The Advisory Committee on Heritable Disorders in Newborns and Children

HRSA Webinar Conference

Washington, D.C.

February 09, 2017

10:00 a.m. - 3:00 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, M.D., Committee Chair, Department of Pediatrics, Louisiana State University

DON BAILEY, Ph.D, M.Ed., Distinguished Fellow, Early Childhood Development, RTI International

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

COLEEN BOYLE, Ph.D., M.S., Director, National Center on Birth Defects and Developmental Disabilities

JEFFREY P. BROSCO, M.D., Ph.D., Professor of Clinical Pediatrics, University of Miami School of Medicine, Department of Pediatrics

KELLIE KELM, Ph.D., Food and Drug Administration, Ex-Officio Committee Member, Chair, Laboratory Standards and Procedures Workgroup

FRED LOREY, Ph.D., Genetic Disease Screening

Program, California Department of Public Health (Emeritus), International Society for Neonatal Screening, North American Council Representative

MICHAEL LU, M.D., M.P.H., Associate Administrator, Maternal and Child Health Bureau

DIETRICH MATERN, M.D., Ph.D., Professor of Laboratory Medicine, Medical Genetics and Pediatrics, Mayo Clinic

STEPHEN MCDONOUGH, M.D., Committee Member, Chair, Follow up and Treatment Workgroup

KAMILA MISTRY, Ph.D., M.P.H., Senior Advisor, Child Health and Quality Improvement

MELISSA PARISI, M.D., Ph.D.

ANNAMARIE SAARINEN, Co-Founder, CEO, Newborn Foundation

CATHY WICKLUND, M.S., C.G.C., Northwestern University, Feinberg School of Medicine, Center for Genetic Medicine

DEBI SARKAR, M.P.H., Designated Federal Official, Health Resources and Services Administration, Maternal and Child Health Bureau

ORGANIZATIONAL REPRESENTATIVES:
ROBERT OSTRANDER, M.D., American Academy of Family Physicians
MICHAEL WATSON, Ph.D., F.A.C.M.G., American College of Medical Genetics and Genomics
KATE TULLIS, Ph.D., Association of Maternal & Child Health Programs
SUSAN TANKSLEY, Ph.D., Association of Public Health Laboratories
CHRISTOPHER KUS, M.D., M.P.H., Association of State and Territorial Health Officials
JACKIE SEISMAN, M.P.H., Genetic Alliance
SIOBHAN DOLAN, M.D., M.P.H., March of Dimes
CATE WALSH VOCKLEY, M.S., C.G.C.S., National Society of Genetic Counselors
CAROL GREENE, M.D., Society for Inherited Metabolic Disorders
NOREEN MURPHY, Batten Disease Support and Research Association
AMY MEDINA
KRISTIN STEPHENSON, Muscular Dystrophy Association

ANNIE KENNEDY, Parent Project Muscular Dystrophy
JESSICA WADE
KIM TUMINELLO, Association for Creatine Deficiencies
HEIDI WALLIS
JERRY ROBINSON
JENNY WOLF
DEAN SUHR, MLD Foundation
THOMAS CRAWFORD, M.D., The Johns Hopkins Hospital
MICHELE CAGGANA, Sc.D., F.A.C.M.G., Director, Newborn Screening Program, New York State Department of Health
JOHN D. THOMPSON, Ph.D., M.P.H, M.P.A., Director, Newborn Screening Program, Washington State Newborn Screening Program
CAROL JOHNSON, Iowa Newborn Screening Program, University of Iowa, Department of Pediatrics
JOAN SCOTT (for Dr. Michael Lu)
KATE TAFT, M.P.H., Associate Director for Child And Adolescent Health, Association of Maternal And Child Health Programs
SUE BERRY, M.D., Director, Division of Genetics

and Metabolism, Department of Pediatrics, University of Minneapolis

ALAN ZUCKERMAN, M.D., Georgetown University Hospital

C O N T E N T S

P R O C E E D I N G S

FEMALE SPEAKER: Welcome. Thank you for standing by. Throughout today's conference, all participants will remain in listen-only mode. Today's conference is being recorded. If you have any objections, you may disconnect at this time. Now I'll turn your conference over to Dr. Joseph Bocchini. Thank you. You may begin.

DR. JOSEPH BOCCHINI: Thank you, good morning. I'd like to welcome everyone to the February 2017 meeting of the Advisory Committee on Heritable Disorders in Newborns and Children. I thank you all for your participation at the meeting.

Let's go ahead and start with the roll call. I guess we need to put up my slides. Okay. Thanks. All right. So, I'm going to do the roll call, first, Committee members, followed by organizational representatives. I'll first let you know that Beth Tarini is unable to attend the meeting today. So, we'll start alphabetically, and just answer that you're here or present. Don

Bailey?

DR. DON BAILEY: Here.

DR. JOSEPH BOCCHINI: Mei Baker?

(No audible response)

DR. JOSEPH BOCCHINI: I'm here. Coleen Boyle?

DR. COLEEN BOYLE: I'm here.

DR. JOSEPH BOCCHINI: Jeff Brosco?

DR. JEFF BROSCO: I'm here, thanks.

DR. JOSEPH BOCCHINI: Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH BOCCHINI: Fred Lorey?

DR. FRED LOREY: Here.

DR. JOSEPH BOCCHINI: Michael Lu?

DR. MICHAEL LU: Here.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETER MATERN: Here.

DR. JOSEPH BOCCHINI: Stephen McDonough?

DR. STEPHEN MCDONOUGH: Here. It's 12 below in Bismarck, North Dakota.

DR. JOSEPH BOCCHINI: Thank you. Kamila Mistry?

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH BOCCHINI: Melissa Parisi?

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Cathy Wicklund?

MS. CATHY WICKLUND: Here.

DR. JOSEPH BOCCHINI: And Debi Sarkar?

MS. DEBI SARKAR: Here.

DR. JOSEPH BOCCHINI: Now for organizational representatives -- two are unable to attend. First is Robert Saul from the American Academy of Pediatrics and Adam Kanis from the Department of Defense. So, the rest -- the roll: American Academy of Family Physicians, Robert Ostrander?

DR. ROBERT OSTRANDER: Here.

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

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: American College of Obstetricians and Gynecologists, Joseph Biggio?

(No audible response)

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

DR. KATE TULLIS: Here.

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

DR. SUSAN TANKSLEY: Here.

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

(No audible response)

DR. JOSEPH BOCCHINI: Genetic Alliance, Jackie Seisman?

MS. JACKIE SEISMAN: Here.

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

DR. SIOBHAN DOLAN: Here.

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

MS. CATE WALSH VOCKLEY: Here.

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

DR. CAROL GREENE: Here.

DR. JOSEPH BOCCHINI: And then, we'll go back for Mei Baker.

(No audible response)

DR. JOSEPH BOCCHINI: All right. Not yet present. All right. Thank you, all, very much. Let's do -- go through the business of the Committee.

I'd like to welcome new work group members. We've had a -- a number of individuals who have been selected and accepted on each of the three work groups -- the Education and Training, Follow-Up and Treatment, and Laboratory Standards and Procedures Work Groups, so we'd like to welcome them. They are already involved with the work of each of these groups, and so we appreciate their involvement and look forward to their contributions over their terms.

We now have two votes that we need to take for prior minutes. As you know, the August 2016 minute meeting -- minutes were not available due to a (sic) electronic glitch. They are now

available. So, we need to have two separate votes, one for the, August 2016 meeting, and then we'll follow that with a vote for the November 2016 meeting.

So, from the Committee members, are there any additions or corrections to be made to either of these two sets of minutes?

(No audible response)

DR. JOSEPH BOCCHINI: Hearing none, we will proceed with the voting for approval of the minutes of the August 2016 meeting. And so, vote "yes" or "no." Don Bailey?

DR. DON BAILEY: Yes.

DR. JOSEPH BOCCHINI: Mei Baker?

(No audible response)

DR. JOSEPH BOCCHINI: I'll vote "yes." Coleen Boyle?

DR. COLEEN BOYLE: Yes.

DR. JOSEPH BOCCHINI: Jeff Brosco?

DR. JEFF BROSCO: Yes.

DR. JOSEPH BOCCHINI: Kellie Kelm?

DR. KELLIE KELM: Yes.

DR. JOSEPH BOCCHINI: Fred Lorey?

DR. FRED LOREY: Yes.

DR. JOSEPH BOCCHINI: Michael Lu?

DR. MICHAEL LU: Yes.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETER MATERN: Yes.

DR. JOSEPH BOCCHINI: Stephen McDonough?

DR. STEPHEN MCDONOUGH: Yes.

DR. JOSEPH BOCCHINI: Kamila Mistry?

DR. KAMILA MISTRY: Yes.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Yes.

DR. JOSEPH BOCCHINI: And Melissa Parisi?

DR. MELISSA PARISI: Yes.

DR. JOSEPH BOCCHINI: Cathy Wicklund?

MS. CATHY WICKLUND: Yes.

DR. JOSEPH BOCCHINI: So, those minutes are approved as distributed.

Next, we have the November 2016 minutes. Don Bailey?

DR. DON BAILEY: Yes.

DR. JOSEPH BOCCHINI: I approve. Coleen

Boyle?

DR. COLEEN BOYLE: Yes.

DR. JOSEPH BOCCHINI: Jeff Brosco?

DR. JEFF BROSCO: Yes.

DR. JOSEPH BOCCHINI: Kellie Kelm?

DR. KELLIE KELM: Yes.

DR. JOSEPH BOCCHINI: Fred Lorey?

DR. FRED LOREY: Yes.

DR. JOSEPH BOCCHINI: Michael Lu?

DR. MICHAEL LU: Yes.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETER MATERN: Yes.

DR. JOSEPH BOCCHINI: Stephen McDonough?

(No audible response)

DR. JOSEPH BOCCHINI: Steve, we can't hear -- We did not hear your response.

(No audible response)

DR. JOSEPH BOCCHINI: We may have lost him for the moment. Kamila Mistry?

DR. KAMILA MISTRY: Yes.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Yes.

DR. JOSEPH BOCCHINI: Melissa Parisi?

DR. MELISSA PARISI: Yes.

DR. JOSEPH BOCCHINI: And Catherine Wicklund?

MS. CATHY WICKLUND: Yes.

DR. STEPHEN MCDONOUGH: Yes. It's Steve McDonough. Yes.

DR. JOSEPH BOCCHINI: Okay, Steve, thank you. All right, so those minutes are, again, approved as distributed.

So, next slide shows the dates of the rest of the 2017 meetings. The May meeting is a face-to-face meeting, and then there's a meeting in August and November, and those of you who like to plan far ahead, the meeting dates have been set through 2020, and they are available at the website that is listed on that slide.

So, next slide. This shows the -- the topics of today's meeting. We're going to review the GAO report on timeliness in newborn screening. We're also going to have a presentation by a -- a panel on newborn screening

cutoffs and algorithms. This is to provide an initial overview for the Committee on how laboratories set cutoffs and establish reference ranges, how newborn screening lab results are interpreted, and how screening results are communicated to providers.

This is a very important discussion, one that will -- will give us the start, as a Committee, to begin to look at issues that aren't related to cutoffs and algorithms. My intent is to have a discussion started today and then have further discussion at our in-person meeting in May.

Next slide. We will also hear a report on the National Contingency Plan for Newborn Screening. We also have a presentation by the subcommittee of the Follow-up and Treatment Work Group, which is putting together the medical foods policy brief that was -- that the Committee had asked to organize, and then we'll have additional work group updates from each of the work groups: Follow-Up and Treatment, Education

and Training, Laboratory Standards and Procedures.

Next slide. Now I'd like to turn this over to Debi Sarkar to discuss some housekeeping issues.

MS. DEBI SARKAR: Good morning --

DR. JOSEPH BOCCHINI: Debi?

MS. DEBI SARKAR: Okay. Good morning, everyone. It looks like we have over 125 people on the webinar, so thank you so much for joining us today.

So, as usual, I have my standard reminders to the Committee members. We want to remind the Committee that members of the Committee, we are advisory to the Secretary of Health and Human Services, and not Congress, so for anyone associated with the Committee or due to your membership on the Committee, if you receive inquiries about the Committee, please let Dr. Bocchini and I know prior to committing to an interview.

I also want to remind members that you

must recuse yourself from participation in all particular matters likely to affect the financial interests of any organization with which you serve as an officer, director, trustee, or general partner, unless you are also an employee of the organization or unless you have received a waiver from HHS authorizing you to participate. When a vote is scheduled or an activity is proposed, and you have a question about a potential conflict of interest, please let me know as soon as possible.

Next slide? And just, lastly, remember, please, to state your name first. We are recording the webinar. So, thank you very much. Dr. Bocchini?

DR. JOSEPH BOCCHINI: Thank you, Debi. So, the first topic on the agenda is the U.S. Government Accountability Office Report on Newborn Screening Timeliness.

Next slide. I'm going to review this report. The full report is in the -- in your agenda book. The Newborn Screening Saves Lives

Reauthorization Act of 2014 had timeliness as an explicit goal for HRSA-supported newborn screening programs. And this Act also included a provision for the GAO to review newborn screening timeliness, and the report of the GOA -- GAO is -- is included in your briefing book. This report examines what is known about timeliness for newborn screening, and also reviews the barriers identified as contributing to delays, as well as strategies used to address those barriers.

Next slide. So, the -- the GAO listed the following resources that were used to develop its report: the time frame goals from the Advisory Committee; the August 2016 report from NewSTEPs, which included data from 38 states looking at the -- the -- the time frame of 2012 through 2015; and the results of the 2014 survey that was done within the work of the Advisory Committee. The GAO also conducted interviews with the Committee members, NewSTEPs leadership, as well as some of the states, and any other relevant documents that -- that were related to this issue.

Next slide. The review was based on the recommendations of the Secretary's Advisory Committee. As you know, our recommendations were sent to Secretary Burwell on April 16, 2015, and just to quickly review them, they stated: To achieve the goals of timely diagnosis and treatment of screened conditions and to avoid associated disability, morbidity, and mortality, the following time frames should be achieved by Newborn Screening Systems for the initial newborn screening specimen.

Number one: Presumptive positive results for time-critical conditions should be communicated immediately to the newborn's health care provider but no later than 5 days of life. Presumptive positive results for all other conditions should be communicated to the newborn's health care provider as soon as possible but no later than 7 days of life, and all newborn screening tests should be completed within 7 days of life, with results reported to the health care provider as soon as possible.

Next slide. And in order to achieve these goals, the initial specimen should be collected in the appropriate time frame for the newborn's condition but no later than 48 hours after birth, and the specimen should be received at the laboratory as soon as possible, ideally within 24 hours of collection. The Committee also encouraged states to monitor their progress in -- in meeting these goals and to make the results readily available to the -- to the providers and to the public.

Next slide. So, these are the time frame goals as outlined by the -- the GAO within its report, and it includes some examples of the barriers that were identified through the surveys that were done for the Committee and through NewSTEPs for each of the -- of the goals.

Next slide. And these are the highlights of their findings. Most states that reported the 2015 timeliness data -- and that was the most recent data available to the NewSTEPs Program -- had not met the Advisory Committee's 95%

benchmark for newborn screening timeliness for all conditions within 7 days. In 2015, states also had not met the Advisory Committee's benchmark for timely reporting of presumptive positive results for time-critical conditions. And the last highlight was: However, timeliness for completing this screening process improved, over time, for the majority of states.

Now, one thing to highlight here is that HHS's Health Resources and Services Administration -- HRSA -- has supported activities to address the challenges that exist for meeting the -- these timelines. HRSA supports Newborn Screening Technical Assistance Evaluation Program -- the NewSTEPs Program -- which collects this newborn screening data. So, there -- there have been efforts and -- and support for states to meet these benchmarks.

Next slide. Twenty-one states have demonstrated improvements from 2012 to 2015 according to the NewSTEPs data, and five of the twenty-seven states had met the ninety-five

percent benchmark for reporting all newborn screening results for all conditions within seven days. One state was -- was within one percentage point of the benchmark. The median percentage of specimens screened within 7 days was higher in 2015 than the previous 3 years.

Next slide. They also identified some of the significant barriers that -- that -- that have been identified within the reports to -- through NewSTEPs and the survey for the Advisory Committee. The first is the lack of understanding why timely screening was important amongst those collecting and submitting specimens, limited courier availability to transport specimens, and insufficient laboratory hours.

Next slide. Now, they also highlighted some limitations. There was missing data and variations in data collection, which did limit a full understanding of timeliness trends. The data was only available from 38 states, and very importantly, states only had 9 -- less than 9 months from which the recommendations from the

Advisory Committee were developed to implement the changes that might be required for states to meet the -- these guidelines.

Next slide. So, the next steps would be that NewSTEPs 360 is standardizing data definitions as a continued data collection, working to improve data collection, involving all states, if possible, and it -- we expect that we will have the next update on where we are with the states achieving the benchmarks we had set to the Committee at the August 2017 meeting. So, I think this kind of gives us the -- the -- the baseline of where we were and some of the early changes that were made subsequent to the reports and -- and -- and the recommendations of the Advisory Committee and certainly demonstrates that progress was already being made to reach our 95-plus percent benchmark by a number of states.

Next slide. Okay. So, are there any questions or comments related to this report? I was going to ask that Committee members have an opportunity to present or make comments or ask

questions first. Let's open for questions or comments.

(No audible response)

DR. JOSEPH BOCCHINI: All right, hearing none, let's open this to the organizational representatives, as well.

DR. SUSAN TANKSLEY: Hi, Dr. Bocchini, can you hear me? This is Susan Tanksley.

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

DR. SUSAN TANKSLEY: I just wanted to comment, we had some discussion during the Lab Work Group meeting last week about issues with timeliness. Kellie will be giving some of those updates in our Work Group update this afternoon, but one of the issues identified with the 24-hour recommendation for the transit time is that, sometimes, it's a logistically impossible issue. Even in -- in labs that are open 7 days a week, all the circumstances have to fall in line perfectly in order for the specimen to actually be received within 24 hours of collection. So, it

depends on the timing of the birth, the timing of the collection, the timing of the courier pickup, and the timing of when the courier drops off. So, if all of those things don't line up perfectly, if that collection -- the specimen has to be dry before it can be picked up -- if all those don't fall in line, then you're going to miss the 24-hour window, even when everybody else has done their job perfectly.

DR. JOSEPH BOCCHINI: Certainly, that's an important -- important issue, and -- and I think that that is something that the Work Group can -- can consider as it looks at the data, and -- and -- to try and see what -- where -- how it can minimize that, and -- and then see if that is something that needs to be addressed specifically within our recommendations.

Are there any additional questions or comments?

(No audible response)

DR. JOSEPH BOCCHINI: All right, hearing none, let's go to the public comment portion. We

have a number of individuals and representatives of organizations who have asked for an opportunity for public comment, and based on the time we have, they've been given an -- a specific amount of time within which to make their public comments.

The first is Noreen Murphy from the Batten Disease Support and Research Association, who will discuss the needs for families in rare disease and how patient advocacy groups can better work with the FDA to inform the process. Operator, would you open Ms. Murphy's line?

OPERATOR: Ms. Murphy's line is open.

DR. JOSEPH BOCCHINI: Thank you. Ms. Murphy?

MS. NOREEN MURPHY: Hello.

DR. JOSEPH BOCCHINI: Morning.

MS. NOREEN MURPHY: Good morning. I'm grateful for the opportunity today to tell you about the perspective we have on the need for early and rapid tests for newborn children. Batten disease is a rare disease of childhood,

with hallmark symptoms of seizures, rapid loss of skills, mobility, feeding, swallowing, and cognitive decline. As a lysosomal storage disorder, it is the primary cause of dementia in children.

In several forms, such as the late infantile, or CLN2, form, we see children progressing completely normally until age 3, at which time they develop unprovoked seizures and language delay. Sadly, these children will rapidly decline for the next 24 months, losing all ability to function independently. G-tubes, suctioning, sleep disturbance, dysautonomia, and other difficulties arise in the spectrum of their short lives. We see this rapid onset of symptoms in others of the 14 forms of Batten, as well.

Like many parents whose children have rare diseases, the path to diagnosis is long, expensive, often incorrect, and leaves them suspended in mystery as they watch their little ones decline in front of them. A parent, just yesterday, said, "Most parents look forward to

the days and weeks ahead to see what new word or skill their toddler will claim. I get up each day worried about what skill he has lost and worry about what the future brings."

With earlier diagnosis of these children through newborn screenings, we can change the course of these parents' experience in a profound way. As new and meaningful treatments appear for Batten and other rare diseases, it can alter the trauma, vast public and private expense, and, most importantly, early loss of life. From our experience and through patient surveys, this is what we find in the diagnostic experience for families.

First, parents report that they have received around three different diagnoses prior to Batten disease. Our parent community could name 32 different diagnoses their children have received, including "kids just fall down a lot."

Second, no matter how bad the eventual diagnosis, parents are desperate to know what it is, so that they can move past the mystery enough

to support an adjustment to the new normal.

Third, parents must be able to plan their families with safety. We have many families who have lost two or three, and sometimes four, children to this deadly disease because by the time the oldest was diagnosed, the others were already born. Technology allows for pregestational testing. We can reduce so much suffering if we are able to help parents know their risks and options.

Fourth, for the first time, our community has human clinical trials moving forward for meaningful treatments. Preclinical and current trial data tell us, not surprisingly, that those children who are enrolled the youngest are the most likely to have few symptoms of the disease, and those who have the most neurological damage have less of a likelihood of full recovery. Missing out on the opportunity of a trial or treatment because of delayed diagnosis is the cruelest letdown of all in the treatment journey. Our Batten clinicians have delivered this news to

parents, and it is devastating for everyone.

And finally, with the correct diagnosis, families can learn from others affected by this disease, go to a family conference, be a part of a community. These are powerful tools to fight the isolation, depression, and perceived disconnectedness that accompany, as many others in their family and social circle don't understand. These problems lead to higher physical and mental illness that can affect all those in the family, especially unaffected siblings.

I appreciate this brief moment to share insights from our patient group and to help the Committee understand the Batten experience, with our offer to help in any way we can. We must move the needle toward more rapid and accurate screening of newborns to help these young children and their families. Thank you.

DR. JOSEPH BOCCHINI: Thank you, Ms. Murphy, for sharing this understanding with us. We would certainly appreciate if you would

provide the Committee with the parent survey, so that we would have that additional information that you have. And ...

MS. NOREEN MURPHY: Sure.

DR. JOSEPH BOCCHINI: Okay. We -- we certainly appreciate that and look forward to working with you more in the future. Thank you.

MS. NOREEN MURPHY: Of course. Thank you.

DR. JOSEPH BOCCHINI: Next, we have Amy Medina, who will discuss the recent developments with respect to SMA therapy and the importance of adding SMA to the RUSP. Ms. Medina -- Operator, can you open her line?

OPERATOR: Ms. Medina's line is open.

DR. JOSEPH BOCCHINI: Thank you.

MS. AMY MEDINA: Hello.

DR. JOSEPH BOCCHINI: Hello.

MS. AMY MEDINA: Good morning. My name is --

DR. JOSEPH BOCCHINI: Morning.

MS. AMY MEDINA: My name is Amy Medina, and my husband and I have two sons who are

affected by spinal muscular atrophy. Mateo is 5, and my youngest is 1. Spinal muscular atrophy, also known as SMA, is the leading genetic cause of death for infants. On behalf of the SMA community and Cure SMA, I am here to comment regarding the urgent need for newborn screening for SMA.

Over the last decades, there have been significant advances in drug developments for SMA, cumulating in the approval, on December 23, 2016, of Spinraza. Spinraza is an antisense drug that treats the underlying genetics of SMA. With an FDA-approved therapy, newborn screening would allow infants born with SMA to immediately begin receiving treatment. Data that -- data suggests that early drug intervention is required for greatest efficacy in SMA. Results from studies of infants treated with Spinraza show that presymptomatic infants treated develop more motor milestones than symptomatic treated infants.

My family's experience reflects this. Mateo showed signs right at birth that included

low tone, lack of crying, and rapid breathing. However, we would not hear the words spinal muscular atrophy until he was 1 month old. At that time, we were told he would most likely never see his second birthday and were given little to no hope. We transferred hospitals and found a doctor that was willing to educate us on SMA and fight with us to give Mateo the best life possible. A G-tube surgery, many scary 9-1-1 calls, hospital stays, and a trach surgery all happened in his first 7 months of life. Five years later, Mateo has lost all movement except very tiny movement of his feet and a small curl on the side of his mouth to indicate a smile.

I had an amniocentesis with Javier and was prepared for him to have SMA. Javi was monitored closely throughout my pregnancy and at birth. I prepared for Javi to be similar to Mateo; However, he was given the opportunity to receive Spinraza at just 12 days old. Javi has gotten eight -- or has gotten six doses. He is able to sit up on his own. He can roll all over

the house, stands with assistance, eats everything by mouth, is very loud vocally, coughs on his own, and does not need any type of breathing support. Javi has battled a cold at home and maintained an oxygen saturation of 97 or higher, even while lying on his stomach to sleep. This is generally unheard of for SMA children, as they are belly breathers, and the common cold can most likely hospitalize them. Javi presents more like a typical child his age, and people are often shocked when I tell them both my -- when I tell them that both my children have the same disease.

In conclusion, the SMA community strongly urges the Advisory Committee to take up consideration of a forthcoming SMA screening nomination, with concerted focus on the availability of a treatment for SMA, the success of the technology and screening for SMA, and the demonstrated benefits of early intervention. I thank the Committee for the opportunity to address you today and appreciate your

consideration.

DR. JOSEPH BOCCHINI: Thank you, Ms. Medina. We appreciate your presentation, and we are aware and look forward to receiving the nomination packet for SMA.

MS. AMY MEDINA: Thank you.

DR. JOSEPH BOCCHINI: Next, we have Ms. Kristin Stephenson, also to discuss new developments in the therapeutic space for spinal muscular atrophy and the impact on the need for newborn screening. Operator, would you open Ms. Stephenson's line?

OPERATOR: Ms. Stephenson's line is open.

DR. JOSEPH BOCCHINI: Thank you. Please go ahead, Ms. Stephenson.

MS. KRISTIN STEPHENSON: Good morning, and thank you for the opportunity to address the Committee today. My name is Kristin Stephenson, and I serve as Vice-President of Policy and Advocacy for the Muscular Dystrophy Association. Over the past months, the SMA community has had the privilege of sharing with you the great

progress that has been made in preparing to approach this body for SMA to be added to the RUSP, and we appreciate the interest that this Committee has shown in receiving those updates.

Notably, as Ms. Medina shared with you a moment ago, on December 23rd, the landscape for families living with SMA changed dramatically when the FDA approved the first therapy for this disease. The approval shifted the paradigm in terms of SMA's eligibility for newborn screening. In addition to this new drug approval, there are also multiple therapies and clinical trials for SMA, with over a dozen other approaches nearing the clinic.

This is a watershed time for the SMA community. With an approved therapy currently being dosed in newborns and infants nationwide, now is the time for newborn screening for SMA. We must ensure that every baby born with SMA is identified and is able to receive treatment, regardless of which state the baby is born in, which is why the SMA community will soon be

submitting its request to add SMA to the RUSP.

As we've shared in previous testimony to the Committee, SMA screening has been successfully piloted in both Taiwan and New York State, both which were able to identify at least one positive infant who was able to enroll in a trial to receive treatment presymptomatically. Not only have two different pilots demonstrated success, but another important consideration of newborn screening for SMA is that we can predict who will develop SMA definitively with a DNA test, because they know that every baby lacking both copies of SMN1 will have SMA. The vast majority of these babies will be affected by the most severe infantile onset form of the disease, usually fatal in early life. Most others will develop progressive symptoms as toddlers or preschoolers. Even in extremely rare cases where disease does not progress until adulthood, we know that the absence of SMN1 predicts an underlying pathological disease process leading to SMA.

With newborn screening pilots in both the U.S. and abroad having shown success in screening infants for SMA, and with an approved drug on the market, we believe now is the time for SMA to be added to the RUSP and respectfully request that this Committee move the nomination forward when it is received. Thank you, again, for your time and for all that you do.

DR. JOSEPH BOCCHINI: Thank you for your presentation, Ms. Stephenson. Again, we certainly look forward to receiving the nomination package and -- and look forward to reviewing the data.

Next, we have Dr. Thomas Crawford, who'd like to also present the potential for substantial clinical benefit that could arise from early, presympomatic identification of infants and children with SMA. Operator, if you'd open Dr. Crawford's line?

OPERATOR: Dr. Crawford is not on.

DR. JOSEPH BOCCHINI: He's not? Okay. All right. Let's go, then, to the next scheduled speaker, Annie Kennedy, who'd like to present

Duchenne Muscular Dystrophy therapeutic approvals update, and the Newborn Screening Infrastructure update, as well. Ms. Kennedy -- Operator, if you'll open her line?

OPERATOR: Ms. Kennedy's line is open.

DR. JOSEPH BOCCHINI: Thank you.

MS. ANNIE KENNEDY: Hi. Hi, good morning.

DR. JOSEPH BOCCHINI: Morning.

MS. ANNIE KENNEDY: Good morning. On behalf of the Parent Project Muscular Dystrophy, I'd like to thank the Committee for providing me with the opportunity to address you here today, and I'm here on behalf of PPMD, Dr. Michele Puryear and Dr. Jerry Mendell, who, together, have been helping to provide leadership for the National Duchenne Muscular Dystrophy newborn screening efforts.

One year ago, I had the opportunity to present before you and share that our Duchenne community's research pipeline was both robust and hopeful. Today, I'm pleased to share that our Duchenne community has finally arrived at the

long-awaited post-approval space. On September 19, 2016, the Duchenne community received our first approval for a disease-modifying therapy targeting the underlying cause of Duchenne: Exondys 51.

Sponsored by Sarepta Therapeutics, Exondys 51 is an excellent skipping therapy estimated to benefit approximately 13% of the Duchenne population whose disease may be modified through a skipping of the targeted Exon 51. The label for Exondys 51 did not restrict access based on gender or age, and the product sponsor is now working to fulfill post-market commitments and additional studies, including trials in a cohort of patients under the age of 4. In addition, as I speak right now, today is the regulatory review deadline date for a second Duchenne-specific product, and we anticipate the approval within hours.

While the standard of care is established through the CDC's Duchenne/Becker Care Considerations published in the Lancet in 2010

have long been -- steroids have always been an off-label treatment for Duchenne. In the U.S., the Duchenne community has typically prescribed prednisone, while outside the U.S., patients with Duchenne have, typically, access to deflazacort. The two steroids have been compared with our -- with our patient community in numerous studies and have demonstrated differing safety profiles causing patients and providers in the U.S. to seek the option to prescribe deflazacort. This product, Emflaza, is not mutation-specific and would represent a treatment option for 100% of patients with Duchenne. Steroids, currently, are prescribed as early as age 3 and 4, sometimes earlier, depending on the clinical provider. Marathon is working to study the safety and efficacy of their product in younger boys, as well.

Additionally, we've been working closely with PerkinElmer on an effort to develop refined -- a refined screening test for Duchenne. PerkinElmer is leading the project, in

partnership with the California Department of Health Newborn Screening Program, and is using newborn screening residual blood spot specimens from the California Biobank.

On Mother's Day of 2016, PPMD launched a national carrier study called the Female Side of Duchenne, with a goal of gaining a better understanding of what it means to be a carrier across the trajectory of carrier phenotypes. PPMD has teamed with Nationwide Children's in Ohio to study 500 women across a range of ages, demographics, and phenotypes.

Our Duchenne community is also fortunate to have many well-developed infrastructure and registry resources, including PPMD's Duchenne Connect Registry, which has been a part of the PCORI/PCORnet Network, and MDA's National Neuromuscular Registry. For this reason, PPMD, MDA, and NBSTRN established an MOU to explore data integration and applicable resources available through NBSTRN. NBSTRN staff has developed common data elements specific to

Duchenne, and these are now incorporated into NBSTRN's longitudinal pediatric database.

Our Duchenne community is hopeful, but we also know that we have much work to do to transform our existing national Duchenne care and support infrastructure into one that fits into the public health model for newborn screening, and we're working hard to accomplish this. We're committed to paving a path forward for Duchenne newborn screening in the United States, and we thank you for your time today.

DR. JOSEPH BOCCHINI: Thank you, Ms. Kennedy, for this update. We appreciate you keeping the Committee abreast of the changes as they are occurring, pretty much in real time. And so -- so, thank you.

MS. ANNIE KENNEDY: Thank you.

DR. JOSEPH BOCCHINI: Operator, let's go back. Is Dr. Crawford on?

OPERATOR: One moment. No, Dr. Crawford is not on.

DR. JOSEPH BOCCHINI: Okay, then, let's

go to Ms. Jessica Wade. Ms. Wade would like to discuss the lack of uniformity of newborn screening programs in the United States -- specifically, Michigan. Could -- Operator, would you open Ms. Wade's line?

OPERATOR: Ms. Wade's line is open.

DR. JOSEPH BOCCHINI: Thank you. Good morning, Ms. Wade.

MS. JESSICA WADE: Good morning. Thank you for this opportunity to speak. I am a mom from Michigan, and I have two sons who were born with congenital hypothyroidism. My son Micah will be 8 tomorrow, and my son Eli is 4.

So, my son, he -- Micah, he does not speak. He doesn't go to the restroom by himself, and he requires 24-hour supervision. He may never get married. He may never leave home and become an independent adult. However, his brother Eli, he is now typical. He is meeting all of his milestones.

The difference between the two of them is that there is a lack of uniformity of newborn

screening programs in that state, especially -- specifically Michigan. Their lab cutoff for congenital hypothyroidism is 33, and that's considered borderline. Micah's TSH at birth was 30, so he wasn't rescreened, and his pediatrician was never even notified of his lab results. He suffered with all of the symptoms of congenital hypothyroidism, and yet, we were sure that his screening was negative, so he must -- you know, there must be some other reason for these symptoms and why he wasn't growing. His endocrinologist, after he was finally diagnosed -- and we do believe he had it from birth, until we got the lab results to see this, and then his baby brother was born with the same condition.

Currently, newborn screening, as we all know, for children with hypothyroidism is one of the first, at the least, tests that was added to, you know, the 50 states. And according to the American Academy of Pediatrics, in -- in regards to the guidelines of newborn screening therapy for congenital hypothyroidism, the thyroid-

stimulating hormone, TSH, concentration, if it's slightly elevated but less than 40 milliliters per -- excuse me, milliunits per liter, a second screening test should be performed on a new sample, and then the results should be interpreted using age-appropriate normative results. So, for instance, typically, you'd see 1.7, 9.1 milliunits per liter in an infant that's 2- to 6 weeks of age, and approximately 10% of infants with confirmed congenital hypothyroidism have TSH values between 20 and 40.

As I said, Micah and my son Eli, they both fell within that 10% of TSH values of 30 and 35, respectively. See, Eli was 35, so his doctor was notified, and, unfortunately, only one of them received appropriate and timely treatment. As I said, Micah's going to be 8 tomorrow, and he's the size of a -- about a 5-year-old because of his growth delays due to the ... You know, and his brother had a TSH of 35, so thankfully, he did receive appropriate follow-up treatment, and we were in a better position to make decisions

about his health, but Micah wasn't so lucky.

Newborn -- newborn screening for congenital hypothyroidism should be uniform, and what I mean by that is, my son's health means no less than that of a child who was born with a TSH that's in the hundreds. This is something that truly needs to be changed now. This is something that has been known about, not only by Michigan, but other newborn screen labs who have solved that problem by changing their cutoffs.

His diagnosis has now become an expense to our state, who, I feel, cared more about operating costs than the chance of having a higher, maybe, false positive rate, and I believe that this is not acceptable, that no baby should have to suffer. I pray that the Committee would take a stand for Michigan newborns and all babies in the United States, who deserve better. Thank you for your time today.

DR. JOSEPH BOCCHINI: Thank you, Ms. Wade, for presenting your personal story, and -- and, clearly, this Committee is -- is committed

to having newborn screening work for every child, and as you may be aware, later today, we're going to begin a discussion on current laboratory practices for cutoffs, and -- and -- and so, we will begin that discussion and certainly have your child, as well as other children, in mind as we do so. Thank you.

MS. JESSICA WADE: Thank you.

DR. JOSEPH BOCCHINI: So, next on -- for public comment is the Association for Creatine Deficiencies to discuss newborn screening for GAMT deficiency, and we have Kim Tuminello, Heidi Wallis, Jerry Robinson, Bess -- Beth Robinson, and Jenny Wolf. I'm not sure whether you're all in the same place or have different lines, so, Operator, do you have a line or multiple lines for them?

OPERATOR: Yes, I have multiple lines for them.

DR. JOSEPH BOCCHINI: All right. So, I guess, Ms. Tuminello, are you going to start the discussion?

MS. KIM TUMINELLO: Yes, that sounds good.

DR. JOSEPH BOCCHINI: Okay, thank you. So, let's go right ahead, and then we'll go from presenter to presenter. Thank you.

MS. KIM TUMINELLO: Thank you. As you know, the ACD is representing not only the families that currently are affected with GAMT but, eventually, those families that will need the patient support group because their child or children were diagnosed too late with this easily detectable and treatable disorder.

In November, we were awfully shocked that GAMT was not moved to the Evidence Review Board, and I know several of you on the Committee are as passionate about adding GAMT as we are, and we're very thankful for that. I know some of you on the Committee even believe that all the criteria has already been met. However, it was seen that the newly added criteria outweighs common sense, and with that being said, we would like to give a couple of our new families the time to speak

about their unnecessary heartbreaking journeys, but once again, I want to thank you for your time.

MS. HEIDI WALLIS: Good morning, can you hear me?

DR. JOSEPH BOCCHINI: Yes, we can. Go ahead, please.

MS. HEIDI WALLIS: Okay, great, thanks. Thank you. This is Heidi Wallis, and thanks for the opportunity to speak today. I just wanted to address -- We've had a steady stream of new families over the last few months joining our support group, and their stories are strikingly similar: young children who are missing milestones and evaluated and told they have autism and sent on their way to figure out life. But some parents are fighting back for more testing and receiving the diagnosis of GAMT for their children.

I want to remind the Committee today about GAMT and to keep it at the top of your mind. It's so easily treatable, and the outcomes

of early treatment are a completely normal life. Your policies and choices on this board literally decide this fate for children in the U.S.: a life of disability or a full life. GAMT outcomes are that black and white, and you will understand that from the stories from our families that have joined us today. Thank you.

MR. JERRY ROBINSON: Hi, this is Jerry Robinson. Is my line open?

DR. JOSEPH BOCCHINI: Yes, it is. We can hear you, Mr. Robinson.

MR. JERRY ROBINSON: All right. Thank you for your time. It's very relevant to follow the update on the GOA (sic) timeliness report because they're tied into that in that our stories are all about timeliness of screening and diagnosis.

So, first, I'd like to tell you that my family, we have 3 children, and two of them -- our oldest, Ben, and our youngest, Celia -- have GAMT, and they were diagnosed at ages 6 and 1. We're a living example of the differences that early detection can make. Before the diagnosis,

we spent tens of thousands of dollars on testing alone for the first 6 years of Ben's life, trying to figure out what was wrong with no results. They ran microarrays, ordered MRIs, took blood and urine, and all with no answers. And we were spending -- we weren't -- if we weren't spending money on testing, we were spending money on EEGs, hospital stays for uncontrolled seizures, ambulance transfers to children's hospitals, and all without a diagnosis until we had a second child that presented the same, and we visited genetics at an alternate hospital.

After our diagnosis, we began treatment. Our daughter flourished soon after and has now caught up to her peers. She does have a G-tube to reach full compliance with her medication.

There are constant reminders of the damage that was done in the first 6 years of Ben's life. Because of his low muscle tone and motor planning difficulties, he often chokes on his food, forcing caregivers to become certified in CPR and first aid, waiting for the next time

he chokes, hoping we don't have to use CPR. And any time he needs a routine dental procedure, like a cavity filled, Ben has to be put under general anesthesia at a hospital, which is dangerous and expensive. And because he's non-verbal, he's unable to tell us what's bothering him, so if he has unexplained vomiting, we might have to put him under general anesthesia and do an endoscopy to figure out if something is very wrong. At 13, Ben is still learning toileting skills. Incontinence products for teenagers are expensive and difficult to find and not covered by insurance. Celia, however, suffering very little damage, deals with none of this.

The biggest issue, for us, is Ben's future after we're gone. We've had to hire lawyers to draw up expensive special needs charts and carefully executed wills, because his future must be diligently planned out and not left to fate. Ben will live with us until the end of our lives. We look forward to our days together, but someone will need to take care of him when we

can't, and it's broken our hearts to know that there's a test that could have changed his future. His sister's future is completely different from his because of that one simple test. Thanks, again.

DR. JOSEPH BOCCHINI: Thank you very much for your -- your comments. We do appreciate them. Next is, I think, Beth Robinson?

FEMALE SPEAKER: She's not online.

MR. JERRY ROBINSON: Beth's not joined, yeah. Beth's not joined.

DR. JOSEPH BOCCHINI: Okay, so Jenny Wolf?

MS. JENNY WOLF: Yes, thank you. I'm a mother to 6-year-old, identical twin boys, who have recently just been diagnosed with GAMT deficiency. My boys, Logan and Lucas, had obvious developmental delays from the start, and we immediately began seeking answers. We had them evaluated multiple times, at multiple centers, for the first 6 years of life. The evaluations provided no diagnosis outside of labeling them

with autism. After a microarray with Yale Genetics, which, you know, had failed to return results, we sought out full genome testing ourselves. We paid for it out of our own pocket, and that is how we finally got our GAMT diagnosis. So, basically, you know, we searched for it, and we paid for it.

The treatment plan at 6 years old -- we know it's not a cure for GAMT. We can only hope that the treatment will alleviate some of the symptoms -- namely, the seizures, especially -- but the damage has already been done to my sons. We wasted 6 years at top-notch Connecticut children's hospitals, as well as various specialists, and they all missed the diagnosis.

So, you know, my -- GAMT is rare, so why are we leaving it in the hands of general practitioners to catch, when, you know, at a hospital like Yale, genetics didn't even understand the disorder well enough to test for it? Testing for this disorder at birth is crucial to the lives of families and children. How many

other children out there are being labeled with autism but, in fact, have GAMT?

So, please, help to avoid causing unnecessary hardships in the lives of these children and families. Your decision to recommend GAMT screening can make a significant impact in the lives of children and families affected by GAMT. Thank you, again, for allowing me to participate.

DR. JOSEPH BOCCHINI: Thank you for your comments. We -- we do appreciate them, and -- and we will continue to work with your support group and -- and others to determine how to move forward with considerations for -- for this condition. Thank you, all.

MS. JENNY WOLF: Thank you.

DR. JOSEPH BOCCHINI: Next is the MLD Foundation RUSP Roundtable update from Mr. Dean Suhr. Operator, please open Mr. Suhr's line.

OPERATOR: Mr. Suhr's line is open.

DR. JOSEPH BOCCHINI: Thank you.

MR. DEAN SUHR: Thank you. Good morning,

Mr. Chairman, and -- and the Committee. Thank you for giving me my 2 minutes here. It looks like we'll keep right on time. You're doing a great job.

I wanted to make a brief report on the last RUSP Roundtable meeting that was held in August, adjacent to the in-person Secretary's Advisory's meeting, as well. And I would like to, also, briefly remind you that while the MLD Foundation is sponsoring these meetings, it's not an -- it's not an MLD-specific project. There's no hidden MLD agenda or any of that sort of thing in this. We're doing this for the community.

Our third day-long meeting was held in Rockville last August. We are a gathering of some two- to three dozen independent, arms'-length perspectives from throughout the newborn screening ecosystem. We span and informally bridge a number of very active and productive newborn screening working groups and forums. We're not meant to replace any of those groups. We don't believe that anybody's doing a bad job.

We are not formally chartered. It is a -- an informal gathering of interested individuals that -- that, as I mentioned, come from a number of different groups and perspectives, including a few from the Committee itself.

Our -- our results are being reported at NewbornScreening dot US. We've got some updates going on there to get our August information there, but there is an initial executive report, which includes a little bit more about our scope and what we're trying to accomplish. So, I know you have some new Committee members. They may want to take a quick look at that. Our next meeting will be in person, May 10th, the day before your next in-person meeting.

One of the things that came out of the August meeting, which was kind of a -- a little bit of a turning point in how we're proceeding, was a strong sense -- because these are not quite Type A personalities but very influential and -- and a strong-desire-to-work personalities -- I don't know if that equates to Type A -- but

through our discussions, there's a strong sense that we want to accomplish something besides sharing and learning and -- and growing from each other. So, we spent quite a bit of time talking about different sorts of work projects and working teams to dig deeper into some specific topics. So, as we go forward, we will probably spend about half our time in -- in this open discussion, roundtable-type format and -- and the other half of our time actually doing some hands-on work.

There are too many topics for me to go through this morning, but I will be sharing that back with the Committee. And I would like to highlight, also, that a couple of those areas included requests by some of the -- the people around the roundtable to make some reports back to the Advisory Committee, so with your permission, we'll probably be asking for, maybe, some time to present some of the summaries of -- of the work that we're doing, as -- as that's appropriate, with the Committee. Thank you for

your time, and thank you, all, for your good work.

DR. JOSEPH BOCCHINI: Thank you, Mr. Suhr. We certainly would like to have feedback from your work to the Committee, and we'll look forward to figuring out how best to get that information to the Committee, of your deliberations and the considerations that you've -- that you have related to this subject. So, thank you.

MR. DEAN SUHR: Thank you.

DR. JOSEPH BOCCHINI: So, Operator, has Dr. Crawford come online?

OPERATOR: Yes, Dr. Crawford is online. One moment.

DR. JOSEPH BOCCHINI: Okay.

OPERATOR: Dr. Crawford's line is open.

DR. THOMAS CRAWFORD: Hi there.

DR. JOSEPH BOCCHINI: Hi.

DR. THOMAS CRAWFORD: You've got me now, good. I think I missed you by a fraction of a minute.

DR. JOSEPH BOCCHINI: All right. Well, we were on schedule, so we're -- we're probably a little ahead of schedule, which is unusual for us, so we -- we appreciate you hanging in there. So, let's -- please, go ahead and -- and provide us with your input.

DR. THOMAS CRAWFORD: So, I'm delighted to be asked. So, My name's Tom Crawford. I'm a -- an MDA clinic coordinator here at Hopkins, and I'm here as a, sort of, representative of medical professionals for SMA. You should know that I started with SMA back in 1978, when I held a baby with SMA, and that baby went on to die, as have, perhaps, 150 that I've followed in the 25 years since that time.

And I've had the opportunity to do, like, pathology and physiology and genetics and animal modeling and -- and, sort of, the whole thing, and the amazing issue is that we have a therapy -- this has been an amazing ride, from the most hopeless of diseases to, now, an approved drug. December 23rd, we were rewarded with an early

Christmas present of a drug that is approved by the FDA for the purposes of -- of this therapy, and it has a -- a -- a substantial treatment effect, so that if -- It -- the -- the label is available for all folks, so that you can give it -- It's -- it's indicated for patients with SMA of all types and all ages.

But what we do know is that there is a -- a substantial benefit of early diagnosis, that in the earliest cases -- We have some kids in a -- in a protocol called Nurture, who were treated presymptomatically, and these were identified because their siblings had it, and those individuals -- we have 25 of them now, and they are doing spectacularly well, including kids who were getting to the point of standing, walking, where their siblings died. And so, the -- the -- the -- the effect size is -- is very, very large, and the -- the -- the magnitude of delay is also large.

So, the way in which we can change the course of this relatively common disease in the

range of newborn screening diseases -- the way we have to get at this is to have a -- a newborn screening process that's effective. So, we have a -- I know you'll be hearing about it -- more about a -- a protocol that is able to find people with a high sensitivity and specificity. The need is tremendous. We have a therapy that makes a difference, and so I just want to point out that this is -- If there was ever a disease that qualifies as a -- a high priority project for -- for the -- the -- the RUSP, it would seem to me that spinal -- spinal muscular atrophy would -- would fulfill that -- that promise. So, thank you very much for the opportunity to -- to -- to -- to -- to pitch this.

DR. JOSEPH BOCCHINI: Thank you, Dr. Crawford. Certainly, we're looking forward to receiving the nomination packet, so that we can begin formal evaluation and work on the project. Thank you very much for your comments.

DR. THOMAS CRAWFORD: Excellent. Thank you. Bye-bye.

DR. JOSEPH BOCCHINI: Bye. So, next on the agenda, we have a panel presentation on newborn screening cutoffs and algorithms, and as mentioned this morning, this is an important topic that we want to begin a discussion on. This has come up in a number of past Committee meetings as a potential item for the Committee to become involved with, as well as some discussion about it in the Laboratory Follow-Up Committee -- Sub-Work Group, as well. In addition, there has been a publication -- a series of publications related to newborn screening cutoffs, algorithms. You heard from Ms. Wade this morning about her son with hypothyroidism.

So, we've decided to begin with a discussion for the Committee to help the Committee, sort of, frame some of the -- of the issues by providing some background on how laboratories set cutoffs and establish reference ranges, how newborn screening lab results are interpreted, and how screening results are communicated to providers. At our next in-person

meeting, I would like to take some feedback from this discussion, as well as -- as other issues that might arise from this, and -- and bring this forward as -- for further discussion, and then some decisions by the Committee on how to proceed, potentially tasking the Laboratory Standards and Procedures Work Group to perform a more in-depth analysis based on what we find.

Our panel discussion today, we have three excellent presenters lined up. The first is Michele Caggana, board certified in clinical molecular genetics by the American Board of Medical Genetics and a fellow of the American College of Medical Genetics and Genomics. She's Deputy Director of the Division of Genetics, Chief of Laboratory -- of the Laboratory of Human Genetics, and Director of the Newborn Screening Program. She is co-chair of the APHL's Newborn Screening Genetics and Public Health Committee.

Second is Dr. John D. Thompson. Dr. Thompson received a PhD in public health genetics from the University of Washington in 2008 and

began working for the Washington State Newborn Screening Program back in 2003 and became director of the program in 2016. He serves as co-chair of the HRSA-funded NewSTEPs Short Term Follow-Up Work Group.

The third is Carol Johnson. She is the Follow-Up Coordinator of the Iowa Newborn Screening Program. She serves as the Co-Chair of the APHL NewSTEPs Short Term Follow-Up Work Group and is a member of the APHL NewSTEPs Cystic Fibrosis Foundation's special interest group, which is designed to improve CF newborn screening.

So, I'd like to turn the discussion over to our panel. I believe the first presenter will be Michele Caggana.

DR. MICHELE CAGGANA: Okay. Good morning. I want to thank the Advisory Committee and HRSA for asking me to speak to you today. My charge for the next few minutes is to outline the laboratories' perspectives regarding newborn screening and cutoff determinations, and,

essentially, I'm going to describe a little bit about validation and our screening results, and as you heard, my colleagues, John Thompson and Carol Johnson, will follow me.

Next slide. Okay. So, newborn screening programs are clinical laboratories, and, thus, we're subject to the laws that govern the practice of clinical lab testing. Most everyone is familiar with CLIA, and that stands for the -- it says here, the Clinical Laboratory Improvement Amendments of 1988. These are federal regulatory standards, and they apply to all of the clinical laboratory testing that's performed on humans in the United States, and that -- that does exclude clinical trials and basic research.

Promulgation of these standards is carried out by the Centers for Medicare and Medicaid Services, or what we call CMS, and if you go to the perspective -- respective websites, you can find all of the activities that are outlined by these groups. But some of the main things that CMS does is issue laboratory

certificates. They also conduct inspections and enforce regulatory compliance. They monitor PT results, and they also publish rules for CLIA.

The CDC also plays a role in this, in the division of Laboratory Programs and Standards -- Standards and Services, and they have a role in clinical laboratory testing by providing analysis research and technical assistance. They also help develop technical standards and lab practice guidelines. They conduct lab -- laboratory quality improvement studies, and they monitor proficiency testing practices. They also manage the CLIAC, which is the advisory committee for CLIA.

And, lastly, the FDA has a role in this, and they -- their roles are to categorize tests based on complexity, and they also review requests for waivers and develop rules and guidance for categorizing CLIA-regulated tests.

So, in New York, we are CLIA exempt, and we have our own regulatory programs. So, being exempt, or having what's called exempt status,

means that laboratories that are operating in New York or laboratories that accept samples that are collected in New York must hold a New York permit, and we're held to the same standards that either meet or are more stringent than the rules dictated by CLIA. So, the four bullets on this slide show the different facets of the New York program, and as you can see, they align quite well with what I had outlined for you for the -- for CLIA.

Next slide, please. So, newborn screening programs can also be accredited. In addition to having a regulatory basis, we also can have various accreditations. And they're not regulatory in nature, but they have standards nonetheless, and they're in place along with site visits that are conducted to ensure lab quality. And, in turn, the labs are adhering to good laboratory practices, and probably the most familiar one is the College of American Pathologists, or CAP. The surveyors for CAP are our peers in our fields. They're not laboratory

consultants, per se, that are regulatory in nature.

In addition, I have here, listed, a couple of the other professional organizations that do provide guidelines and publications for our laboratories to use to ensure that we are practicing good laboratory -- good laboratory -- and providing good laboratory services. The Clinical Laboratory Standards Institute provides a whole series of different documents that are updated on a regular basis. These documents are written by experts in the field, and the writing of these are constituted by a -- it's a very formal process. I actually participated in -- in one of them, and several colleagues in -- on the phone probably have, as well. Other organizations, such as the American College for Medical Genetics and Genomics and ANP also have similar roles in providing guidance to laboratories on how to conduct good laboratory science. And we all use these combinations of programs to help us ensure that we're doing the

best that we can for the youngest citizens in our state.

Next slide. So, with that in mind, I'm going to start off with a couple of definitions that are familiar to newborn screeners. So, the first one is a "fixed cutoff." Some tests are conducted using this fixed cutoff value, which means that there is a fixed numerical number and a decision point, and the decision point is predetermined for -- predetermining -- predetermined whether the analytical result is deemed a screen negative or a screen positive. And this number can obviously be revised, and it may incorporate baby-specific factors, which I'll get into in a couple of slides.

The next is a "floating cutoff." This type of cutoff is used when the analytical result might be subject to environmental factors. The most commonly one that we know of is temperature. And so, for immunoreactive trypsinogen, which is the analyte that's used for cystic fibrosis, we're aware that this value changes with season

and temperature. And since the population mean isn't stable over time due to the seasonal variation, we use a percentile cutoff. So, in our state, specimens that have an IRT result in the top 5% of the population are then sent on for molecular testing. So, that's a floating cutoff.

An algorithm is basically a flow chart. It's a schema used that helps determine the results, and previous presentations to this Committee have shown these types of flow charts. The algorithms outline the various decision points for the determination of the recommendation for or against a diagnostic evaluation and follow-up and can consider different aspects of the baby's health and the laboratory components.

The next term that we use is a "retest," and this is used when an infant has an out-of-range result, and we go back to that baby's specimen and re-punch that same card, usually in duplicate or triplicate, and then we use the same test again. This helps us to determine whether or

not there were errors in punching or if there's any specimen-specific variation that we should be concerned about.

After the retest, the sample can still be tested by yet another method prior to reporting, and the sample may also be reported at this point as a "borderline result," or it could be referred for diagnostic evaluation.

So, when we talk about a "borderline result," these are test results that are slightly out of range. A second specimen is generally requested, and then we use that to make a final determination. The second specimen is usually collected by either the pediatrician or the hospital of birth, at least in our program, and at this point, we don't notify the specialist. And, also, in our program, two borderline results can constitute a referral.

Next slide. "Repeat testing" means -- and that's different from "retest." Repeat testing means that this is done after a borderline result. So, programs may get in another specimen,

and they may test it for only that analyte that was out of range, or they might repeat the entire panel, and this differs from the retest because it's freshly collected. So, when we talk about "repeat sets," another sample coming in. When we talk about "retests," that means an in-house test on the original specimen.

The next common term that we use is "second-tier," or "reflex," test, and this means that there is a different test conducted in-house on the initial specimen prior to reporting out the results. This is done to reduce the number of referrals, and second-tier tests are done prior to notification of the medical community, except, maybe, under an extenuating circumstance, such as an analyte that's extremely out of range. We might give a heads-up call to the medical community for that.

And people often confuse the next two. One is "tier testing", and then "confirmatory testing." So, tier testing, in our minds, is the use of multiple tests to determine the follow-up

actions that are required for that infant. And this could be a combination of two biochemical tests, like T4 and TSH for hypothyroidism, or it may be GALC activity in psychosine for Krabbe disease, or it can be a biochemical test coupled with a molecular test, such as IRT-DNA for cystic fibrosis.

The confirmatory testing is what's done outside of the purview of newborn screening. So, this is done after a positive result is obtained for newborn screening during the follow-up, clinical, and diagnostic evaluation period. And this could be, perhaps, molecular analysis collected on -- on a freshly collected sample that's sent out to a diagnostic laboratory or an enzyme analysis that's using a different specimen type, such as skin, in some cases.

Next slide. So, I want to emphasize that newborn screening is not diagnostic, and this is a point that I try to make, at least, whenever we talk with physicians. Yesterday, I gave grand rounds in New York City, and one physician did

comment to me that sometimes they rely too heavily on newborn screenings on -- on the reports that we issue when they make an assessment of a critically ill infant in the nursery or an infant who returns to the hospital.

Newborn screening is a partnership between families and providers and specialists, and screening is a risk assessment. We have to set our values for follow-up in order to minimize the false negative results. In doing so, we cull a lot of infants for extra evaluation. Newborn screening programs work hard and continually strive to reduce these false positives, but we can't do so if the number of missed infants increases.

That said, unfortunately, we do miss infants, and we do follow up on those cases whenever we are informed of that, and we conduct a formal root cause analysis to determine if there were any preventable errors. We simply can't predict the biology of more than four million infants. Newborn screening is a high

throughput program, and because of that, we identify the entire spectrum of disease. Those textbook-classic cases that we see, and also many cases that are considered mild. Some cases might be so mild that they might not ever have come to clinical attention except for the newborn screening result, and in this case, an abnormal biochemical result might not always equate to a recognizable clinical phenotype.

Next slide. So, I would like to further discuss some of the differences between screening and diagnostic testing. When we receive a specimen, it's from an asymptomatic infant, so since it most often does not have any family history of a genetic disease, and we really have no clinical indication or concern for testing, thus the specimen arrives to us for a risk assessment. This is very different from a specimen that arrives in a laboratory in order -- for which there is a clinical context.

As I mentioned earlier, screening has to accept some false positive results. This doesn't

mean that we don't assess what we do and make every attempt to minimize those; it is a consequence of what we do. Screening programs have to tolerate this, and we must communicate this information to the clinical community in an understandable and thoughtful way. Diagnostic testing cannot tolerate a -- a -- a false positive result. Screening programs, by practice, do tolerate them.

I, again, want to emphasize that screening is in place to narrow down an entire population and find those infants that are at the highest risk for these conditions. It caters to the entire population and takes all comers. Diagnostic testing deals with the one, the one that may be the sick individual or that family. Screening is not diagnostic, and thus, infants that are determined to be at risk must undergo confirmatory testing. The screen alone should never be used as a basis for the clinical diagnosis.

We know we miss cases, as in cystic

fibrosis, and many studies have been conducted to determine how these false negative cases can be detected. There's always a balance between the false positive and false negatives reads, and as a community, newborn screening programs share our experience and look for solutions to prevent this from happening. No one wants this to happen.

We also rely on the medical community to inform us, as soon as possible, if they have a baby with a diagnosis that we didn't tell them about first. From the clinician's perspective, we need to remind them that we conduct screening, and then, if they have an infant with the symptoms of a panel in that condition, they need to rule that possibility out with confirmatory testing.

For context, I included some familiar examples. It is of interest that a screening test such as a mammogram has a 20% false negative read. And many of us have screening colonoscopies, and -- but if there's a clinical indication -- excuse me -- such as low

hemoglobin, the colonoscopy is conducted in a different manner, and that's become a diagnostic colonoscopy.

Similarly, we are all familiar with glucose and cholesterol screenings. Abnormal results are followed up depending on clinical experience of the provider. In some cases, repeat testing might be sent to another laboratory, or other forms of follow-up testing may be ordered. Different laboratories have different cutoffs for these analytes. They may get different answers on different days and with different instruments. Clinicians may choose to manage these results based on the patient's other medical conditions or their complaints, et cetera.

Next slide. So, I like to think that screening is interesting because it's both simple and complex. One thinks that the screen is a simple laboratory test, but it's actually very complicated. Moving towards focusing on the validation of a new newborn screening test, it is onerous to be mandated to conducted a population-

wide test when there is little experience in the field except for that of the diagnostician. Remember, the diagnostic lab operates with clinical context, while screening does not.

So, if the -- a program is mandated to begin a screening test, the first lab is the one that creates the experience. It behooves that lab to set very conservative cutoffs, and the tests have to be conducted in a high throughput way. We are looking for rare conditions, even amongst the more than 99-plus percent negative results, and I always remind my staff that we are looking for the one among the many.

In a practical sense, we must have redundant equipment in place. We must ensure high quality reagents are consistently available, and other items that must be covered in considering the validation of a new test are the states' composition of their population, the variabilities that are introduced with temperature and fluctuations, and thus, the time of the year.

Next slide. After that short list, there is another list that deals with the baby. Most that I can think of are listed on this slide. When considering population-based screening cutoffs and validation, we must incorporate differences in infants due to their gestational age, their birth weight, their feeding status, their transfusion status, any treatments or underlying medical conditions. And maternal health can also impact our screening results.

We also know values that can be impacted by the infant's race and ethnicity. And, further, while we know that these factors can impact screenings, we sometimes don't get accurate information from the birthing hospital, and this -- this, in turn, impacts our turnaround time when this information must be gathered after the specimen is received.

Lastly, we do operate, as I mentioned, in a bit of a vacuum, as we cannot be sure the baby has been fed well. This differs a lot from a physician, who may order a fasting glucose and

instructs the patient to do so, for example.

Next slide, please. When you consider the regulatory requirements for test validation, CLIA is silent on how programs should do this. However, the Clinical Laboratory Standards Institute, or CLSI, does have a document that includes all factors that need to be considered. CAP has a similar list for laboratories to follow. We must find individuals with a condition and get permission from their parents to use those specimens for test development and validation, because the newborn sample is the correct matrix in the correct age range that we must use in order to validate a test.

Next slide. When we get to the point of actually trying to establish the decision point, the cutoff value, we need to select the population to screen. The number of sample screens can be variable, and that depends on the items I discussed previously, including the number of births in the state, the composition of the state population, the frequency of the

condition, what is known about the condition, and other factors. These tests must be conducted on the same matrix, i.e. the newborn screening specimen. And I must say, this process has been hampered a bit by the Section 12 -- the -- the Newborn Screening Saves Lives Act, as some laboratories have elected to disallow the use of these specimens for this purpose.

After we complete that population -- sort of, the normal population screen, we conduct statistical analysis on the population. And these exercises and analyses ultimately lead us to what the cutoff values should be. And, importantly, once we begin screening, we then conduct continuous quality improvement. This encompasses many things, including assessing new technologies, assessing new analytes that become available, or tests, or combinations of these analytes, and experience after we get feedback from the clinical community.

Next slide. As I alluded to above, we must have positive controls to conduct this work,

and with the help of advocate groups and specialty care centers, and sometimes other states who have bio repositories, we're able to gather positive specimens. The rarer the condition, though, the more difficult this becomes. It's near impossible in states with low birth rates and/or have rules about specimen storage and destruction to actually have newborn screening samples for some of the conditions, particularly when they're rare. In New York, we get consent from parents to use their child's specimens for this purpose, and this effort entails institutional review board submission and approval.

And this is important, because there's many examples in screening where the adult sample, while it's a lot easier to obtain -- the adult samples just aren't the same as the newborn screening sample, even if they're collected on filter paper without anticoagulants. It's important to get specimens from known newborn carriers, as well, to factor these into -- to

factor the results from these individuals into the cutoff establishment. And, lastly, there are some synthetic controls available to test, but we don't commonly use them, and they're not commonly available for some conditions.

Next slide. So, this slide reiterates, kind of, in bullet format, the items that I just discussed regarding the identification of normal samples and positive controls. And, fortunately, we have the CDC's Newborn Screening Quality Assurance Program to help us in these efforts. This program provides us with materials to use for quality assurance and, importantly, a system for proficiency testing so that we satisfy our CLIA requirements and, most importantly, ensure that we are operating in a proper manner. The NewSTEPs Program from the Association of Public Health Laboratories also helps quality improvement and timeliness, and they act as a portal for community members to share their experience.

Both the CDC and APHL programs are

extremely helpful in the newborn -- extremely helpful to newborn screening programs and their quest to be as good as they can be. The APHL also has a QHUC Committee that looks at many of the items that we're talking about today.

Next slide. So, in the definitions section, I went over several terms that we use to talk about results, and this slide emphasizes all these considerations that we take into account before we actually report out a result. The first thing we have is the primary analyte or the first test result. We call this, sometimes, the primary marker. We can incorporate other analytes or ratios of analytes in order to assess risk status for the baby. Third, we have to consider those baby-specific factors, and we have cutoffs that are based on baby's gestational age or the baby's birth weight. We also consider any retest results, second-tier test results, and, lastly, whether or not this is the first specimen we've seen from this instance or whether we have tested this baby previously, so respectively called the

initial result or the repeat result.

And so, the results, in the end of the day, that we give out to the medical community doesn't necessarily equate to what simply comes off the instrument. And I'd like to remind everybody that despite all our efforts, that infants can have these conditions, even after a negative screen, and thus, clinical expertise must be considered when the infant appears sick.

Next slide. This slide shows us a very simple example of a reporting algorithm that we use for MCAD in our state. There are several ways that an infant can become a referral, meaning that they go out for diagnostic evaluation. There can also be a couple of ways that a repeat specimen can be requested, i.e. a borderline result, and several analytes are considered in making this decision. Even though we always think of a high C8 value as equivalent to MCAD disease, various states use the markers -- the marker results from many markers and their ratios.

Next slide, please. I'd like to give just

a minute to method verification, because this falls in line with our CLIA and our regulatory requirements. Method verification has to be conducted on multiple instruments, and it has to be conducted by multiple analysts. CLIA does not -- does tell us ways that we can achieve this. We can either retest previously tested samples, in this scheme, and in that case, we set tolerable limits for differences to allow for possible degradation of analytes in the sample. We -- Use of our equipment and our algorithms must give us the same answer over time. If the answer is different, this has to be rectified, and corrective actions must be conducted and be available for onsite review by the private sector. We can also meet this requirement by testing QC materials and calibrators. We are required by CLIA to demonstrate concordance in our results.

Next slide. So, in closing, I thought about this and listed some things that we as a community can consider in achieving in the best

possible results for all babies. We need to have a concerted effort to provide physician information and education about newborn screening and what it can and can't do. We need to remind them to consider an ill child's condition as if this baby was never screened. I believe case examples work well for this.

We also need to ensure that these clinical reminders travel along with our electronic reports and electronic medical records and that there -- there is room in the message for that disclaimer, so that it can come to light for a clinician who's looking at a newborn screen result. We should strive to have as much information available as possible on the report, and this should and could include analyte values.

We can work together to standardize how we actually validate new tests. We can use the previously published guidance documents and regulatory requirements to come up with a schema that's acceptable to all states. We should create a forum to share our continuous quality

improvement efforts in -- to discuss this method validation process.

While it's actually in code in some states, it's in statutes, it's clear that we don't get told where the cases are missed by newborn screening always. Information from the community -- the medical community who follows these children and case definitions for us to use are very important. By this, I mean, we need to make sure that a missed or reported case is truly a case and then use that in our continuous quality improvement efforts. Follow-up in medical community -- in the medical community has to feed directly back to the laboratory, and by working together, we can improve all of our efforts.

As above, it's very important that we are defining cases in the same way. No matter how we use the information, we need to be sure that we are considering the same case, i.e. going back to those long examples from Sara Copeland of, we have to compare the same types of apples.

So, lastly, I want to thank the Committee

and you for listening. This is a view out of my window on a sunny morning, but today there's a nice, windswept snow out there right now, so thanks so much for your attention.

DR. JOSEPH BOCCHINI: Thank you very much, Michele, for your presentation. Really excellent. Next, Dr. Thompson -- let's open his line and make sure -- Ready to go. Dr. Thompson?

DR. JOHN D. THOMPSON: Good morning.

DR. JOSEPH BOCCHINI: Good morning. We can hear you.

DR. JOHN D. THOMPSON: Great. Thank you for the invitation to present today. I'm really glad to be able to share some thoughts with you about interpreting newborn screening results. I want to emphasize a few key points at the beginning of this presentation.

First, clear and consistent communication is critical to the interpretation of newborn screening results, and this happens between newborn screening laboratories, follow-up programs, and the clinical consultants.

Next, a screening test is not a diagnostic test, as we heard from Michele. Inherent to screening is the imperfect nature of the test. There will be some babies that we miss because the screening test says normal when they actually have the disorder. This is a false negative, and the impact to babies and their families of false negatives can be devastating. We refer some babies for diagnostic testing, based on positive screening tests, who do not have the disorder. This is a false positive, which can be an impact on both families and the medical system.

So, I'll -- I'd like to define a few important terms so that we're all on the same page as we move forward. The "sensitivity" is the ability of the test to correctly determine whether a baby has a certain condition. The "specificity" of the test is the ability for it to correctly determine if a baby does not have a certain condition. And the test's "positive predictive value" is the percent of babies with a

positive screen who are diagnosed with the screening condition. Usually, we calculate this based off the total babies referred for diagnostic testing.

For most newborn screening conditions, we quantitatively measure a biochemical marker that is either elevated or low in affected babies. We want to understand the natural distribution of these analytes. Retrospectively, we can separate patients with the biochemical disorder and compare the distributions of these markers for them and the population of unaffected babies. Ideally, the screening test is able to separate the two groups completely. Usually, there's some degree of overlap between patients and unaffected babies. Newborn screening programs must wrestle with this situation and decide what to do.

This is an old slide, but it illustrates the main point of this overlap. It was put together by colleagues in the California Newborn Screening Program about the distribution of immunoreactive trypsinogen, or IRT, prior to

implementing cystic fibrosis in California. We can play through some "what if" scenarios with this type of data. So, if we establish our cutoff so that we have zero false positive results -- where the orange line is -- we would miss close to 20% of the true cases. So, this is the group on the top graph, to the left of the orange line. On the flip side, if we chose a cutoff to catch every baby with CF, more than half the normal population would have false positive results.

So, this is what it looks like for one disorder. This type of analysis needs to be done for 20-plus other disorders. There are very few easy answers. Lab and follow-up work together to come up with cutoff algorithms, which are schemes to stratify results based on their predictive value. The urgency of follow-up protocols also reflects the chances of bad things happening. For example, follow-up specialists treat a baby with profound enzyme deficiency for galactosemia as a medical emergency. Our staff don't go home until we know the baby has been identified and that

milk has been removed from the diet while diagnostic testing is being performed.

This level of intense intervention is contrasted with follow-up for a positive result for a not-life-threatening condition in the newborn period, such as carnitine uptake deficiency. There's a larger window of time in which to operate for that disorder.

Please note: Follow-up doesn't wait for all of the test results to be completed before calling out an urgently positive result. In fact, for critical results for a life-threatening condition, our staff may contact the pediatrician while the retest on the original sample is being performed, just to check on the clinical status of the baby. That allows us to expedite clinical care if the baby is already symptomatic, potentially saving a baby's life.

There's no standard set of terminology for newborn screening results. Normal results are sometimes called "normal," "within normal limits," "in-range results," "negative," or

"passing." Not normal results are called "abnormal," "out of range," "equivocal," "indeterminate," or "positive." In my home state, we call results "normal" or "abnormal." Abnormal results are stratified into presumptive positives, which require diagnostic testing, and borderlines, which need a follow-up newborn screen. For some conditions, even stratified further, having "borderline passive," which is just wait for a routine second newborn screen, "borderline active," which is calling to request that newborn -- the second screen, "presumptive positive," which is for a referral, and then "urgent presumptive positive," which is a baby that needs an immediate clinical evaluation and a referral for diagnostic testing.

So, when we started screening for biotinidase deficiency in 2004, our cutoff for normal was greater than 30% enzyme activity. Over the first few years of screening, we experienced a high false positive rate, so our biochemical geneticist consultant suggested that we adjust

our cutoffs to reduce the number of positives. So, we changed our cutoff to our current level, which is greater than 20% enzyme activity is normal. This experience highlights that when we first establish a test, we often use a conservative cutoff. We collect data longitudinally to understand how the screening test is performing. Guidance from our clinical experts, in conjunction with data analysis, allow us to iteratively improve the cutoff schemes.

So, LCHAD and trifunctional protein deficiency has a more complex algorithm. The initial deciding factor is the concentration of the C16 hydroxy acylcarnitine level in the blood. If it's elevated, then we look at secondary ratios, and using schemes where secondary ratios and primary analytes are considered together, then we can weed through the -- we can sift through the group of babies that have the high primary analyte level and determine the urgency of follow-up for each of the cases.

In 2004, in an effort to improve our

sensitivity for detecting congenital hypothyroidism, our program decided to change screening tests from primary thyroxine to primary -- to thyroid stimulating hormone, or TSH. In the first 2 days of screening, we learned that TSH levels spike just after birth, so having just one cutoff for all babies didn't make sense. We quickly adjusted our cutoff algorithm using information from Michigan's newborn screening program, who had already been screening using primary TSH. Over the next couple of months, we timed up our cutoff scheme, and for many years, we utilized this set of cutoffs, which stratify into six groups based on the age of the baby at the time the blood was collected.

After the change, the data showed that we had improved our sensitivity. Things were going pretty well until we noticed a ripple caused by an unrelated group of tests. We had expanded screening in 2004 and in 2008 by adding more amino acids and acylcarnitine tests to our mandatory screening panel using tandem mass

spectrometry. Several of these newly added conditions can be influenced by therapies commonly administered to premature or sick babies. Our program recommended early newborn screening collections to avoid interfering substances for this subpopulation. The ripple was that because specimens were being collected earlier, we had a higher number of false positive hypothyroidism results.

So, a former follow-up staff member recognized this problem and worked with another colleague to perform a complex data analysis of 7 years' worth of our screening numbers to determine a better set of cutoffs. Her analysis predicted that we would reduce our false positive -- number of false positives by about 35% by modifying the stratification, especially for the specimens collected during the first day of life, while maintaining our good sensitivity. So, now we are -- we have 11 different age categories, and this -- this -- the story is, really, a great example of using a large amount of data to help

refine the newborn screen.

So, in the previous examples, we've covered that the age of the baby at collection of the blood can influence the newborn screening results. Other factors are the baby's birth weight or gestational age, the clinical status of the baby at the time of collection -- for example, was the baby receiving life-saving therapy for extreme prematurity, which could affect our results -- the baby's race and ethnicity, and then specimen handling procedures. For example: Was the specimen exposed to heat or high humidity?

So, I will highlight some important resources available to newborn screening programs for help with the challenges of interpreting newborn screening results and establishing and refining cutoffs. First, we have each other. We can learn so much from other newborn screening programs, especially from early adopters of screening for new conditions. Funding from HRSA and the CDC and technical expertise from

organizations such as the APHL, NNSGRC, and the ACMG, among many others, have helped facilitate this type of learning in both past and present efforts.

There are two collaborative databases for newborn screening information that I'll highlight today. The first is the R4S tools developed at the Mayo Clinic and mentioned in the recent Milwaukee Journal Sentinel articles. The second is the Newborn Screening Data Repository administered by APHL and New -- the NewSTEPs Program. While each of these databases has its own limitations, they are both rich in their ability to provide information to programs about newborn screening. Many states administer their own databases or tracking spreadsheets to monitor trends in newborn screening results and to inform future follow-up actions based on the experience of past cases. Clinical specialists publish case studies in the primary medical literature, and many of the experts are either contracted by newborn screening programs to provide clinical

expertise or are willing to consult about particular cases.

No single one of these resources is sufficient to help with all of our challenges. Our ability to be successful is strengthened by each of these resources, and, if possible, it's best to use several of these options when grappling with the challenges surrounding cutoffs.

So, I like the analogy that a chain is only as strong as its weakest link. This certainly is true to newborn screening. I shared the previous slide of resources with you, well aware that many newborn screening programs do not have the capacity to utilize all of these options. This manifests itself in different ways depending on the program. So, it could be one or more of the following: a lack of technical expertise to perform complex data analysis, not enough manpower to enter confirmed cases into the data repositories, challenges with information technology -- and that could mean on a technical

or an administrative level -- and disagreement among clinical specialists. These are real challenges for most newborn screening programs.

We recognize and are grateful that our non-state newborn screening colleagues and the Federal Government, non-profit organizations, and parent advocacy groups have provided much-needed support for decades. We will continue to rely on our partnerships with them and each other as we seek to improve the infrastructure across the country for interpreting newborn screening results and establishing and refining cutoffs. Thank you.

DR. JOSEPH BOCCHINI: Thank you, Dr. Thompson, for an excellent presentation. Let's turn this, now, to Carol Johnson. Can we make sure her line is open?

MS. CAROL JOHNSON: This is Carol. Can you hear me?

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

MS. CAROL JOHNSON: Thank you for this

opportunity to speak with you today about how newborn screening results are communicated to providers.

Next side -- slide, please. Thank you. So, there are some typical results that get reported to primary care providers by newborn screening programs. These include a variety of reasons to obtain a repeat screen for a poor sample quality, post-transfusion, or, more importantly, due to a borderline or an indeterminate result.

We also report results to primary care providers and provide them with recommendations for further testing due to a presumptive positive result. We also communicate false positive results to the PCPs, and, in some states, we also report carrier or trait status.

Now, when a baby has a presumptive positive result and it's determined that they need to see a specialist, then the conversation happens between the specialist to the PCP, and, usually, that conversation is, "Yes, we've

confirmed MCAD in this baby," or, "We've determined this baby is an MCAD carrier," or, "This is a false positive." That's just an example of some of the things that would be discussed.

Next slide, please. There are a variety of communication methods that we use to talk to our primary care providers. They include mail, fax, email, a verbal conversation, electronic communication systems, web portals, or a combination of any of the above.

Next slide, please. So, it's important to note that communication methods can vary depending on what's going on. For a time-critical disorder, like galactosemia that John mentioned, those are a situation where the follow-up staff are going to pick up the phone and talk to that primary care provider. When you think about repeat screens, the communication method will vary depased on -- based on why that repeat screen is needed. If it's needed because of a borderline result, then that might also be a

phone conversation with that primary care provider. If it's a repeat screen that's needed post-transfusion, that -- that conversation may happen via email or fax or mail. We also need to point out, as John has already pointed out, that the level of communication and the follow-up that occurs will vary depending on program infrastructure.

The type of result also determines how we communicate with PCPs. Again using the example of carrier or trait status -- that's something that is important for them to know, but it's not a critical -- time-critical situation, so that would be communicated via fax or email or mail. And I wanted to make sure that people understand that when there is a normal newborn screen result, there is usually no contact by newborn screening follow-up staff to that primary care physician.

Next slide, please. So, we thought we would take an opportunity here to kind of compare and contrast reporting results for newborn

screening versus reporting diagnostic test results. Newborn screening results can be sanitized by the time it gets to the primary care provider, and what I mean by that is, if follow-up calls to talk to the physician with an abnormal result, although we like to, we don't always get to talk to the PCP, and we end up talking to a staff member. What that staff member says to the PCP may not be exactly what was said to that clinical staff member.

The same is true with electronic medical records. Not everything that's on that newborn screening report gets put into the electronic medical record or the laboratory information system. So, we have to be cognizant of the fact that the PCP may not have all of the information or may not have totally accurate information.

So, the other thing to think about, too, is that newborn screening results are complex, particularly when we're doing second-tier testing in the screening context. I know that we have questions a lot -- and I will -- we do -- For CF

testing, we do IRT in reflex to CFTR, and if we report out two disease-causing mutations to that PCP, they don't understand that that's not a diagnostic test, and we have to explain that this was still done within the confines of a newborn screening program, and it has to be followed up by a diagnostic test.

When you look at diagnostic testing, the results generally provide a numeric value and a reference range. Michele went over this, as well. In newborn screening, that may not be the case. Some states' programs do have numeric values and reference ranges; others report out things like "within normal limits," "abnormal," or "borderline indeterminate."

Most newborn screening disorders are rare, and the PCPs may have varying levels of familiarity with the disorders that we're screening for. Many may know about congenital hypothyroidism, but how knowledgeable are they about some of the new disorders that we've added, like Pompe disease or X-linked ALD? When you look

at that compared to a diagnostic test, PCPs are probably going to have more familiarity with the diagnostic tests that they are ordering.

Another thing to think about is that the newborn screen is usually ordered in that newborn nursery or NICU by the hospitalist or the attending physician for the day. That PCP may not even know a baby has been born, and they may not know that that baby is going to be their patient. So, they may get these results and not have any connection to that patient yet, whereas in a diagnostic test, that provider knows their patient, and they're the ones who are going to get those results back. And we have to remember that there's the potential for false negatives in newborn screening, and diagnostic testing is required.

Next slide, please. So, what are some of the strategies for communicating complicated results to our PCPs? Often, there is a verbal communication that occurs between newborn screening program staff and that primary care

provider. That conversation can be supported by written recommendations and educational materials, like the ACMG ACT sheets or similar tools, that will help explain those results or provide more information about those disorders. And then, we have those unusual cases that come up, and when they do, some programs are able to have either their lab or their medical director or their specialist have a direct conversation with that PCP.

Next slide, please. Although this wasn't part of the original ask for this presentation, we thought we would be remiss if we didn't talk about this: What are the challenges regarding communicating newborn screening results to parents? In general, newborn screening programs report results to the infant's PCP, and then it's up to the PCP to communicate those results to parents. It's important to remember that sometimes this communication is coming from clinic staff and not the actual PCP, and that clinic staff member may not have as much

knowledge as the PCP does about newborn screening in general or about the disorder that they're talking about with that family member.

And then, we're not always using the same terminology. I think John alluded to this in his presentation. In our programs with each other, we may call it "SCID," we may call it "Severe Combined Immunodeficiency," we may talk about T-cell lymphopenia, but when we talk to a parent, we might call it the "bubble boy disease." This can lead to confusion.

Also, the person communicating the result may not provide specific information. They may call and tell the parent, "Your baby's newborn screen was abnormal," and that's all they say. But here's a story about how that can backfire. We had a baby that was presumptive positive for methylmalonic acidemia or proprionic (acidemia. C3 is the analyte. When the PCP called the parent, he told the parent, "Your baby's screen is abnormal. You need to go into the local lab and have some blood drawn for confirmatory

testing." The parents complied, went to the lab, and the lab member said to the parents, "Oh, you're here for the PKU test."

So, this was the first time that the parents had heard any kind of a -- a word that -- about what might be wrong with their parents. But that -- what might be wrong with their baby, excuse me. So, these parents went home and googled about PKU all weekend long. Then, they came into the metabolic clinic on Monday with a whole bunch of questions about PKU, when, indeed, that was not what was potentially wrong with their baby. So, again, it's important about the words we use and how we communicate results.

We also know that newborn screening programs may provide educational materials for the PCP and the parents, but sometimes they just don't get used, and information gets lost in translation. This is another true story that has been related to me. So, a physician had a baby. She received a phone call and was told that her baby's PKU test was abnormal. It got to be day 2,

then day 3, and she hadn't heard anything from anybody about this test, and she knew enough to know that PKU needs a timely intervention.

She happened to know the metabolic specialist in that state, so she called that specialist and said, "Can you tell me what's going on? I haven't heard anything." So, the specialist was able to get into that newborn screening data system and discovered that it was just a poor-quality screen, and all that was needed was a repeat screen. But because the staff member called and told the mother, "Your baby's PKU test is abnormal," this was another problem and caused a lot of communication.

So, things get lost in translation. People do the best that they can do, and we know that, and people are busy, but these are things that we all need to know about and step back and consider when we develop educational materials, when we develop communication plans, and when we talk to each other.

So, next slide, please. In summary,

communication methods with PCPs often vary by the severity of the disorder. Communication strategies can vary depending on program infrastructure, and consistency in communicating information is important. And, again, thank you for your attention, and we'll turn it back for questions, I believe.

DR. JOSEPH BOCCHINI: Thank you very much. I want to thank all three speakers for excellent presentations to help give us a background and help frame a going-forward discussion. I'd like to keep the phone lines open for our three presenters, and, Operator, if you would, open the lines for Committee members and organizational representatives.

I want all of you to remember that we did include a hands-up feature, so that if you want to ask a question or make a comment, please use that so that we can then go through the -- the list of questioners based on who puts their hands up first. I would like to hear from Committee members first, and then we'll open it to

organizational representatives, as well. So, let's open it to questions and comments.

First, we have Dieter Matern. Oh, and then, if I don't mention your name, please go ahead and mention your name before you start so that the recording can reflect exactly who's asking the question or making the comment. Dieter?

DR. DIETER MATERN: Yeah, so, this is Dieter Matern. Thanks for all those presentations. I think it's good to get more information about the context and how cutoffs are created. I have to notice, of course, that there was an absence of mentioning R4S and CLIR, except in Dr. Thompson's presentation, where he mentions it as a data repository, which it is not -- at least, not just a repository.

So, I also have a question for Michele. PRLN, that we recently hosted for a full week, someone from the New York Screening Laboratory who came to learn about CLIR and how we use it at Mayo. And after that week, she seemed genuinely

excited about it and left for home, but she's fallen off the face of the earth since then. And so, I wonder, Michele, why did you not mention R4S and CLIR, and what are you going to do about it going forward? Thanks.

DR. MICHELE CAGGANA: So, Monica did visit the Mayo Clinic, and she did come back, and she talked to Joe. We haven't sat down, the three of us, because of scheduling, and Monica's involved in a lot of activities in the laboratory. But as you know, Joe has been looking at our data and did supply a lot of data to the database, and our goal is to do parallel testing and then compare and be able to report to the newborn screening community about how it aligns with what we're currently doing. So, that's, sort of, the plan. You know, her and Joe and I, again, have to sit down, but he's been traveling, and I've been traveling.

As far as the use of the tool, we do upload all of our normal data into the R4S system. I know Mark Morrissey in our lab uses it

to look at specific cases and compare what the R4S result -- you know, what the R4S result might return compared to what we think might be going on with the infant, and so we do use it in that manner.

The -- the point -- The -- the -- the issue, I think, that we need to discuss and -- and figure out how to best use it for considering how we, you know, report results in the end have to do with the fact that the number -- the result can't change over time. And so, we need two things. One is, we need to determine exactly what cases are in there and what the case definitions are, because we all need to be talking about the same thing, and then we also have some -- have to have some kind of a lockdown, so that at one point in time, a result that comes back has to be the same later on if it's going to be used in a clinical way. So, those are two issues that -- I think that part of this process, going forward, we need to sort of hammer out and work through.

DR. DIETER MATERN: So, I think some of

that is addressed already in that paper that is in the briefing book following these three presentations, where PRLN, working with California, looked at their data retrospectively and could show that R4S would not have identified any additional cases or uncovered false negatives. Again -- On the other hand, I mean, if -- if that is what you need, I think that could be easily done and accomplished.

DR. MICHELE CAGGANA: That sounds good.

DR. JOSEPH BOCCHINI: I see no further questions at this time from the Committee members. Let's open this up to organizational representatives, as well.

MS. JACKIE SEISMAN: Hi, this is Jackie Seisman with Genetic Alliance. Can you hear me?

DR. JOSEPH BOCCHINI: Yes, we can. Go -- go ahead.

MS. JACKIE SEISMAN: Great. I want to thank you all for giving such great presentations, and thank you, both, to Michele and Carol for kind of talking about some of the

challenges of both communicating with providers and parents. I know that Michele mentioned, at the end of her presentation, talking about the need for a mechanism for constant physician education, and I was wondering if she had, through her experience, any ideas of what those mechanisms could be.

DR. MICHELE CAGGANA: So, many states have written materials and fact sheets and information about newborn screening, and then also some specific conditions that are made more available, I think, for parents. And we have -- the ACMG actually is for providers, but I think we have to get away from that on some level. We've -- we've managed to put a lot of things on our website, but, again, making sure people read and understand what we're trying to get across, what information they need to move forward --

Just -- just the point Carol was talking to, about the PKU slip and the PKU test. On that level, that very basic education is what we need to get out and keep talking to people about it. I

gave a talk, my grand rounds yesterday, to the head of nursing, and I said, "Please call it a newborn screen. Please call it a newborn screen," three times. And we went back to the nursery, and she talked about the PKU test.

So, you know, I think we need to get it out in the public domain and sort of push it out on a social media level or on a, you know, public service announcement, or something that we're sort of always -- sort of always bringing to the forefront. We do our best to talk to parents. We involve advocates. We do education whenever I'm asked, and, you know, we're always sort of left, at the end of the day, with hoping the message gets across. And I think some of what we need to maybe work on is to work with people who actually, sort of, market, so that they can tell us how to craft that message so it gets across. So, that's, you know, maybe a little bit out of the box in, you know, writing a nice brochure.

MS. JACKIE SEISMAN: Great. Thank you.

DR. JOSEPH BOCCHINI: Next, we have

Coleen Boyle.

DR. COLEEN BOYLE: Yes. Good afternoon, and thank you, Michele and John and Carol, for the great overview, and it sounds like this is a really important foundation to better understand how cutoffs are established at the state level. Maybe I'll direct my -- my question, specifically, to Michele and John, and that is, recently, we've heard two state experiences -- New York and Washington -- but I don't have a sense of how variable the -- the way states go about establishing cutoffs may be from -- from state to state. Do you have a sense of that? I mean, are -- are you -- Do you feel like your -- the examples that you provided us are -- are -- are -- are, sort of, emblematic or -- or good examples of what's done in other states?

DR. JOHN D. THOMPSON: Maybe I can speak to it first since Michele's already had some time fielding questions. The -- I -- I -- I believe that it varies across the board. Some programs spend a fair amount of time and energy and have

technical expertise to be -- and resources to be able to be very careful about the -- the -- establishing the cutoffs and making state-specific or regional-specific modifications. I know that some laboratories are using FDA-developed kits, and so the -- I -- I think that they will follow the manufacturer's recommendations pretty carefully. So, they may have less -- less involvement in establishing or refining cutoffs based on that fact and how they interpret what those recommended cutoffs are. Michele?

DR. MICHELE CAGGANA: I agree. The -- You know, there's different ways to conduct the testing, and so that behooves -- what John said, the rationale for why the cutoffs might be different. I think, you know, as part of this process going forward, certainly, it would be advantageous to take a look at the different algorithms and how they work in the different states, and maybe get a committee of people together to kind of look at how we -- you know,

that these get done in the various states. I -- I, for one, don't know. I'll be honest: I don't know what the cutoffs are in the states around me, but I know for -- certainly, for hypothyroidism, ours has been modified over time and -- similar to what John showed, and all of our mass spec analytes -- In -- in using the R4S, actually looking at the tools and then looking at our data over many, many years, we've made changes to our CF algorithms; we've made changes to thyroid. And so, CAH we've changed in many of our mass spec tests. So, it certainly is an exercise that would be helpful for states to -- to participate in.

DR. JOSEPH BOCCHINI: Next, I have Carol Green and then -- followed by Kellie Kelm, and then Dieter Matern, again.

DR. CAROL GREENE: Hi. I want to say thank you for fabulous presentations that -- I want to bring back -- or come back to -- I think one of the questions that's driving the current interest in this subject in the idea of having --

- maybe this is not a direct quote, but the same cutoffs in -- in every state -- I wonder -- It's been talked about a little bit, but -- but my recollection is that the example of carnitine levels in Alaska and CAH levels in Alaska, where disease frequency is different, is one of the stronger arguments for needing each state to be able to set appropriate cutoffs, and I wonder if some of the speakers could address that.

And then, the other thing I wanted to mention is that -- Now, speaking as a clinician for the SIMD, we have a lot of challenges, and I think the last speaker really made the point about some of the -- the communication and the language. And I think using examples really helps. I -- I use a letter from a family that explains how she was so relieve to hear it wasn't PKU, and in fact, what her child had was much more dangerous, but I can't get nurses to change what they call it until I give them that example. So, I think examples help. Contributions from the families help, and, also, the ACMG and the

Genetic Alliance and the Education Committee is working on a tool that we hope will include some recommendations for communication. But the question is, maybe, to hear something more about the reasons that states need to be using state-specific cutoffs.

DR. MICHELE CAGGANA: I think, Carol, that's a -- This is Michele. That -- that's a prime example of why you -- you do need to consider what your population is in your state and the people that are -- you know, that you are screening. We know that there are variabilities based on race and ethnicity and people's backgrounds. We know that there, in some cases, might even be some differences ... You know, for -- for -- Cystic fibrosis is another example. We know that African American babies have higher IRT levels, and a clinician might be less inclined to think cystic fibrosis in an African American baby. And so, you know, we need to be able to encompass all of those different groups when we're setting a cutoff that's going to work for

our entire state.

DR. JOSEPH BOCCHINI: All right. Next, Kellie Kelm.

DR. KELLIE KELM: Hi. Thank you. Just, first of all, I want to say that the -- the three speakers gave great presentations, and they were very helpful. Thank you very much. And I just wanted to clarify, having reviewed work done on many newborn screening assays going through the FDA review process, that most -- most of them do not specify cutoffs and give example -- you know, example data using, sort of, an example or a conservative cutoff, and that, you know, FDA acknowledges that most states, you know, determine and validate their own cutoffs for use in their state. So, there may be a handful of assays where a cutoff is specified, but I know, in most cases, that that's not the case. So, I just wanted to clarify that. Thanks.

DR. JOSEPH BOCCHINI: Thank you. Dr. Matern?

DR. DIETER MATERN: This is Dieter.

Sorry, I had to unmute. I just wanted -- and, you know, Michele actually had said it as soon as clicked my hand up, that with R4S, you can compare the cutoffs and reference ranges between programs. So, as long as you participate, you can see how you compare, and if you bring up a new assay -- and others have done it already -- you can see whether your test performs, basically, as good as others and should facilitate a correct choice of the appropriate cutoffs.

More importantly, however -- that goes to the comment by Dr. Greene about ethnicity and -- and giving CPT1 as an example. I -- I think -- and, again, it's an R4S/CLIR comment -- the disease range is extremely important, and the disease range, even if it's for an ethnicity, doesn't really -- it's not limited to a region; it's limited to an ethnicity, and -- and someone of a specific ethnicity could move to a different state.

And so, I think it is more important to have a disease range versus having a cutoff that

applies to a presumed ethnic background in a state, and then as soon as these people move across state lines, then they wouldn't be caught anymore with the newborn screening test. So, I -- I think this a -- really, a universal issue, and one cannot base things based on -- on a state.

DR. JOSEPH BOCCHINI: Thank you. Any comments from the presenters on Dieter's comments?

DR. JOHN D. THOMPSON: I have -- I think it was a fair point, and it -- I'm -- I'm not aware -- I -- I'm not aware of any analyte-specific cutoffs in a program based on ethnicity. I think it's something that we take into -- into consideration, in combination with the other demographic information and the biochemical test results. So -- but there -- there certainly may be out there that I'm not aware of, but it's a -- it's a great point.

DR. JOSEPH BOCCHINI: Next, we have Bob Ostrander.

DR. ROBERT OSTRANDER: Actually, I think

Dieter said, more or less, what I put my hand up about, is that we're talking about using state-specific cutoffs because of state-specific averages in several incidentive (phonetic) conditions, assuming that states have unimodal distributions of those. And, I mean, New York, for example, is very lumpy-bumpy that way, and you know, maybe Michele could -- could comment specifically on how New York addresses that situation.

DR. MICHELE CAGGANA: So, I mean, I think that gets back to the point that I was trying to make, that when we're doing the -- when we're establishing the cutoffs, that we have to look at a population, and -- and when we do the validation, we have to look at quite a few samples. We -- we generally don't implement new testing unless we look at several thousand babies, which, you know, we're -- we're sort of a larger state. We're not the largest, obviously, but when we're validating a new assay, we -- we try to test specimens coming in the door for at

least 10 to 20 and even higher numbers of thousands of infants before we come up with what the cutoff value is, and it's a combination of factors looking at people who are already affected, pulling the newborn screening samples of kids that we know are affected, and, you know, factoring that all in, along with prematurity and -- and birth weights and all of those to come up with a cutoff that we're comfortable with that weighs the false positive of -- you know, the false positive rate, and then, as John discussed, go back, over time -- and we do this consistently -- and see where things fall out. If you have very rare conditions, it becomes quite difficult to -- to be comfortable adjusting a cutoff.

And so, we need to look at that over time, and while we look at retrospective data, we also have to look at prospective data going forward, no matter how we're going -- you know, going about this, whether we're using the Mayo system or we're using our own data. So, it becomes a combination of factors that we need to

take into consideration. We don't have race- or ethnic-specific cutoff. Some states do, I believe. But we have to factor the -- what our population is at a given time, and that may explain why, over time, we actually do adjust cutoffs, because we have migration in and out of the state.

DR. JOHN D. THOMPSON: So, I -- I'd like to jump in, too. From a quality assurance standpoint, we are running standards and controls with every plate of patient specimens, and our laboratory lead workers provide monthly QA reports and monitor the trends within the different analytes. The mass spec report is particularly interesting; it -- it fills a three-ring notebook every month.

One thing, also, that is important to think about when -- for, like, home brew tests, when a new set of standards and controls is created, sometimes there are shifts, so we have to monitor when we bring in new standards and controls. Also, if we're purchasing kits from a

manufacturer, different kit lots perform at different levels, and even different instruments. So, we have three tandem mass spectrometers that we've had for many years, and we just purchased a new one because the old ones are getting old, and the new one performs at a different level than the previous ones. So, there's the inter-instrument variability that's also important to think about. So, when there's a discussion about having one cutoff across the board throughout the United States or throughout the world, that doesn't really work for a number of these reasons I've just outlined.

DR. JOSEPH BOCCHINI: Thank you. Next, I have Carol Greene.

(No audible response)

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

OPERATOR: Ms. Greene, your line is open.

DR. CAROL GREENE: Okay, I -- I -- I was on mute. I apologize.

DR. JOSEPH BOCCHINI: All right. We can

hear you.

DR. CAROL GREENE: So, just to add a little bit to -- I -- I -- come back to the response that Dieter Matern had. Absolutely, the cutoff, ideally, would be specific for ancestry; however, we don't get accurate information about ancestry even if we ask for it, and in some places, it's not asked for. In addition -- and -- and I -- I think it was said, but -- but I think maybe to be a little more explicit -- it is still a screen.

So, in an ideal world, you would have ancestry-specific cutoff if you could know the ancestry, but in a practical world, it's a public health laboratory, and you're going to have to make your cutoffs specific for the population, taking into account your equipment and all the other things that were -- were considered, and when we get to personalized medicine, we will, hopefully, be able to be taking into account all of the issues with -- When you adjust for all the laboratory equipment, hopefully we'll be able to

have baby-specific cutoffs. But in the meantime, we're still dealing in a public health world, and you're going to have to have a cutoff that works for everybody, balancing false positives and false negatives.

DR. JOSEPH BOCCHINI: Thank you. Next, we have Dr. Matern.

DR. DIETER MATERN: Yeah. So, I don't think we need any cutoffs. We need disease ranges. And is there a specific ethnic group that -- where a disease is very common? As long as we have enough cases where we can look at what the disease range -- and, actually, the metabolite profile for that disease in that ethnic group is, then wherever a patient is being tested with a disease, and maybe not of the same ethnic background, you would still pick them up.

So, I'm always coming back to the issue of -- that we really need more disease ranges and not cutoffs, and we cannot look at single analytes; we have to look at the profiles. And if you want to bring out a new system that can do

that, that is fine, but currently, you have R4S and, specifically, CLIR as an updated and better version. So, I suggest we move quickly to use it, or come up quickly with something else that it does the same.

DR. JOSEPH BOCCHINI: So, I see no additional questions or comments, so I think, in summary, this -- these -- I -- I would like to, again, thank our -- our presenters. I think they have framed the issues very nicely for the Committee, so that we can go back and think through potential next steps to go forward.

I think, clearly, the evidence is that -- that not all states may approach these issues in the same way, and there might be some opportunity for the Committee to provide the best practices. There certainly could potentially be better use of repositories or a specific tool for looking at data and improving performance. Education seems to be really important for identifying the difference between screening and diagnosis, and certainly, clearly, communication of information

seems to be something that -- that can potentially be addressed, and, as indicated, the Education Training Committee -- Work Group is certainly looking at trying to improve at least one aspect of that at the present time.

Would the Committee members like to hear some specific considerations at the May meeting that might then be reviewed and added to and potentially to go forward with? Dr. McDonough?

DR. STEPHEN MCDONOUGH: Yeah, this issue that -- that the Laboratory Committee could come back with recommendations for us on how to improve quality of screening and -- and prevent children from being missed with the lack of a consistency on -- on cutoffs.

DR. JOSEPH BOCCHINI: So, I think that's an important consideration, and I think that -- Let's put -- let's put some thought into what we've learned today, so that we could potentially frame what we would ask the Laboratory group to consider and that who might need to be involved along with the Laboratory group or, perhaps, a

separate work group, sort of an ad hoc work group, that might be with the expertise on it to then flesh out some guidance from the Committee, to bring back to the Committee for consideration. Melissa Parisi?

DR. MELISSA PARISI: Yeah, I just wanted to make the comment that there might be some value in hearing of specific examples, perhaps, where states have used the R4S or CLIR tools as a way of improving their disease ranges. That might actually make it a little more concrete, because I think a lot of us are sort of -- we have a general understanding of it, and I know Dr. Rinaldo has given presentations on this in the past, but maybe some concrete examples might be helpful to see how those tools can be used to help with this process.

DR. JOSEPH BOCCHINI: Perfect. That might be something for the May meeting. Very concrete. Thank you. Additional comments, suggestions?

(No audible response)

DR. JOSEPH BOCCHINI: All right. Hearing

none, we will go forward with putting something together for May, with, then, making some decisions about what would be the best way to go forward, through one of our work groups or multiple work groups, depending on the issues that we feel are most important to pursue. So, with that, that'll conclude our morning session. We now have a 1-hour lunch break. We're going to begin promptly at 1:30 Eastern Time with the afternoon portion of our meeting. So, I want to thank everybody for their involvement, their comments, participation this morning. We will see you all in an hour. Thank you.

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

OPERATOR: Welcome back. As a reminder, all participants are in listen-only mode, and today's conference is being recorded. Dr. Bocchini, you may begin.

DR. JOSEPH BOCCHINI: Good afternoon. We're ready to start the afternoon session, and so, first, I will record the attendance of the

Committee members and organizational representatives. So, again, I'll go alphabetically. Don Bailey?

DR. DON BAILEY: Here.

DR. JOSEPH BOCCHINI: Mei Baker?

DR. MEI BAKER: Here.

DR. JOSEPH BOCCHINI: Coleen Boyle?

DR. COLEEN BOYLE: I'm here.

DR. JOSEPH BOCCHINI: Thank you. Jeff Brosco?

(No audible response)

DR. JOSEPH BOCCHINI: Kellie Kelm?

(No audible response)

DR. JOSEPH BOCCHINI: Fred Lorey?

(No audible response)

DR. JOSEPH BOCCHINI: Michael Lu? Or Joan -- Joan Scott for Michael Lu?

MS. JOAN SCOTT: Here.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETER MATERN: Here.

DR. JOSEPH BOCCHINI: Steve McDonough?

(No audible response)

DR. JOSEPH BOCCHINI: Kamila Mistry?

(No audible response)

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

(No audible response)

DR. JOSEPH BOCCHINI: Melissa Parisi?

(No audible response)

DR. JOSEPH BOCCHINI: Cathy Wicklund?

MS. CATHY WICKLUND: Here.

DR. JOSEPH BOCCHINI: Thank you. And our DFO, Debi Sarkar?

MS. DEBI SARKAR: Here.

DR. JOSEPH BOCCHINI: Bob Ostrander?

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: Michael Watson?

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: Joseph Biggio?

(No audible response)

DR. JOSEPH BOCCHINI: Kate Tullis?

(No audible response)

DR. JOSEPH BOCCHINI: Susan Tanksley?

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Chris Kus?

(No audible response)

DR. JOSEPH BOCCHINI: Jackie Seisman?

(No audible response)

DR. JOSEPH BOCCHINI: Siobhan Doyle?

DR. CHRIS KUS: Hello.

DR. JOSEPH BOCCHINI: Hello? Who --?

DR. CHRIS KUS: Oh, this is Chris. I just got on. Dr. Kus.

DR. JOSEPH BOCCHINI: Okay, Chris, thank you.

DR. CHRIS KUS: Sorry.

DR. JOSEPH BOCCHINI: Not a problem. Siobhan Doyle?

(No audible response)

DR. JOSEPH BOCCHINI: Cate Walsh Vockley?

MS. CATE WALSH VOCKLEY: I'm here.

DR. JOSEPH BOCCHINI: Carol Greene?

(No audible response)

DR. JOSEPH BOCCHINI: Okay, let's go back and see -- Jeff Brosco?

(No audible response)

DR. JOSEPH BOCCHINI: Kellie Kelm?

(No audible response)

DR. JOSEPH BOCCHINI: Fred Lorey?

(No audible response)

DR. JOSEPH BOCCHINI: Steve McDonough?

(No audible response)

DR. JOSEPH BOCCHINI: Kamila Mistry?

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Here. Annamarie Saarinen?

(No audible response)

DR. JOSEPH BOCCHINI: And Melissa Parisi?

(No audible response)

DR. JOSEPH BOCCHINI: Okay. So, we have a quorum, and so we will get started, and I'm -- I'm assuming that the rest of the Committee members will get on in the next couple of minutes.

The first item for this afternoon's agenda is an update on National Contingency Plan for Newborn Screening, and here to make that presentation is Kate Taft. Kate Taft is the Associate Director for Child and Adolescent

Health at the Association of Maternal and Child Health Programs, AMCHP. She leads and supports the development, implementation, and evaluation of program activities related to child and adolescent health, including children and youth with special health care needs. So, we really appreciate Kate Taft for being here and preparing and making this presentation for us. So, if we could put up her slides, and, Operator, if you'll open her line?

OPERATOR: Her line is open.

DR. JOSEPH BOCCHINI: Thank you.

MS. KATE TAFT: Good afternoon. Can you hear me?

DR. JOSEPH BOCCHINI: Yes, we can. Go ahead. Thank you.

MS. KATE TAFT: Yes, thank you, and it's a pleasure to be here before the Committee today and provide an update on the National Newborn Screening Contingency Plan.

Next slide. So, I -- I know that the Committee and -- and those on the phone are well

aware of the breadth and benefits of newborn screening, and how critical it is for all infants to receive timely screening so that if a child has a condition, it can be diagnosed early and the condition can be successfully managed or treated to prevent severe and, often, lifelong health consequences. In general, contingency planning for an emergency helps to ensure the availability of critical resources, the continuity of operations, and set standards for those entities participating in the activation of the plan. Adhering to established standards and maintaining continuity of testing and follow-up are critical in the screening, diagnosis, referral, and treatment of disorders identified through newborn screening, especially during a public health emergency.

Next slide. And by way of background, interest in the effective implementation of newborn screening has had a significant place in the U.S. public health arena for decades. In 2004, the Association of Public Health

Laboratories, or APHL, established a subcommittee of its Newborn Screening and Genetics in Public Health Committee to develop a framework to assist public health labs to prepare for and respond to disasters caused by nature, terrorism, and interruptions of testing materials and supplies.

In 2005, Hurricanes Katrina and Rita destroyed Louisiana State Public Health Laboratory and eliminated the state's ability to perform newborn bloodspot screening. At that time, the chief of the Louisiana Public Health Laboratory determined that the state's newborn screening program was one of the highest public health priorities, and, fortunately, the Iowa Public Health Newborn Screening Lab was able to rapidly assume the screening of Louisiana's newborns, which was facilitated by the Emergency Management Assistance Compact, or EMAC.

So, following this long interest and emphasis, as well as the hurricanes and natural disasters, HRSA and the HRSA-funded Regional Genetic and Newborn Screening Service

Collaboratives, their national coordinating center and APHL initiated a process to create regional newborn screening emergency preparedness plans, and it also contributed to the development of the National Newborn Screening Contingency Plan. These plans were essential for preparedness and recovery from the effects of Hurricane Sandy in New Jersey and New York in 2012, and they've provided a mandate for emergency preparedness for all state newborn screening programs.

Next slide. The Newborn Screening Saves Lives Act of 2008 directed the CDC, along with HRSA and state agencies, to develop a National Newborn Screening Contingency Plan. This plan could be used by a state, region, or a consortia of states in the event of a public health emergency or interruption of services. In 2008, the CDC and HRSA held a workshop for federal partners, state public health programs, including newborn screening, state labs, and maternal and child health programs, as well as state emergency preparedness programs and clinicians. They used

an objective-based planning process to develop the National Newborn Screening Contingency Plan, along with CDC and HHS leadership, and that plan was published in 2010, which is the current version of the plan. The 2014 reauthorization of the Newborn Screening Saves Lives Act added a stipulation that the CONPLAN should be updated at least every 5 years, which led us to the current process and project to revise and update the plan.

Next slide. Which led us to this current effort. So, in the latter part of 2015, AMCHP partnered with the CDC, HRSA, APHL, and expert stakeholders to provide updates to the National Newborn Screening Contingency Plan, or CONPLAN, and this is a project that was supported through funding from the March of Dimes Foundation and support from the CDC. Specifically, this project sought to provide updates to the plan, with a focus on addressing gaps in laboratory, clinical, and long-term follow-up, addressing point-of-care screenings, and also incorporating a strong

emphasis on family engagement. The process presented an opportunity to incorporate changes in the newborn screening systems since the last plan was published in 2010, as well as what's been learned from states' experience and addressing newborn screening service interruptions caused by natural disasters or a manufacturer inability to provide testing materials. Like the existing 2010 plan, we considered the variation in resource system capacity across states when making updates to the plan.

Next slide. In order to carry this out, AMCHP and our partners at CDC, HRSA, and APHL worked closely with an expert advisory committee, and that committee was chaired by Scott Shone, the Program Manager for New Jersey's Newborn Screening Lab, and it included representation from state newborn screening coordinators and program staff, public health labs, the regional newborn screening collaboratives, family leaders, consumer representatives, HIT, metabolic

specialists in maternal and child health, and children needs -- special health care needs directors. We also had representation from many national organizations and partners, which provided the perspective from pediatric providers, local health departments, state health directors, and preparedness directors. And some of the -- the members may be on this webinar today, so I just wanted to recognize and thank them for their time, expertise, and efforts, which resulted in the success of this process.

Next slide. So, the revisions and the recommendations to the CONPLAN were developed throughout the winter of 2015 through June of last year, and that process included calls -- regular calls with the Advisory Committee members, a public comment survey, which was fielded broadly through December 2015 to January 2016, an in-person working meeting in which the Advisory Committee incorporated feedback into the revisions, and subsequent subcommittee work and revisions to provide the final edits, as well as

develop some resources to accompany the plan. The final document of recommended revisions was compiled and approved by the Advisory Committee, and that was submitted to the CDC and HRSA in June of 2016 and since then has been in the federal internal editing review and clearance process.

Next slide. I'd like to just provide an overview -- a high-level overview of the revisions that were recommended, you know, acknowledging that the -- the document is still in the clearance process. But updates were made to the language in the strategic objectives as listed in the 2010 plan. The major changes that were recommended for the section included the addition of a new communications objective and reordering some of the objectives so that the communications and family education objectives were at the front of the document, as the Committee felt that those really were the first steps to consider in contingency planning for newborn screening programs.

And then, there was also language added in the objectives around connecting infants and families to long-term follow-up services and ensuring those connections were made.

The revision also included an expanded section on legal issues and considerations involved in interstate agreements for newborn screening contingency planning, particularly incorporating a stronger presence of EMAC in the document and how that structure for emergency support between states can pertain to newborn screening contingency planning.

And they all -- Finally, the revisions included language around newborn hearing and point-of-care screening, which were not included in the 2010 version.

Next slide. So, on this screen is list (sic) the new strategic objectives as listed in the plan, and if you go to the next slide, that should highlight the changes in terms of major restructuring, which was to add the communication objective and to move the objective around family

education to the front of the -- the document. And these strategic objectives broadly describe what should be achieved to ensure comprehensive newborn screening, and within the full document, they're supported by operational objectives and activities.

The next slide, I also wanted to highlight just a couple other revisions and updates that were made, and these are in the appendices to the plan. The Committee provided updates to a responsibilities matrix, which outlined the various strategic objectives and supporting activities in which entities in the -- the state or federal programs would be responsible for those objectives, and updates were made to reflect the new strategic objective, as well as to recognize some of the -- the varied ability among states and ensure that those were reflective of the state capacity and resources.

The Committee also created some new appendices, and those were based on feedback from the public comment survey, as well as the

individual Committee members, and those included a flow chart, a contingency planning checklist along with tips, as well as a resource list that included, you know, articles and state examples of tools and templates that they've used in their own contingency planning or responding to emergencies to ensure continuous and comprehensive newborn screening. And the impetus for developing these new appendices were that they would be more practical planning and implementation documents that states could use in their own work and could also be updated in a more timely manner, rather than, you know, having to wait to go through a formal plan revision.

Next slide. This slide just highlights what two of those new appendices look like. The first one is the Newborn Screening Contingency Planning Checklist that includes the strategic and operational objectives from the full document, as well as a column for consideration, resources and tips that may be helpful to states when they're doing their own contingency

planning. And then, the second graphic is the flow chart of the newborn screening contingency and planning process, which the Committee felt would be really helpful as a communication tool when engaging program staff and partners in contingency planning.

Next slide. So, finally, I just wanted to provide an update of the next steps and where we are in the process. As mentioned, the -- the final documents are in the final review and clearance processes within CDC and HRSA, and the goal is still to have them be released by March 2017, and we're hopeful that that will be the timeline.

We are planning to host a conference workshop at our AMCHP annual conference, which will be on March 06, in Kansas City, Missouri, to provide an update on the plan, hopefully officially release the plan to members there, and have some discussion on how various Title 5 agency families can work with their newborn screening partners to ensure comprehensive

planning for newborn screening within their states and communities.

APHL symposium, which will be held in September of this year, will also have -- I know that they're planning to have focus sessions on emergency preparedness for newborn screening labs, and as part of our work with the Advisory Committee, we did develop a dissemination plan for when the -- the new version was released, so the word could get out quickly and this could be a document adopted and used by states, and that includes website updates, newsletters, national webinars, fact sheets, and other communications.

So, overall, we hope that the revised Newborn Screening Contingency Plan will reflect updates and changes in the field of newborn screening and public health since the 2010 plan was published, lessons learned from state experience, a stronger emphasis on follow-up, and format and new resources that will increase the usability and applicability of the document by states in their own planning.

Next slide. And so, my contact information is there if anyone has any questions, but thank you very much for your time, and I appreciate this opportunity to present an update on this project to the Committee.

DR. JOSEPH BOCCHINI: Kate, thank you very much for this presentation. I think it's certainly very clear how much work was done to bring this revision and update to the point where it is now. What -- As it's rolled out, the Advisory Committee is certainly very happy to work with you and -- and others to help disseminate the information and -- and -- and to help speed up the incorporation of the new plan into state newborn screening programs.

Let's open this for if there are any questions or comments from Committee members or from organizational representatives. I think we have a couple of minutes we could devote to this. Dr. McDonough?

DR. STEPHEN MCDONOUGH: Thank you for your excellent presentation. Are there dedicated

funds in FEMA, or do you have funding needs you're going to -- when this plan comes forward, and -- and what dollar amounts will be needed, and do you know where they'll get them?

MS. KATE TAFT: That's a good question. So, we -- we currently have funding through the March of Dimes Foundation and CDC to disseminate the plan once it's released and to at least get the word out to states. We've -- we've not identified further funding to help states implement the plan or use it on their own; however, as part of this update process, the Committee did provide some recommendations on support, technical assistance, that would be helpful to really take this to the next step to states. So, that was shared with our federal partners, as well, so I assume that they are considering that, and, you know, hopefully, we'll see what the next steps are in that regard.

DR. JOSEPH BOCCHINI: Jackie Seisman?

MS. JACKIE SEISMAN: Hi, yes, I'm with Genetic Alliance, and I just had a couple of

questions. Thank you for the great presentation.

In updating the con -- contin -- contingency plan -- sorry -- can you talk a little bit more about how you engaged with families in this process, or groups that work directly with families? Is that just through the Committee? Just a little bit more information on that.

MS. KATE TAFT: Sure. So, we did have a family leader representative who was on the Committee to bring that perspective, and through the public comment survey, we also asked each of our committee members to -- to send that out to their respective memberships to -- to get as much feedback as we can. I know that, certainly, we engaged with Family Voices and Genetic Alliance to help send out the survey --

FEMALE SPEAKER: Mm-hmm.

MS. KATE TAFT: -- for that. But the -- the main engagement was through the -- the family leader on the Committee.

MS. JACKIE SEISMAN: Great. Thank you.

MS. KATE TAFT: Mm-hmm.

DR. JOSEPH BOCCHINI: Coleen Boyle?

DR. COLEEN BOYLE: Yes, thanks so much, Kate, for the -- the great work and the terrific overview. When I was listening to you, I -- I was thinking about an activity that I participated in last week that our -- our Office of Public Health Preparedness funds. Actually, our center spearheads it, but it's -- it's funded out of that, and it's really in collaboration with the American Academy of Pediatrics and a number of other child focus entities, and this is around children's preparedness. And I don't know -- I was thinking that would be really important to inform them. They're doing a number of tabletop exercises, sort of what to do in the end -- end times of emergency that's particular around children. And I'm not sure they're aware of this, so I -- I would -- I'd love to connect the dots on that one.

MS. KATE TAFT: Thank you, Coleen. Yes, I think it would be great to connect the dots. We -

- The folks we are working with at CDC, I think, may have connections to that organization. So, I'd be glad to follow up with the contacts -- the contacts that we were working with on this project, but --

DR. COLEEN BOYLE: Yeah, and maybe if you could follow up with me, I will -- I'll put you in touch with the people that I know. Sound good?

MS. KATE TAFT: That sounds good.

DR. COLEEN BOYLE: Okay. Great.

MS. KATE TAFT: Thanks.

DR. JOSEPH BOCCHINI: Mike Watson?

DR. MICHAEL WATSON: Oh, yeah, hi. Thanks, Joe. I'm curious: When we did the original CONPLAN, back in 2010 and '11, there was not an awful lot of preparedness in place for anything outside of the state screening component. So, I'm wondering if, in the course of developing the new CONPLAN, or the revisions, whether you -- you were able to determine whether preparedness -- which -- you know, in the absence of preparedness, you don't have much contingency

to put into place. So, I'm curious if you found gaps at -- that still exist at the current time.

MS. KATE TAFT: Mm-hmm. Yes, and I think that's one of the areas we were trying to strengthen with this plan, you know, involving the state health -- or state preparedness directors and providing input and providing a stronger, as I mentioned, incorporation of the EMAC into the document so that that could be part of this planning process, and as it rolls out, I would hope that those connections could be made at the state level so that newborn screening is involved in the emergency preparedness. And I know that's also one of the focus for some of the sessions at the APHL symposium, as well.

DR. MICHAEL WATSON: Thank you.

DR. JOSEPH BOCCHINI: And Carol Greene. We'll make this the last comment so that we can move on to the next subject. So, Carol?

DR. CAROL GREENE: Thank you, and I'm wondering if Mike's question -- I didn't fully understand the answer. I'm wondering if Mike's

question might have been related to the issue of -- Beyond the newborn screen, when the disaster happens and the kids are displaced, how do the kids with PKU and methylmalonic get their treatments continued? How do we get the records to the right place, and the medications and all the access?

MS. KATE TAFT: Oh, okay. Yes, so that was also part of the goal in incorporating the follow-up piece. So, within the strategic objectives and supporting activities, the Advisory Committee members strengthened the language around, you know, ensuring that the -- the follow-up care and -- and services were a part of the planning pieces in there, and -- And I'm trying to see if there are some examples I could pull.

So, there was also some stronger language around -- and -- and guidance -- you know, for states, this isn't prescriptive -- but around, you know, infants who receive a diagnosis, that they receive appropriate, multi-disciplinary care

through an established medical home, and that can include, you know, establishing a mechanism to track populations who are displaced, you know, planning for how you're going to initiate that chronic condition management, mechanisms for care coordination between primary care providers and specialists, and how that would change given the nature of a public health emergency, and ensuring referrals to follow-up programs, whether it's early intervention, children with special health care needs services, and just continuing to make sure those connections are facilitated and -- and part of the contingency planning at the beginning, so when a -- you know, whether it's a natural disaster, or some emergency happens, those -- those mechanisms are in place and the appropriate partners have been engaged in thinking about continuing newborn screening services and follow-up services in the event of an emergency.

DR. JOSEPH BOCCHINI: All right. Kate, again, thank you for an excellent presentation,

and thank you for the subsequent discussion afterwards. One thing that we can easily do is, when the -- when the document goes through clearance and -- and is published, we will certainly put it on the Advisory Committee's website and then certainly help you in any way to disseminate the -- the information, that it exists, and help with any other communication that might be helpful. Thank you.

MS. KATE TAFT: Thank you.

DR. JOSEPH BOCCHINI: The next item on the agenda is related to medical foods for inborn errors of metabolism. As you know, we tasked the -- the Follow-Up and Treatment Work Group to develop a white paper to serve as a -- as providing the current evidence of issues that remain for providing medical foods to infants who are found to be positive for inborn errors of metabolism through newborn screening. And the Work Group has been hard at work trying to come -- bring this together. So, Dr. Berry is going to present where they are.

What I'd like to see happen is that -- They're at a point where they need feedback from the Committee, and then we'd also like to begin a discussion of how to utilize the -- the white paper and how to then best work towards resolution of the problems that still exist with providing medical foods to children and families with the inborn errors of metabolism.

So, I'd like to turn this over to Dr. Berry. Dr. Berry is a medical genetics physician who has a special interest in outcomes after newborn screening. She has devoted a significant portion of her academic and professional interest in clinical assessment and improvements in care for persons affected with newborn screening conditions.

So, Sue -- Let's open up Dr. Berry's phone line, and we'll turn it over to you.

DR. SUE BERRY: All right, then. Can you hear me?

DR. JOSEPH BOCCHINI: Yes, we can. Thank you.

DR. SUE BERRY: Great. Thank you. It's kind of odd to have it not be hearable by me. You just -- I just hear my own voice, so. I am very grateful to the Committee for this opportunity to catch you up on where we are with this work and to really begin the discussions that I hope will come to -- help us come to some resolution about this very thorny problem.

I want to take this opportunity, as I get started, to thank our work group as a whole, and then, particularly, the co-chairs of our Medical Foods Subgroup -- Cathy Camp, Carol Greene, and Christine Brown -- and our chair, Steve McDonough, for their devotion and interest in this project.

Next slide, please. All right. As Dr. Bocchini mentioned, it's now my privilege to report on our actions and progress regarding this charge, and we were asked to provide a policy analysis brief that summarized the current state of coverage for medical foods, previous work by this Committee, and a -- a synthesis of previous

efforts, beyond the Committee's work, to improve coverage for medical foods. Our point in this is to give you an update on where we stand with this and to begin the discussion about how we can come to some final solutions that should impact this difficult issue. As Dr. Bocchini mentioned, this is a preliminary report. We hope to bring this to an action statement at a subsequent meeting.

All right, next slide, please. Well, this is not a new issue for the Committee. That is no surprise to any of you who have followed this -- this Committee's work. Could I have -- In May of 2009, the Committee sent a letter that offered recommendations to address gaps in coverage and reimbursement for medical foods. We suggested a more uniform approach and to amend Medicaid for uniform coverage by state programs. As is required, we received a response from the Secretary, but, basically, it says, "You asked me for something I can't do. Enacting legislation is beyond the Department's authority." I'm not sure we phrased it quite that way, but that was how it

was reported, and basically, it was a -- an expression of understanding, but no action took place.

A year -- a year later, we were in the midst of discussing health care reform in the ACA, and we recommended that health care reform ensure access to medical foods and foods modified to be low in protein as essential services irrespective of the source of health coverage. At that time, the Secretary sent us, essentially, a temporizing response, saying she couldn’t adopt our recommendations at that time. She noted that they were awaiting a -- the -- a Department of Labor survey, a public workshop by the Institute of Medicine, and basically said, "Don't have enough information." And, subsequently, those meetings have, in fact, happened, but it -- nothing else has happened for medical food. So, now's a good time for us to keep moving forward.

Next slide, please. All right. Just to remind the Committee a little bit about how we've already devoted a -- some good attention by the -

- by the Committee in meetings to give you some preliminary information and frame the question. There was an excellent presentation by Cathy Camp that really was a call to arms regarding this in the last year. Christine Brown presented her specific data, using PKU as a salient example of the challenges in -- that families encounter in accomplishing to medical foods. We also had a very important update with the Catalyst Report that you heard about in our last telemeeting that summarized state -- state access to medical foods. And this really highlighted one of the challenges that I'll -- I'll be mentioning in, sort of, a summary of our actions, which is that if you know the access to medical foods in one state, you know the access to medical foods in one state.

All right, next slide. So, where are we with regard to the progress of the charge to this work group? We've had two full Work Group meetings, one of which was completely devoted to this topic, and the other one was 50/50 with

another important action of the -- of the group. The subgroup that was working on medical foods has actually been meeting on a monthly basis, and what we wanted to let you know about is, sort of, what we have in our hands now.

As requested, we are preparing a detailed document that regards -- that's regarding the issues and access to medical foods. The draft for this is in progress, and we included that in the briefing book, because we really would appreciate feedback about this white paper, its organization, with your understanding that there are place holders for some of the early important data that we want to make sure is fully vetted and fully encompassed. So, I think it's coming along quite nicely, but any feedback that members of the Committee or related individuals have that they can supply to us will only strengthen our hand.

We did, as part of this, end up preparing what I -- what we ended up calling a two-pager -- I would love to have it one page, but it's not --

and we've submitted that draft for this discussion, and I'll highlight some of the information that's in that two-page summary, with the idea that this is a useful document that can be shared to describe the problem in a short-hand fashion and to highlight its important issues.

I want to conclude -- and I was given a -- a very generous opportunity to have this be a point for discussion, and I'm hoping that the members of the Committee will offer their thoughts and -- about the potential outcomes that I'm going to outline.

Next slide. I don't want to spend a lot of time going through the problem itself, but I do want to remind the group that this is particularly difficult, in part because of regulatory environment. So, just a reminder that the medical -- medical foods are actually a defined class of -- of articles. The Orphan Drug Amendments of 1988 defined medical foods. Salient issues in this are that foods are defined, formally, to be consumed or administered

enterally -- and it doesn't say it has to be through a tube; "enterally" means "goes into the gut," and it doesn't say how -- under the supervision of a physician and which is intended for specific dietary management of a disease or condition for which distinctive nutritional requirements based upon scientific principles are established by medical evaluation. There are other -- there's other language that specifically ends up talking about the degree to which the -- sort of, the nature of medical foods as opposed to drugs.

So, could I have the next reflection? Medical foods aren't drugs. Next. They're not for -- Drugs are for diagnosis, cure, mitigation, treatment, or prevention of disease. Medical foods are intended to be used under medical supervision as primary intervention for disease, and, most notably, they're supposed to be agents that would not be accessible or would -- could be an element of a diet that could be obtained without the special processing of the medical

food. If you can go to the -- if you can go to the grocery store and buy it, it shouldn't be considered a medical food. So, the -- an example -- and I'm going to go into detail on that -- is that gluten-free foods, while they may be very important medically, are not medical foods.

All right. Next slide, please. What we found, in a nutshell, as we -- as we sorted through all of this, is probably no surprise to people who've thought about this for a while. Our full brief will detail this in more detail and establish the magnitude of the challenge, but access to medical foods, in today's environment, is highly variable. It depends on the age of the individual. Oh, my goodness, my thing just turned off. Okay, got it. All right. So, it depends on the age of the individual. In many places and many circumstances, the medical foods might be available to children and babies who are impacted by these newborn screened conditions, but once somebody turns 21, they no longer have access because of the way the statutes or laws or

programs in individual states are set up. And that's a tremendous gap and a tremendous barrier. It's dependent, to some degree, on the disorder. In some states, the statutes specify which things they'll cover for but don't have a general allocation that will pay for other conditions.

The state of residence is key in our thinking about this. Each state defines what medical -- how medical foods are covered because they define the insurance laws in that given state. And so, the nature of insurance cover -- coverage is an element that is defined by the state of residence, as well as the product and the -- the way that the contract, individually, in a given company that provides insurance coverage has established the expectations for coverage for a given contract.

So, in -- in -- in summary, it's -- there -- it -- there's no specific strategy by which medical foods have been provided, and it's highly variable whether it's provided at all.

Next slide. We are very fortunate -- The

Committee's request of the -- the Work Group was very timely. It turns out that this is a question that has risen to the surface of concern for a number of supporting organizations that really see this as a barrier for an important group of families that have been disadvantaged.

The AMA created a resolution that was authored, in part, by the American College of Medical Genetics that specified a need for support and coverage for medical foods. The Society for Inherited Metabolic Diseases has just completed a revision of and a reinforcement of our endorsement for coverage of medical foods and their essential nature. The American Academy of Family Physicians cast a resolution, at their most recent meeting, supporting coverage for medical foods, and the AAP, whose governing committee, the Annual Leadership Forum, votes annually on resolutions impacting pediatrics, has the medical foods coverage as a resolution for discussion in their upcoming meeting shortly. The Genetic Metabolic Dietitians International has

been central in both organizing and -- and promoting the need for medical foods. So, all of these organizations have recognized the need for this activity and have offered their strong support, together, to endorse the actions that will allow coverage for medical foods.

Next slide. So, to kind of sort this all out and to remind you of the whole big picture, inherited metabolic diseases are included on the Recommended Uniform Screening Panel because effective interventions are available. We hear about this each time we make those difficult decisions. Medical foods for management of these conditions, for which the screening is mandated, are not available for many. Legislation has been introduced and not passed. Advocates have continued to speak and continued to enforce the need for this, and professional organizations, as I've just outlined, have provided both expert opinion and recommendations. The difficulty of divisions of responsibilities between federal and state regulations and some ambiguities about the

status of medical foods and regulations really resulted in inaction, which is costly both in terms of dollars to the family and, even more importantly, costly in terms of the health and wellbeing of the affected individual.

So, next slide, please. What we had hoped to do today was to tell you what our draft policy recommendation for Committee consideration would be, and the -- this slide summarizes what we think we need to make sure happens, which is that medical foods have to be considered medical benefits and be in coverage -- included in coverage as essential health services, irrespective of the age of the individual, and whether it's specified on the RUSP or identified clinically, they should have access to comprehensive coverage for care of their inherited metabolic disease. So, that's a big takeaway for what we will offer as a conclusion that we need the Committee to consider for potential endorsement.

Next slide. We thought one option that

might be, also, worthy of discussion is to make a recommendation to the Secretary of Health and Human Services that they lead the way in federally supported health programs, over which the Secretary does have purview, to include coverage for medical foods in the programs. Here, we've specified Medicaid, Medicare, Children's Health Insurance Program, Indian Health Service, as examples of that. The key piece of this is that this is, essentially, a leading by example and that when the Federal Government's approach to medical coverage includes a -- a specific element, this is a means by which other coverage systems and processes can be encouraged to change.

Next slide. So, I'm going to finalize my remarks with a suggestion for a possible next step for accomplishment that I'd like us to discuss, which is that recognizing the complexity of actions to get comprehensive coverage, we recommend a meeting of stakeholders to come to some final conclusions about how to reach this --

this goal expeditiously. Bring people into a room, put their hats on together, and see how we can hammer out something that will allow this to come to a resolution that will best serve the children and families that we identify through the important programs of newborn screening.

Elements of what I'd like us to at least think about discussing at this meeting is who should convene the meeting. We need to anticipate who to include. And I need, also, as part of our discussion today, your general thoughts about our draft policy recommendation and the action option that the Committee -- the -- the Work Group is offering for discussion. With that, I'll conclude my remarks and open the door for Dr. Bocchini to be the excellent moderator that he is.

DR. JOSEPH BOCCHINI: Thank you, Sue, and thank you for an excellent summary of the activities of -- of your work group, your subgroup, and bringing the Committee up to speed as to where you are. I -- I'd like to have the discussion kind of go in -- in -- in two

directions, one related to the white paper and -- and some feedback from the Committee about their current review of the white paper and their thoughts about whether we're right on target or whether there need to be additional things or other things addressed, or how best to address some of the issues so that we have the database and the evidence base that we need to make a strong case for what we've already told the Secretary twice that we -- we would like to see happen.

And then, the second part is to -- So, that's feedback to the Work Group as to how to bring the white paper, hopefully, to its completion, maybe, by our May meeting if that's possible. And then, the second thing -- because we -- we've spoken, when we discussed this issue before, about the fact that we've already been to the Secretary twice, whether we should be considering other approaches for how to move forward to try and accomplish what we want to have done, and that's part of this discussion is,

as we consider as a Committee what recommendations we would make, how -- how would we best utilize those recommendations, or promote them, to try and resolve an issue that, clearly, has -- we've -- it's been tried to be addressed, both from our side, through evidence, and the consideration for this is essential benefit versus advocacy groups and professional organizations, which have approached this, as well.

So, let's open this discussion, and -- and let's hear from Committee members and -- and then from organizational representatives related to where we are. And, again, use your "hands up" button so that we can make sure we have everybody in the queue.

All right. First is Cathy Wicklund. Cathy?

MS. CATHY WICKLUND: Sorry about that. I wasn't ready. So, that was a great presentation. Thank you so much. Can you guys hear me?

DR. JOSEPH BOCCHINI: We can. Go right

ahead, Cathy.

MS. CATHY WICKLUND: Okay. Okay. That was a great presentation, and I do like the idea of having a meeting to bring all the stakeholders together. You know, I don't know, obviously, if that's -- the Secretary's Advisory Committee would be able to do something like that, but it would be interesting to think about that more, and who could sponsor it, as you suggested, and really to get some of the major third-party payers, representatives from CMS, and different organizations to actually be at that meeting to have these discussions. So, I do really like that idea, a lot.

DR. JOSEPH BOCCHINI: Thank you. Next is Kellie Kelm.

DR. KELLIE KELM: Thanks. I have some questions for Dr. Berry from the -- you know, since she brought up the example of the medical foods, the regulation, and I know there was a recent, sort of, FAQ guidance document that FDA published, so I don't know if she could speak to

it so I could get my hands around it a little more. So, there's quite a list of foods and other things that were in the report that, you know, a lot of the -- the children with inborn errors need, so if you could let us know if all of those sort of sit -- You know, the -- this -- this regulation that they have for medical foods, do all of those sit within that regulation? And what is the impact of this regulation on -- on moving forward with reimbursement of medical foods? And then, I guess, just touching on -- It looks like our last couple of letters have touched on reimbursement, so, you know, are you guys thinking, still, about targeting CMS, mainly, in -- in where you thought that we should go?

DR. SUE BERRY: Okay. Thank you, Kellie. So, with regard to the broad scope of products that are used for medical foods, many people, when you think about medical foods, we start by thinking of the infant formulas that babies take, like the ancient -- well, Similac, for example. But of course, for -- even for PKU, at this

point, there are many products that fit into the rubric of medical foods. This includes special bars, almost anything that is modified in a way that is designed to treat one of those inborn errors of metabolism.

And so, there is a broad scope of products that are encompassed by the rubric of medical foods. I think the -- the real distinction that -- And it's one -- I think one of the things you're kind of alluding to in this is that some of the -- you -- we need to make a very clear distinction between medical foods to treat inborn errors of metabolism and other special foods for medical conditions. We don't want to be getting on the territory of trying to find special foods that are used for diabetic care, for example, sugar-free foods. While, you know, that -- that certainly might be an impact on the health of a person with diabetes, those are not foods that are specially modified to be used in the management or treatment in the way that the medical foods are used for inborn errors

of metabolism.

So, the regulations -- the modifications of the regulation -- I think that's what you're talking about, the update of the guidelines that came out in 2016 -- did increase that degree of specificity to help us, I think, tie this in more closely to the treatment of -- actually, I'll be careful -- to the management of inherited metabolic diseases.

We do think that we should be working directly with CMS as one of the partners in this, yes, because CMS -- as CMS goes, so goes the nation, I would think, on this one. So, I -- I do feel like this would be an important -- they would be a really important partner in the discussion. Do I -- Did I get what you were getting at there?

DR. KELLIE KELM: Yeah. I guess I was trying to -- I think, previously, the regulation had come up as a barrier or -- or an issue, and I didn't know whether or not it still complicated things or not.

DR. SUE BERRY: It's still complicated, yes, because it's hard for people to get their hands around what a medical food is and why it's not -- why -- why it's different from a drug. At -- in the -- in the white paper, in more detail, we go through that regulatory sequence and include some clarification about this specific issue, so that we can be as pointed as we can in defining what our target for attack for this is and -- and what -- what the impact would be.

DR. KELLIE KELM: Thanks.

DR. JOSEPH BOCCHINI: Thank you. And, certainly, CMS was one of the -- the groups that we did talk about at our last meeting that might be very important to serve as a partner, potentially a convener, but certainly a potential way to go to try and make them aware of the -- of the patchwork that exists in states and perhaps get some help in understanding what needs to be done globally.

Okay, Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Hi. Thanks, Dr.

Berry for your good presentation and updates. Would Kellie Kelm, who just asked the question, have any specific recommendations or guidance based on her role and what she has seen over the last 5 or 6 years, anyway, in this space, and then, secondarily -- I feel like I should know this serving on the Subcommittee -- but have we had a conversation or is anyone even part of this meeting today from CMS that could weigh in from their perspective just to give us a little more guidance and a boost that we're going in the right direction?

DR. KELLIE KELM: I just wanted to -- This is Kellie. And I don't have much that I can touch on in terms of experience; I'm not in the Food group. And I -- I knew that this had been an issue a few years ago and wanted to make sure that I understood whether or not the wording -- the regulation and what it encompasses had been issued. And unfortunately, you know, we only work with CMS peripherally from time to time. And I know one of the questions I think I was going to

ask -- and, you know, people may or may not have experience here -- is whether or not -- You know, there's been some work sometimes on committing CMS to, for example, to try to ask for universal coverage of -- of things like this when states haven't been doing so, whether or not there was a -- an experience that -- that we could build off of.

DR. JOSEPH BOCCHINI: All right. Annamarie, as part of your -- the other part of your question -- We have not directly approached CMS, but as a Committee, we certainly can see whether there is someone within CMS who we should make contact with and potentially have discussions with, and we will go forward with doing that as -- as part of our approach to prepare for the next meeting.

MS. ANNAMARIE SAARINEN: Thank you. I'd be happy to help to the degree that I'm able to.

DR. JOSEPH BOCCHINI: Thank you. Next, we have Carol Greene.

DR. CAROL GREENE: Hi. Thank you. And

there -- Since I'm also organization rep, phone line is open, other two co-chairs of Sue's committee may even be better able to provide some insight about the -- sort of, the -- the -- the question with respect to the regulation and CMS, and those are Christine and -- and -- and Cathy, if they're on the line and if they're able to speak. I do have a little experience, and I think Sue -- fabulous presentation and answered very well, but I think, to add a little bit more detail, the clarification was very, very important with respect to making sure that the definition stayed -- stays appropriately narrow but had no impact on coverage.

Coverage is still -- Coverage is an issue. It's still tied to the question of essential benefits. TRICARE has made, you know, some advances recently, but the coverage issue is more that it is not a drug, and there's no essential benefit for this category. And there -- as Sue mentioned in the -- in the full of the white paper, there's the history of the extremely

good reasons why this is classified separately from drugs and -- and -- and -- and the reasons that many -- and I'm certainly among them -- experts think that it should remain so.

But the improvement in the clarification of the regulation has not helped at all with coverage in that a number of people have been working quite hard, directly with FDA and CMS, and part of the reason for trying to approach this, obviously, with the most information you can but with a meeting of all people is, there's been a tendency to, you know, meet with CMS, and they say, "Well, it's FDA's problem," and FDA clarifies and -- and then you meet with FDA, and they say, "Well, but it's CMS's issue." And the idea would be to get everybody in the room together, because, historically, it's been a little hard to do otherwise.

But the bottom line is, the answer to the question is, the clarification was most welcome, very useful, but did not address, in any way, the issue of coverage.

DR. SUE BERRY: So, this is Sue, again. Could I comment briefly just to be -- because I have -- I would have the advantage to open up the -- the white paper so that I can be more distinct about what the wording says so people can hear it.

The FDA clarified their draft guidance for industry with final language that, really, just came out last year, and what it ends up saying is that medical foods are specially formulated and processed, as opposed to naturally occurring, and designed for partial or exclusive feeding, orally or by tube. They're designed for persons with limited or impaired capacity to ingest, absorb, digest, or metabolize ordinary foods or nutrients whereby dietary management can't be achieved by modification of the normal diet alone. You can't just tweak the normal diet. They have to have -- that these are special products that are not part of any normal diet. They're supposed to be using -- used to manage unique nutrient needs of specific diseases or

conditions that are determined by medical evaluation and have to have ongoing medical supervision. They called inherited metabolic disorders out as diseases that a medical food could be used to manage. So, that -- they were -- it was more specific in a way that we haven't had before.

Carol, is that what you were thinking you wanted Cathy to -- I'm using Cathy's words here in the paper, so.

DR. CAROL GREENE: Yes. That -- I think it's very useful for people to hear the clarification and also to -- to make very clear that we have people like Christine who have been working very, very hard, and the clarification is important, but it does not solve the access or coverage problem.

DR. SUE BERRY: Exactly. We -- we have a better definition of things that aren't paid for.

DR. KELLIE KELM: This is Kellie, again. Thank you for providing all the information. It was helpful just to understand whether or not

that issue had been solved. But, yes, unfortunately, you know, tests that we work on -- just because FDA proves they're clear, that, unfortunately, doesn't mean that CMS or any insurance company will cover it, and we -- we are forced to hear that complaint a lot. So, that, I guess, helps us.

You know, I wanted to -- my main question was just about understanding and sort of thinking about how to focus your issue and -- and where we should put our tension, because I think a -- your policy statement was just unclear to me where -- where you're thinking about going. So, it sounds, mainly, like you're interested in figuring out, you know, people in terms of coverage, so CMS and those partners might be where -- where you're looking to bring attention and -- and get those folks to the table.

DR. SUE BERRY: This is Sue, again. Could I briefly throw in a comment that I received from Christine Brown? Would that be acceptable?

DR. JOSEPH BOCCHINI: Sure.

DR. SUE BERRY: Because she's -- she's listening but not open, so she emailed me. She says that patient organizations have met with CMS in the past but haven't moved many thing (sic) forward because they passed it on, just as Carol described. And she wanted to reinforce to the group the importance of a multi-stakeholder meeting, from the point of view of her group and her own personal perspective.

DR. JOSEPH BOCCHINI: Thank you. Thank -- thank her for -- Well, we'll thank her for that comment. Thank you. Chris Kus?

DR. CHRIS KUS: Yes. Sue, I -- I -- I mean, the idea of seeing -- working with CMS and seeing what they could do so that, at least, federal insurance programs would have coverage is -- is -- is a great idea. The concern I have is, the question is, what can CMS do? An example: If you take Medicaid, Medicaid is a state-run program, so coverages in Medicaid programs differ among the states.

The -- the second thing I'd say is, Sue,

do you have anything that you think we could recommend to the Secretary that she would be able -- that she would be able to act on?

DR. SUE BERRY: So, one of the things that happens in insurance worlds is, if one big payer does something, sometimes that leads others to do the same. What we find in state-to-state bases -- and I think you're right about this -- is that if Medicaid in a state offers coverage for something, sometimes that means private insurers are more likely to do.

I think the lead-by-example concept is what we're thinking might be something that the Secretary would have the possibility to -- to do. Whether that is accomplishable on a short-term basis is harder for me to answer, and we are -- we're being pretty careful not to try and say that the Secretary should offer alterations in how coverage is accomplished in things over which the Secretary has no specific purview. For example, we could say that we'd like TRICARE to do -- to do everything, and, actually, TRICARE

has moved further than most in coverage for medical foods. But the Secretary wouldn't have any influence over TRICARE because it's something that the Department of Defense manages. So, we do want to be very specific and ask the Secretary things that can be accomplished through HHS. And I -- I -- I -- I'm hopeful that we can identify elements that HHS does control that will have an impact that may have a domino effect.

DR. JOSEPH BOCCHINI: Thank you. Next, we have Annamarie, again.

(No audible response)

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

MS. ANNAMARIE SAARINEN: Sorry about that.

DR. JOSEPH BOCCHINI: No -- no problem.

MS. ANNAMARIE SAARINEN: I just wanted to weigh in really quickly after Dr. Kus's comment about state programs. So, my -- This is just a -- a thought process for me as someone who, sort of, analyzes things from a policy standpoint in most

situations. So, when this Committee has sent things to the Secretary in the past, and then the Secretary sends her letter back to you, Dr. Bocchini, there has been -- and I can say this to be true with CCHD screening -- a list of calls to action from the Secretary for each of the agencies. So, it will say -- and I'm paraphrasing -- that, you know, the FDA shall do this, and the NIH shall do this, and the CDC shall do this. And -- and CMS -- and -- can -- should be included in a similar way if there was to be a letter to the Secretary that the Secretary could respond to that would just have some strongly worded directives to the agency world in carrying out what seems to be a, sort of, common-sense, unmet need. So, that is piece one of how I think that HHS can interact with CMS and the other agencies in a way that's been done before.

CMS, in its own right, is able to send strongly worded letters, guidance, recommendation down to the states for how things could be and should be carried out. You're right, each state

has the authority to do what they want under Medicaid, but that -- it's certainly not setting a precedent to think that CMS would send a letter to the states saying, "This is our recommendation for how medical foods would be handled in your state, and here's how CMS -- the federal level can help support the rollout of such an initiative."

Additionally, for state Medicaid programs, they are outsourcing a good amount of their CHIP and pediatric coverage program to the private sector already, so, as Sue suggests, when, you know, one does one thing, the private payers tend to follow along. In this case, sometimes the private payers are -- are the first on board to actually support reimbursement for something like this, and there's a little bit of push-pull between Medicaid and -- and the private payers kind of following on each other's guidance.

DR. JOSEPH BOCCHINI: Thank you for those comments. Coleen Boyle?

DR. COLEEN BOYLE: Yes, thanks so much. I was actually -- I think Annamarie said -- said most of what I was going to say. I just wanted to relate an example of -- in another area that we were working and have had conversations with CMS about coverage, and it's, really, in the -- in the Medicaid lane. And they encouraged us to -- I think as Annamaria may have said -- to actually reach out to some of the states -- the Association of State Medicaid Directors and to see whether or not you -- we could get on board a number of the, you know, stronger states or larger states or whatever, but -- but to use that as a way and a means to sort of establish the best practices, and that, you know, maybe that would have an impact, sort of, downstream in terms of bringing other states on board there. So, just -- just another partner to think about.

DR. JOSEPH BOCCHINI: Great, thank you. Next is Chris Kus.

DR. CHRIS KUS: No, I -- I think I forgot to take my hand down.

DR. JOSEPH BOCCHINI: Carol Greene.

(No audible response)

FEMALE SPEAKER: Carol.

DR. JOSEPH BOCCHINI: Carol, you're next.

DR. CAROL GREENE: Sorry, I have to -- had to unmute myself. I apologize. Fabulous discussion, and I -- For me, it feels like thinking about who would be participating in a meeting, and I think part of the issue -- and I think Chris brought it up very well, and then some examples of how to move forward -- is, it's really hard to make more specific recommendations without having all those partners at the table. And one of the goals of the white paper is to lay out all that history so that this meeting would start with an informed group of people attending who could then move forward to -- to explore some of these options.

DR. JOSEPH BOCCHINI: Thank you. Next is Bob Ostrander.

DR. ROBERT OSTRANDER: Yeah, I just wanted to fill folks in. I -- I've been talking

with our legislative and policy contact in Washington from the AAFT, and I think it would behoove us to focus, as -- as the groups of folks that are interested in this, perhaps, on the HHS Secretary with a lot of our concerns, and, obviously, that's the purview of this Committee, as well. He tells me, with everything going on with the ACA and so on, that the words "require" and "mandate" are pretty toxic right now.

DR. JOSEPH BOCCHINI: Thank you, Bob. Dieter?

DR. DIETER MATERN: Yeah, this is Dieter. I think Bob just answered my question, because I was wondering, given the questionable fate of the Affordable Care Act but its replacement by something that is better and cheaper, whether this couldn't be just fixed that way.

DR. JOSEPH BOCCHINI: Thank you. Yeah, I think, obviously, there are changes going on, and I think that we need to pay attention to those as we work through these issues over the next couple of months, so that by May, we may have a clearer

idea of whether one group would be better than another. And -- and I think that's something that's evolving that -- that we'll just need to pay attention to over the next couple of months.

I have no other questions or comments -- commenters on -- on the hands-up side, so, Sue, I want to thank you for your presentation. I think it's very clear from the comments that you had from Committee members and -- that they feel your -- your -- your group is right on track with the white paper and that -- that we continue to flesh out those -- those details to make it stronger. I think we'll come back with -- with, hopefully, a final product in May and that some of the discussion that we had today can help us inform where to go with this product and -- and how to move forward in the best way possible to have an impact in -- in this important area.

I think, as people continue to review the white paper draft, if you could provide input back to Sue and her subgroup, or through Debi, and -- and then we'll get it to the -- to the

Work Group. I would certainly appreciate that. We want to move this along as quickly as possible so that we could be where we want to be in May. And, again, I want to thank everybody who's working on this. I think this, obviously, is an important issue that we hope we're going to be able to help solve in the near future.

So, with that, we have, you know, 3 10-minute presentations from our -- our work groups. The first is the Education and Training Work Group update, and this is a work group that is co-chaired by Cathy Wicklund and Beth Tarini, and I think, Cathy, you are making today's presentation.

MS. CATHY WICKLUND: I am.

DR. JOSEPH BOCCHINI: Thank you, Cathy.

MS. CATHY WICKLUND: I am right here. Okay, great. So, we had a great meeting on Tuesday morning, and I want to thank everybody on the Work Group for participating in that meeting. Yeah, Beth is unable to be on this call, so I will be presenting on both of our behalf.

Next slide. So, I just wanted to quick put up the members. We had, as you guys know, as many of the Work Group, had a call for nominations for new members. I also -- and I apologize for not having this on there. I want to recognize the members that rolled off the Committee for all of the hard work that they have put in, in the last few years. We were able to enlist some new members, as well, so the -- they're -- all the members are listed here, and, again, we just had a great conversation. So, I want to thank everybody for participating.

Next slide. So, because we had so many new members, we did do introductions of all members on the Work Group, and we also asked for relevant -- relevant updates, as we always do, just to make sure we know what different organizations are doing and also thinking about some potential education and training projects in the future, and then we reviewed the Work Group projects and also briefly discussed additional educational needs. And most of our conversation

on Tuesday was focused on the current Work Group projects that we have right now.

Next slide. So, I'm just going to remind you guys of what our projects are and talk about each one. So, the first project that we were working on is creating a tool that provides primary care providers with guidance and tips for discussing out-of-range and positive newborn screening results with parents, and our original idea was that it could be, kind of, a companion piece used alongside the ACT sheet.

Next slide. So, we had some ACT committee members that were identified to work on this, and if you guys remember, Natasha and Carol Greene and the group that is cited on this paper had put together a summary of what parents, I believe, wanted -- There was a qualitative study looking at parents, at what kind of information they would want during a discussion about a positive newborn screen. So, we took that product that they put together and went to ACMG, had Genetic Alliance collaborate with ACMG to determine how

to best incorporate some of the research findings from this paper into ACT sheets or, again, to have a completely separate document.

Next slide. So, there have been -- I'm not sure exactly how many -- calls between the two groups, and we have definitely recognized that there are, just like with any professional organization, several hurdles or several things that a companion piece would need to go through before it was incorporated or linked to a standing ACT sheet. So, we decided not -- we are still, kind of, continuing along that path, but we also decided we should go ahead and just create a standalone tool which we're now, kind of, remaking as a communication tool, and we're going to go ahead and work on refining that communication tool, again, because we have something already in place already, as a standalone piece, to be potentially disseminated in other ways. And we're going to have a small work group work on reviewing and revising that tool, and one of the things we talked about on

our call is to invite, perhaps, like, Tracy Trotter or some other primary care providers to provide input as we work through the development of that tool.

Next slide. And then, we had two arms of our educational outreach project. The first one was a mapping of educational resources, and this project has evolved into something that we feel is very doable and relevant. And the current objective of this is to develop a matrix with relevant stakeholders on topics that would be important for stakeholders to understand or know regarding newborn screening. If you guys recall, we did show you this last time, but, again, I'll just throw it up here so we can refamiliarize ourselves with it. But Jeremy Penn is the leader/driver of this initiative, and he presented an initial framework for discussion, and what subsequently happened was, a subgroup of the Working committee -- or the -- the Work Group, I should say, worked on further refinement of the framework by adding additional

stakeholders, adding additional educational pieces, and then our call -- this was really the main discussion of our call on Tuesday.

Next slide. So, just to remind you guys, this was the Excel -- just kind of a snapshot of the Excel -- Excel spreadsheet that the committee started working with. On the left are the different stakeholders, and, again, this has been fleshed out further. This is not a -- not where the actual matrix stands right now. And then, the topics are listed across the top. And the small work group basically went through each one of these -- has been working hard on going through each one of these and determining -- thinking about what educational piece would be required or, I guess, recommended or used as a guideline to include on educational resources for these particular stakeholders.

Next slide. So, just to let you know who was on the subgroup, Jeremy Penn, Natasha Bonhomme, Joyce Hooker, Cate Walsh Vockley, and Amelia Mulford have all been working on this, and

we are also extending this group to a little bit bigger.

A couple things came out of their work. So, first of all, we did not go through the matrix column by column but had a general discussion about some of the things that the Work Group ran into and wanted some input from the Committee on. The Committee -- The broader, I should say, E&T Work Group is going to review the matrix and send comments into the small work group that we have working on this and -- But a couple of discussion points came up.

One was whether or not the matrix should be specific for the current newborn screening paradigm or should also consider the potential movement into the age of molecular medicine. And, in particular, the group was thinking about some of the genomic sequencing projects that are going on, and, in particular, the issue of return of carrier results came up.

And we've had, as we know, on this Committee, several conversations about that

already, and we also, if you guys recall, at the last meeting, I think it was, we had representatives from the four different in-site grants come in and talk about what they were doing at their sites. And we were wondering -- And -- and what I can't remember -- and I apologize; somebody else might know off the top of their head -- is whether or not we spent a lot of time about return of results and whether or not they were returning carrier results, if we said -- I don't think it was the focus of the conversation, but, again, I can't remember. So, we were thinking that this might be something that we need to have a broader discussion about with the entire Committee and, perhaps, invite back, you know, the -- the PIs from these grants to talk about how they're managing return of carrier results.

And, also, the other discussion points we thought we might want to bring back to the broader Committee is, again, whether or not should -- we should be focusing on the current

paradigm, a future paradigm, or, potentially, both, and compare the differences between those two matrix and what might be used as a guideline.

Next slide. So, as far as next steps with this project, we're going to continue to refine the framework, with input of the E&T Work Group, and then the next step is really determine how to utilize this actual framework. One of the suggestions is actually to apply it to existing educational resources, which you know are really broad, to actually identify gaps, and that might then help inform future work and education. And the Subgroup is all going to -- also going to work on brainstorming next steps: how to use the framework, how to disseminate it, and we -- also, we're going to talk to the Committee -- Debi -- to think about, what are the rules with which we can disseminate some of the work, as well.

Next slide. So, project 2 was -- We did not get to this, actually, in our phone call, but I didn't want to lose this, and this was how we could leverage our work group's organizational

relationships to encourage submission of educational materials into the newborn screening clearinghouse. So, Natasha from the Genetic Alliance was going to put together a summary of the project so that we could disseminate to our relevant professional organizations in order to encourage submission on the clearinghouse. We actually did not get to talk about that, but that is still on our agenda.

Next slide. And then, we also did not get a chance to talk about this, as well -- the matrix took up most of our conversation -- but we didn't want to lose this piece. Because we do not have the Timeliness Work Group anymore, we want to make sure that we continue to monitor timeliness education. One thing that was suggested at one of our meetings was, the phlebotomists might be a good group to target. We haven't had much luck in this, and that, unfortunately, isn't on the call, but did some research in trying to target an -- a specific organization, and we -- we really were not able

to target anything. And so, if anybody does have any ideas or suggestions for us, that'd be great. And then, also, we need to still touch base with Committee members who attended the NewSTEPs 360 meeting in November to just try to see if there were any educational or training opportunities that came out of that meeting that we could help or be a part of.

Next slide. Yeah, and I think that's it. Does anybody have any questions?

DR. JOSEPH BOCCHINI: Cathy, thank you for -- That's a great summary. There's a lot of activity in the Education and Training Work Group. I think one of the things that certainly take under advisement: the suggestions you had for what might be topics for the entire Committee. That would then inform some of the work that we've given to the Education and Training Work Group, as well as for the rest of the Committee, and also, it would be good that as you are developing these projects, it might be reasonable for us to have a time for you to show

us them in progress, so that they can be evaluated by the Committee and give you some feedback, as well. So, thank you.

MS. CATHY WICKLUND: Yes, that'd be great. We -- we will definitely be doing that.

DR. JOSEPH BOCCHINI: Okay. Let's open this up if there are any additional questions or comments for Cathy for the Education and Training Work Group.

(No audible response)

DR. JOSEPH BOCCHINI: All right. Seeing none, let's go ahead to the next presentation, which is from the Laboratory Standards and Procedures Work Group. Kellie Kelm and Susan Tanksley are the Chair and Co-Chair of this work group. I guess -- Kellie, will you be making the presentation, or will you be sharing it?

DR. KELLIE KELM: Well, I think I'll do most, but I hope that -- You know, Susan is available to chime in as -- you know, especially since, you know, she did great giving the -- the lab perspective. So, we had a great Work Group

call about a week ago, and I want to thank -- We had a -- a great participation from our work group, and if you go to the next slide, we have our current Work Group roster, and we do have three new members, and I'd like to thank them for joining us last week. And we didn't have anybody, yet, rolling off, but we will next year, so we'll be looking for some new people or, you know, people who are looking to continue next year.

But I just wanted to mention that we have Travis Henry, who is a clinical research scientist at the State Hygienic Lab at the University of Iowa, Holly Winslow, a research scientist in Newborn Screening Tandem Mass Spec Unit at Minnesota Department of Health, and Tricia Hall, who is Director of the Biochemical Genetics Laboratory at Emory University, which is now EGL Genetics. So, it was great to have them join us, and they were all immediately participating. It was great to have them. As -- So, it will be great having them.

So, next slide. So, we spent most of the

time with an oral presentation, basically introducing some thoughts on implementing screening for lysosomal storage disorders and X adrenoleukodystrophy and some of the difficulties with implementing the screening and meeting the timeliness goals. So, I'll go into that a little bit, and then, at the end, we had -- and I'll touch on a discussion that we had on California and their experience with the R4S postanalytical tool.

So, next slide. So, this has already been up today, and this is just a reminder of the timeliness goals that the Sub -- that the Committee -- sorry -- made after the timeliness work was done, and, obviously, that was based on some of the limited data that we had at the time, and, unfortunately, the fact that we knew that what we had available was -- Unfortunately, some of the data was not uniform, and so, we -- we had very limited data, but the recommendation was -- and I won't read it again here, but listed here in terms of the timeliness and included the

additional three bullets at the bottom that in order to achieve the timeliness goals that all newborn screening specimens should be collected in the appropriate time frame for the newborn's condition, but no later than 48 hours of birth, and that newborn screening specimens should be received at the lab as soon as possible, which would be, ideally, within 24 hours of collection.

Next slide. So, some of the information that was shared during our Work Group call was a note that most states have seen an improvement in transit time with the addition of a courier, but there was still room for improvement in timeliness of hospital submissions. And many states noted that meeting the timeliness goals for transit time are still challenging and, obviously, whether or not, in the end, you know, we could still get to the 5- and 7-day goals in terms of returning results and -- and -- and whether or not the transit time, you know, was a big impact or not.

Next slide. So, the discussion -- for

example, screening for lysosomal storage disorders by a state that's using a mass spec method requires an overnight incubation as part of the testing process, and that screening for X-ALD often uses a second-tier mass spec test to reduce false positives. And so, it was also noted that some states perform a second-tier DNA test to reduce call outs, and so these -- You know, this was information specifically cited by states in terms of, these tests give you more time to complete, and impact, for example, getting results back within 5- to 7 days, especially with some of the issues that they're having with hospitals getting their testing done and getting it to the courier in order for, for example, transit to happen in 24 hours. So, the transit time and the issues with this screening methodology, they compound, and so states are having difficulty meeting timeliness goals reporting, especially for these conditions.

Next slide. And so, just a reminder: As discussed earlier, transit time is time from

collection to receipt in a testing lab, and there's a number of logistical issues that Susan had already, sort of, touched on in her comment earlier, that a lot of things have to happen, almost with luck, in -- at -- at the right time for transit to happen in 24 hours. So, you have to look at the timing of collection versus the time of pickup and then the time of delivery, and whether or not those are all aligned -- for example, one -- collection and -- and when it dries. And that's another tier. The time of collection should occur between 24- and 48 hours of life, although it was noted that California has been doing some collection earlier. Specimens must dry 2- to 4 hours before shipping. Specimens that are drawn too close to courier pickup times can't be shipped until the following day because they have to dry, so then, that will exceed the 24-hour recommendation. And then, large commercial couriers do not pick up 7 days a week and have holidays, and so states that are relying on those large commercial couriers also have

those issues to contend with. So, these are just some reminders about why, sometimes, meeting these -- these timeliness goals can be very difficult.

Next slide. So, as I said, so many local factors can affect timeliness, as well, and -- and so, we had two examples of the mass spec screening for -- for LSDs, as well as thinking about second-tier tests. So, testing methodologies do differ in length. Some, like the mass spec for LSDs, utilize longer incubation. You know, we -- we -- Many states use second-tier testing due to call outs. Tandem mass spec is a good -- is often used and is generally faster than when DNA testing is used, and DNA testing can use several different methodologies, and two are given here that are -- are more typically used, PCR based, and then we have states that are moving towards sequencing, for example, next gen sequencing.

Next slide. So, some of the discussion points that our group had, sort of, touched on --

on -- on these bullets here. So, despite efforts to improve transit time, one state mentioned that they still only get about 50% of their specimens within 24 hours of collection. So, one thought was that the Work Group could look at some of the more recent timeliness data that's being accrued, and assess more recent data, and consider whether there could be suggestions for changes to the recommendations presented to the Committee based on more -- more recent and updated data. So, for example, should we develop a new measure -- for example, age of the baby when specimen is received -- versus the timeliness goal that we have right now?

And one of these suggestions was considering whether there should be different timeliness goals for different conditions, so not just time critical and -- and the -- in the remainder, but maybe some further -- further regularity in -- in the list in terms of goals. And another suggestion that I know we've talked about sometimes -- We've talked about regional

screening labs and whether or not there should be a -- a network or availability of stat labs for second-tier tests, so that, for example, states could also work together to -- to get their second-tier testing done, especially when, you know, this may be a -- a more low frequency test for some states. So.

Next -- next slide. So, I didn't have slides here, and I wanted to touch on -- on briefly that Fred Lorey from California, who's a member of the Work Group, had shared with the -- the Work Group a publication that California had -- along with folks from Mayo -- had published, about, California had done a retrospective analysis of some of the samples and the screening results using the R4S tool, and so they had shared how this study was done and some information on -- on what the results were, including a decrease in the false positive rate from .5 to .02% and that none of the cases that had been babies -- affected babies in the sample that had gone through the R4S tool for analysis -

- none of them were missed, so there were no false negatives. So, that was an additional discussion that we had, and there were some questions about how the study was done and some questions for California about how they were proceeding with the R4S tool. So, we had some discussion about that, as well.

And, lastly, here are some few discussion topics. So, we haven't had a chance to talk about -- You know, one of our projects is the infrastructure and services that state labs use in order to form safe and efficient newborn screening, and we haven't, sort of, gone and -- and talked to states and see those states that are implementing X-ALD screening, find out how that's going and whether or not they have -- You know, we talked about some issues already talked about today in -- with regards to timeliness, whether or not there are any other interesting lessons that could be shared, as noted, as part of the timeliness issue.

You know, NewSTEPs has received more

recent data, and of course, they've also -- there's been an effort to make the data more uniform so that we're seeing the same data from states, and so the great -- I know that the -- that it sounds like they're presenting to the whole Committee in August, but there's some thought about reviewing the data by the Work Group in order to, once again, inform us in terms of the -- the recommendations and -- and some of the new screens that have been -- that are being performed, and whether or not we should revisit or -- or provide any thoughts on the recommendations that we currently have.

And then, we've touched on, in our discussion, as well as, we've even touched on it earlier today, about case definitions and, you know, states that are sharing data -- you know, whether or not we're talking about the NewSTEPs database or the R4S, and thinking about whether or not they're all using the same case definitions within the databases, which would help us with, you know, sort of, comparing these

apples to apples, which we're talking about data analysis, so. There was some talk about having us discuss that in our work group, so. That's -- that's where we are.

Susan, I didn't know if you had anything to add?

DR. SUSAN TANKSLEY: No, nothing to add right now. Thank you, Kellie.

DR. KELLIE KELM: So, I'd like to hear if anybody had any questions for the Work Group?

DR. JOSEPH BOCCHINI: Thank you, Kellie. Again, lots of activity and -- and work. Great project underway, so we appreciate the work that you have in leading this Committee, as well as the -- the Work Group members who are contributing to the effort. So, thank you, all. Any questions or comments for Kellie or Susan related to this work group?

Dr. Matern?

DR. DIETER MATERN: This is Dieter. Thanks, Kelly, for the presentation. Given previous discussion about cutoffs and all the

stuff, and Dr. McDonough's suggestion that we take on as a subcommittee the issue of R4S and CLIR by the next meeting, I wonder if one should either add to the future discussion topics list or basically take a look at Pompe versus X-ALD screening at this point and ask our new Subcommittee member, Dr. Hall from Emory, to give an update how she is using that for that pilot study for Pompe and MPS1 in Georgia.

DR. JOSEPH BOCCHINI: So, is that directed to the -- to the Work Group, Dieter, to consider that through the Committee?

DR. DIETER MATERN: Well, I guess it's a suggestion to the Work Group and, of course, if the rest of the Committee agreed, then that subcommittee would probably be more eager to address it that way.

DR. JOSEPH BOCCHINI: Yeah, I think that we need to consider that as a Committee, and then, based on that, bring it as a request to the Work Group to pick that up. So, I think we'll -- we'll look at that suggestion, and then get some

feedback from Committee members, and then make a decision as to whether to put that on the agenda for the -- or recommend that -- that the Work Group looks at that. Thank you for that suggestion.

I see no other questions or comments, so let's move to the Follow-Up and Treatment Work Group. Dr. McDonough?

DR. STEPHEN MCDONOUGH: Good afternoon. Are we connected?

DR. JOSEPH BOCCHINI: Yeah, we can hear you.

DR. STEPHEN MCDONOUGH: Okay. Go to the next slide. We have new members to our work group, and I welcome them. They're listed there. We had 11 excellent candidates, and 4 were chosen.

Next slide. I'm going to go through these slides quickly, because I'd like Dr. Zuckerman to have some time to update the Committee on his -- and his work group and co-chairs on clinical quality measures.

Go to the next slide. These are the Sub-Work Group members on Medical Foods, and Dr. Berry and -- did an outstanding presentation earlier today, and appreciate the work of the Sub-Work Group members and the co-chairs.

Next slide. Keep going. We've been busy. Keep going. And I'm going to turn this over to Dr. Zuckerman now. Well, I'll go through these slides real quick. These are our Sub-Work Group members on the Quality Measures.

Go on to the next slide. We've had two -- two of our -- our -- our Committee members, Annamarie and Jeff, who have been outstanding additions to our -- our work group.

Go on, next slide. And next slide. Okay. And these are -- The Quality Measures Sub-Work Group have been busy, also.

Next slide. Okay. Dr. Zuckerman, take it away.

DR. JOSEPH BOCCHINI: Operator, do we have Dr. Zuckerman's phone open?

DR. ALAN ZUCKERMAN: -- Hear me now?

DR. JOSEPH BOCCHINI: Yeah, we can hear you now. Go ahead. Thank you.

DR. ALAN ZUCKERMAN: Very good. The next slide -- Thank you for the opportunity to update the Committee on the work which we're doing on quality measures, which begins with answering the question of, why are we looking at them now?

Next slide, please. And quality measures are essentially standardized assessment tools that are a first step and an essential part of quality improvement activities or designing proactive decision tools. Typically, they're ratios, such as percentage of children with sickle cell disease who are prescribed penicillin. Each one expresses a definition of quality or a goal for care. And some of these are subsets to more comprehensive research databases, like the NBSTRN LPDR. They're used for new knowledge discovery. They require informed consent, often duplicate entry.

But quality assessment improvement is part of routine care, can be embedded in

electronic health records, and eliminates the need for separate data entry or chart review. And new standards enable us to have electronic definitions and tools for measurement reporting of quality measures that can be shared across states. But the real driver is the interest and need to use and report these quality measures for maintenance of certification for various incentive programs that creates an opportunity now to apply them to long-term follow-up for newborn screening.

Next slide, please. And this goes back to the past decade of work on long-term follow-up in this Committee, as revealed by this 2008 definition of "long-term follow-up" that's been driving our work. It emphasizes the need for quality chronic disease management, condition-specific treatment, age-appropriate preventive care, and mentions continuous quality improvement through the medical home and the evaluation of data related to care and outcomes. This is the next logical step in a lot of previous work.

Next slide. And one of the most important findings of our initial 6 months is the realization that there are really 3 types of approaches to quality measurement for long-term follow-up of newborn screening. The most familiar, of course: the disease specific measures, a process and physiologic outcomes, but there are also public health services that children require after being identified through screening and which may be provided outside the state newborn screening program to connect children to the care they require.

Finally, there are patient- or child-specific measures of wellbeing, access to medical homes and services that are best measures directly from consumers. All three overlap in the populations they are applied to, in settings, provider organizations, health departments, or consumers, where they are measured. We found that consumer advocacy groups may be going directly to consumers to get some of these disease-specific measures.

Next slide. Another important part of our work has been the collection of case studies to illustrate the feasibility and value of using quality measures for follow-up of newborn screening and which also reveal barriers that we seek to overcome. EHDI measures were put through the extensive certification by a national quality forum, and we learned a lot from the work that that required. Sickle cell measures have revealed barriers to start recommended preventive care. Cystic fibrosis care has evolved dramatically by comparing best practices in centers of excellence. We found an EHR embedded checklist for MCAD in mountain states that has helped to find gaps in care and alert providers to children-special emergencies. And the National Survey of Children with Special Health Care Needs reveals gaps in access in use of medical homes, and we found state health departments that are applying some of these questions to their own populations.

Next slide. Next slide, please. And just

to summarize, we've been holding monthly meetings. We have three outstanding co-chairs that bring stakeholder perspectives in informatics, clinicians, and consumers. We have public health participation from several states, and Jeff Brosco, who's a -- a member of the Advisory Committee of Bioethicists, has provided some very important guidance and insight to the group the roll we can play. We anticipate having a final report ready by August of this year, which we would like to share with you to enlist your help in promoting quality measures as an important strategy at this time for ensuring long-term follow-up of newborn screening. Thank you.

DR. JOSEPH BOCCHINI: Alan, thank you for that presentation. It sounds like a lot of work has been done, and you're focusing in on -- on some of the key issues that would, certainly, potentially, be really helpful in identifying what's important for quality measures for long-term follow-up. Are there any questions or

comments for either Alan or Dr. McDonough?

(No audible response)

DR. JOSEPH BOCCHINI: Seeing none, again, thank you both for your presentations, and thank the members of the -- of the Work Group and the Sub-Work Group work groups and the work that you've been doing. It sounds great.

So, the final topic on the agenda is to bring forward, from Committee members or others, organizational representatives, any potential future topics. We've already heard some. One was Dr. Matern's recommendation, and then we heard some recommendations from the Education Work Group, and are there any other questions or comments?

FEMALE SPEAKER: Jeff's got one.

DR. JOSEPH BOCCHINI: All right, Jeff.

DR. JEFF BROSCO: So, as a relatively new member of the Committee, I guess I can ask the -- the, sort of, crazy question, and that is: Since I joined the Committee, a whole bunch of people have come up to me and said, "Are there -- What

is the mechanism, or are there such a mechanism, for removing any conditions from the RUSP?" And so, I -- I guess I ask just as a question of ignorance: What -- If something didn't meet the criteria that we've set for entering a condition into the RUSP, is there any mechanism for -- by which something might be removed from the RUSP?

DR. JOSEPH BOCCHINI: This question has come up, and the -- it -- it has been filed as a future topic for the Committee, and -- but it has not been addressed. And so, it's good to remind us, Jeff, that that certainly needs to be put into the -- the future in terms of something to consider in -- in terms of developing a strategy or -- or an approach. So, thank you.

FEMALE SPEAKER: Dieter.

DR. JOSEPH BOCCHINI: Dieter?

DR. DIETER MATERN: Yes, Dieter, again. In suggestion to that, I think you have the option to nominate a condition on the website. I think it shouldn't be too hard to add a button to remove a condition, or upgrade it from secondary

to primary target, and all you would have to do is modify, slightly, the current form to ask for the evidence why you would want it to be changed, as it is right now, on the RUSP.

DR. JOSEPH BOCCHINI: Okay, good suggestion. I think that we're going to -- based on these comments, we might bring this up higher on the list of things to do in the next couple of meetings to address this issue, either as a Committee in -- or whether to assign a work group to -- to look at the issues on how to do that most efficiently and effectively. Okay? All right. Other comments?

(No audible response)

DR. JOSEPH BOCCHINI: Okay. None. So, that will conclude the items that were on our list for today. I want to thank the Committee members, the organizational representatives, the families who presented, and additional individuals who presented for -- in the public comment section, and all of our presenters, who really did an excellent job in informing the

Committee and helped form the approach for discussion, and -- and I believe a number of important things were discussed today that we could potentially move forward on in an effective way. So, again, I want to thank everybody. I want to thank the people here at HRSA who have made this work so well, both for the structure of the meeting as well as the electronics. And so, thank you all for your participation. We look forward to having an in-person meeting in May. Thank you, all.

FEMALE SPEAKER: Thank you.

MALE SPEAKER: Thanks, everyone. Bye-bye.

(Whereupon, the above-entitled matter was concluded at 3:26 p.m.)