -- and -- and at the end of the May discussion, we sort of divided things into two

parts related to this topic. One was the -- the issue about cutoffs themselves and how laboratories do them and how they utilize them and -- and -- and how they change them, and then how they address some of the issues related to having a false negative that, as Susan said, gets -- if it gets reported back to the state, what -- what happens.

And so, that was one portion of it, and the second portion of it was that it was clear that, in some cases, a screen was being considered to be diagnostic, and so that there seems to be an educational component for providers, and as Natasha said, I think we can add, to the public, as well, about understanding that a screening test is a screening test, and it's -- if it's negative and the patient comes with symptoms, then the -- the -- the diagnosis needs to be considered regardless of what the screening results were.

So, we sort of divided things into two parts, and one thought that because the APHL

Subcommittee that's developing the guidance document was working through the document and we had people on the call involved with that, that it would be good to have the -- the Laboratory Standards and Procedures Workgroup here where they were and provide feedback. And -- and so, there will be a discussion today at the Laboratory Standards and Procedures Workgroup related to where that guidance document is.

There will be some feedback from them, and then, in their report to the full committee, we'll see if there's any issues that the full committee needs to address at this point in time. And our goal would be to help provide our input into that guidance and how it should be utilized, as well as what it might contain. And -- and so, that might help get to the points that were being made by the committee members.

The second point -- the -- the second part, the education, we've -- we've tasked the Education and -- and Training Workgroup with addressing issues of provider education related

to understanding what a newborn screening result is, including a -- a patient that has a result in the normal range and then develops presentations that is consistent with a disorder that was screened for, for which the screen was negative, and make people understand. And that might be at a practice level or even going back with -- with the representatives of the various AAP, AFIP, family practitioners, et cetera, that we could then maybe even go -- go back to resident education to have better understanding of screening tests, not only for newborn screening but the understanding, as well.

And then, I think, based on Natasha's comment -- I think we need to be sure that we have -- we -- we look at any issues that the public needs to understand related to newborn screening if that's not being -- that message is not clear at the present point in time.

So, I think that's where we are, going forward, and then it was brought up that there would potentially be some infrastructure needs

that states may have, and that was already brought up as to one of the reasons why the CLIR data's not -- data's not being put into CLIR is that there's not enough personnel time to make that happen. And so, there may be some real infrastructure needs that play a role in what states can and cannot do, at the present time, to keep up.

So, those were, sort of, the -- the general things that we thought we needed to do going forward, and I wanted to see if there's any additional questions or suggestions that the committee may have to help further that, so that these discussions, when they take place this afternoon, have better impact. So.

DR. CATHARINE RILEY: All right. Dr. Bocchini, thank you. This is Catharine Riley, designated federal official. I am -- I just want to remind the committee, as special government employees and federal employees, we -- you are not allowed to endorse any products as individuals or committee members or committee as

a whole. So, just in the -- in the discussion, please remember that. Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Okay. So, nothing from the committee? Carol Green?

DR. CAROL GREEN: This may be just of some use, because I'm not sure how many of the people in the Education and Training Workgroup actually actively educate residents and are engaged in ongoing education of physicians in practice. And I'm -- I'm not sure who it was, but absolutely, there's this mental barrier. You're told something's negative, and so -- But I've been engaged in teaching residents for more than 35 years, and we've always been teaching that.

And it's true: It doesn't matter if it's the blood spot in galactosemia, or I've had people with kids with no language. "Did you have a hearing test?" "Oh, his hearing screen was normal," and he's 2, and he doesn't talk. And it's true of a TB test, it's true of an X-ray, and it's -- it's a fundamental -- You know, we can try to come up with a word, but it's -- it's

a fundamental thinking issue that we have to continue to work on the education.

But I don't want anybody thinking there's going to be a magic bullet, because -- I'm -- I'm not the world's expert in educating. I'm just one of the people that's been doing it, and it's a chronic problem, forever.

DR. JOSEPH A. BOCCHINI, JR.: No, I -- I certainly agree with that, and I -- I think one of the things that might be important is when newborn screening results come back on an individual patient, that it is -- that there is a clear statement on what the results mean. And -- and I think that that would be at least some point-of-care reading by the provider to understand that the -- what that result is.

We'll go back to Carol. And I know that that's still an issue. Go ahead, Carol.

DR. CAROL GREEN: I -- I'll jump in, probably, before Bob and say the same thing, probably, is, absolutely. And I know a lot of tests include such a statement, and other --

other labs can't include such a statement because of the way that the -- it's reported, and it's not -- you know, comes out in the system and the comment about LIMS, but nobody reads them. Doesn't matter.

DR. JOSEPH A. BOCCHINI, JR.: Bob?

DR. ROBERT OSTRANDER: So, I mean, I was just going to share with everybody that, finally, on June 01, 2015, the cover article on our journal was: Newborn Screening, Basics and Background. There's a baby with blood spots on there, and it divides all the categories. It looks a lot like the front page of the ACT sheet, where it talks about categories, it talks about the history.

But what it doesn't, unfortunately, cover is this last little issue about, these are screening tests, diagnostic tests. Positives need to be confirmed; negatives don't excuse you from including things in your differential diagnosis. And I'm actually writing back to the author as I'm listening to this conversation about how we

might follow up on that.

But I -- I think the fundamental problem with education isn't around newborn screening of people who take care of children. The fundamental problem with education is, this is year 1, basic science, medical school stuff about what a screening test is. There's a science of screening.

And I -- and, I mean, this is the tiniest little aspect for most of us in primary care. I mean, we screen for breast cancer. We screen for prostate cancer. And we -- some of us do, and some don't. But -- but we should be teaching that science as year 1 medical school stuff, and pardon me, Dieter, we probably could get rid of a couple of the biochemical cycles and teach about screening.

So -- And I don't -- I don't have a fix for that, but to say we need to do this just in the newborn screening world is kind of missing the -- missing the big picture. If we were doing what we should be doing, every physician would

understand what screening is.

DR. JOSEPH A. BOCCHINI, JR.: All right. Sue, if you'll come to a -- any microphone, whatever's convenient?

(Off-mic speaking)

DR. SUE BERRY: So, I'm Sue Berry. If -- On beyond what people understanding screening or not -- As a general rule, negative results aren't conveyed effectively to families.

We've -- I have a project that we're working on in Minnesota, where we're surveying families 2 months after their newborn screening has taken place, and most of them don't know it's happened. So, it's kind of hard to tell them about false negatives and false positives and -- if they don't even know the test was done and what it meant.

So, an element to twist your minds a little further. We'll -- we'll give you some update on that when we know more.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. Jeff?

DR. JEFFREY P. BROSCO: Yeah, I -- I really like the suggestion that in our newborn screening report, we figure out a way to tell more about sensitivity and specificity. I mean, we know that newborn screening for hearing has much lower sensitivity than newborn screening for many metabolic disorders.

So, I think that would be a helpful thing to move toward, and -- and maybe some of the state lab people can answer how they do that. I know, in Florida, we don't really do that. We just sort of say normal or not.

DR. MEI WANG BAKER: Actually, I was going to say a little bit. It just wouldn't allow me online.

(Off-mic speaking)

DR. MEI WANG BAKER: Mei Baker, committee member. When he said sensitivity specificity, I think come to laboratory performs, I think APHL started that is a emphasize on the positive predictive value. So, that's like, you know, you can practice in a such a fashion, whatever, but

we have a common, you know, measurement. I think, actually, this data is what I would want to see, right? So, I think that's part of the thing we possibly need to think about that.

DR. JOSEPH A. BOCCHINI, JR.: Carol Green?

DR. CAROL GREEN: Sensitivity and specificity is -- or positive predictive value, one or the other, is absolutely the goal, but this is cycling me back to the discussion that we had -- Oh, yeah, I'm with you, Kellie. That's exactly where I'm heading -- the discussion we had with the genetic testing registry, and they insisted on the sensitivity and specificity of every test.

It's like, what's the sensitivity and specificity of plasma amino acids? Is the kid sick? Is the kid well? Is the kid fasting? I can get completely normal plasma amino acids on a kid with intermittent MSUD or a kid with MSUD who's in good treatment.

So, I can't tell you the sensitivity and

specificity of blood amino acids, which was one of the reasons that we had an argument about, you know, you can't require that from the -- the GTR, and I definitely can't tell you the sensitivity and specificity or positive predictive value of a newborn screen for MSUD, because it's not going to pick up the intermittent cases.

And even if I can come close on MSUD, I can't tell you about the positive predictive value of a newborn screen tandem mass spec. I can maybe do it disease by disease, and that's going to give you a five-page list on the newborn screen, and all they really want to know is, does this baby have to be called back for more testing?

They -- I don't think any pediatrician or family practice doc wants to have the -- I mean, due respect, that's our goal. That's what the cutoffs all are about, is to make the positive predictive value the best you can make it, but I don't think anybody wants it on the report. And if they wanted it, I couldn't do it.

DR. BETH TARINI: This is Beth. I have a quick question. I -- I thought that sensitivity and specificity of tests were independent of the population.

DR. CAROL GREEN: Probably Alaska or Carla or all sorts of people could do that better than I can, but they are -- they are not independent of the population, because I think the sensitivity and specificity, if I understand it, depends on the disease frequency.

DR. BETH TARINI: Isn't that the positive predictive value?

(Off-mic speaking)

DR. CAROL GREEN: Didn't somebody -- Scott. Somebody else.

(Laughter)

(Off-mic speaking)

DR. SCOTT GROSSE: In principle, specificity is independent, whereas the positive predictive value is of the function of the frequency.

FEMALE SPEAKER: Right.

DR. JOSEPH A. BOCCHINI, JR.: Did you hear that, Beth?

DR. BETH TARINI: I did. Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Okay.

FEMALE SPEAKER: Oh, Mike.

DR. JOSEPH A. BOCCHINI, JR.: Oh, Mike, sorry.

DR. MICHAEL WATSON: Yeah, only one comment, which is, you -- you -- you know, you have to -- there are trade-offs throughout this. In rare diseases, you need to capture as much data from as far and wide as you can, and many states just won't have that much data. So, having a tool like CLIR that actually captures data from everywhere helps you tremendously in rare diseases. And then, you have to overlay your population differences. It may be the order in which we worry about things that we need to be thinking about with these kind of tools.

DR. JOSEPH A. BOCCHINI, JR.: All right, if there --

DR. ALAN ZUCKERMAN: Just to be clear

about that sensitivity/specificity thing -- Sensitivity and specificity are intrinsic properties of the test but are going to depend on the population in which the cases and healthy population are valued. The positive and negative predictive value depends on the prevalence of the disease in the population that's screened.

So, normally, while we say sensitivity and specificity are properties of the tests that don't change, the way positive and negative predictive value change with different prevalence, a situation like that in Alaska is a case where sensitivity and specificity may in fact be different, because their normals and their cases of disease are going to be different from a comparable population of normal and diseased individuals in a different state where these were measured.

One last comment I wanted to make is that I have a lot of trouble using the term cutoff in connection with R4S and CLIR, because these are inherently multi-variate, multi-hypothesis tools

that don't really fit the traditional lab test cutoff model. And this may be another area in which we need to communicate better how they really work and the fact that they're looking at several different parameters of data and not at a single test at the same time.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. Okay. There are no --

Okay, so we have one more public comment. Ms. Jana Monaco, come forward. Yeah, you can go to big -- big microphone.

MS JANA MONACO: Thank you for squeezing me in at the end of the day. I had a little glitch with sitting. But good afternoon, and I just wanted to share a little bit in relation to all the conversations that take place now with conditions, whether they're infantile symptomatic or whether they're late onset.

As you know, as a parent of a child who suffers the consequences of a late diagnosis, I know the hardship on every level, but thankfully, our condition is part of the comprehensive

newborn screening now. However, as you strive to maintain the integrity of this committee and to work -- and its work, you will continue to be faced with conditions that are vying for their place on the Recommended Screening Panel, conditions that pose the issue of an infantile form or late onset with great uncertainty. You may also question the effectiveness of the treatment. And I wanted just to share a little bit about a family of a friend of mine who has been caught up in this situation.

Alex and Zack are two brothers who were born into an air force family and were seemingly normal since birth, except Alex had received several diagnoses over the years, to include: ADHD, autism, and sensory integration, all the classic ones that children are given when exhibiting certain behaviors and symptoms. Both boys -- both boys led normal lives, participating in sports, church activities, and Boy Scouts.

After a bad fall at age 9, Alex's diagnostic odyssey ended, and he was diagnosed

with adrenoleukodystrophy, or ALD, and the family was told that he had 6 months to live. Zack, his other brother, then age 12, was tested immediately and given the same diagnosis. He was still inactive though.

Despite their devastation, the family was proactive and opted for a bone marrow transplant for Alex. It was his only hope for survival. As his mother said, it's very hard when you don't have any approved medications or treatments, but you have to still try everything to keep fighting. And that, they did. Alex went through the transplant process, which wasn't easy, and they knew the risks.

Unfortunately, it did not halt the rapid progression of the debilitating disease and the symptoms he had already been exhibiting early on. It also didn't stifle Alex's zest for life and determination that he and his family had to ensure that his life was a full one. They did their part to help raise awareness for ALD, to support research for it, and they wanted ALD on

the newborn screening list.

Meanwhile, Zack did not receive the transplant because he was not symptomatic. Instead, he received treatment with Lorenzo's oil.

Alex lost his battle with ALD last September, at the age of 16. It was a loss that was anticipated but one that no family can truly ever prepare for. Zack not only lost his brother but his best friend. And as this family grieved the loss of Alex and tried to go on with life, the grief and the survivor's guilt was just too much for Zack to bear, and sadly, he took his own life on June 19th of this year, just after turning 20.

You can't even imagine the depth of the parents' sorrow. They have been destroyed, they have been left childless, and they grieve for both sons. These parents are dealing with great guilt, ranging from passing on the condition to not getting a diagnosis early on for Alex and Zack, along with wondering whether they provided

enough support for Zack. They are living with all the obvious "what ifs".

As you proceed with discussions around conditions like ALD that don't quite fit the desired criteria and come with the prospects of a late onset, as you ponder on these decisions, the possible outcomes to include those to the family, please keep this family in mind and remember his mother's words, that it is very hard when you don't have any approved medications or treatments, but you do have to still try everything to keep fighting.

So, I thank you for your continued committee and dedication to this committee and the public that it serves. Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Jana, thank you very much, and thank you for your continued advocacy for children with rare disorders. Thanks.

So, that will conclude this full session. Now we will have a short break, and following the break, we'll have our three workgroup meetings,

and listed here on the slide are the rooms for each of the three workgroups. Education and Training will meet in Room 5E45, Laboratory Standards and Procedures Workgroup will meet in 5N54, and Follow-Up and Treatment Workgroup will meet in 5N76.

Catharine, do you have any guidance as to how to get there?

DR. CATHARINE RILEY: Yeah, just to add to that: So, in about 10 minutes or so, there'll be three HRSA staff towards the back of the room with -- hopefully they'll be holding the escort signs. They'll be able to escort folks to the -- the three different rooms. You're welcome to, you know, make your way. There are signs outside, with arrows, to help you make your way there, as well. So, the -- the escorts will come at about 20 'til, and then they'll come back and do another round at about 5 minutes 'til for those who want to, you know, take a break, grab a snack, or talk with folks here.

So, thank you so much, and we look

forward to seeing everyone tomorrow morning.

DR. JEFFREY P. BROSCO: Can -- Catharine, can I say something very quick?

DR. JOSEPH A. BOCCHINI, JR.: So, 9:30 tomorrow morning we'll reconvene. Thank you.

DR. CATHARINE RILEY: Oh, wait --

DR. JEFFREY P. BROSCO: Dr. Bocchini -- So, Jeff Brosco. Just quickly, for those who are going to the Follow-Up and Treatment Workgroup -- One of our tasks on our agenda is to think about future topics and issues, so please use your 20 minutes to think about what you might want to bring up. Thank you.

(Whereupon, the above-entitled matter was concluded.)