U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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DISCRETIONARY ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

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MEETING

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FRIDAY
FEBRUARY 13, 2015

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The Advisory Committee met in the Terrace Level Conference Room, 5635 Fishers Lane, Rockville, Maryland, at 9:00 a.m., Joseph A. Bocchini, M.D., Chair, presiding.

MEMBERS PRESENT:

JOSEPH A. BOCCHINI, JR., M.D., Chair, Professor and Chairman, Department of Pediatrics, Louisiana State University Health Sciences Center in Shreveport
DON BAILEY, Ph.D., M.Ed., Distinguished Fellow, Early Childhood Development, RTI International
JEFFREY BOTKIN, M.D., M.P.H., Professor of Pediatrics and Medical Ethics, Associate Vice President for Research, University of Utah
CHARLES HOMER, M.D., M.P.H., Chief Executive Officer and President, National Initiative for Children's Healthcare Quality
FRED LOREY, Ph.D., Genetic Disease Screening Program, California Department of Public Health

DIETRICH MATERN, M.D., Ph.D., Professor of Laboratory Medicine, Medical Genetics and Pediatrics, Mayo Clinic
STEPHEN McDONOUGH, M.D., Sanford Health Bismarck
ALEXIS THOMPSON, M.D., Division of Hematology/Oncology, Children's Memorial Hospital (via telephone)
CATHERINE A.L. WICKLUND, M.S., C.G.C., Northwestern University Feinberg School of Medicine, Center for Genetic Medicine
ANDREA M. WILLIAMS, B.A., The Children's Sickle Cell Foundation, Inc.

EX OFFICIO MEMBERS:

COLEEN A. BOYLE, Ph.D., M.S., Director, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (CDC)
KELLIE B. KELM, Ph.D., Chief, Cardio-Renal Diagnostic Devices Branch, Division of Chemistry and Toxicology Devices, Office of In Vitro Diagnostic Devices Evaluation & Safety, Food and Drug Administration (FDA)
MICHAEL LU, M.D., M.P.H., Associate Administrator, Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA)
IRIS R. MABRY-HERNANDEZ, M.D., M.P.H., Medical Officer, Center for Evidence and Practice Improvement, Agency for Healthcare Research and Quality (AHRQ)
MELISSA PARISI, M.D., Ph.D., Chief, Intellectual and Developmental Disabilities Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH)

DESIGNATED FEDERAL OFFICIAL:

DEBI SARKAR, M.P.H., Health Resources and Services Administration, Genetic Services

Branch, Maternal and Child Health Bureau

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P-R-O-C-E-E-D-I-N-G-S

(9:05 a.m.)

CHAIR BOCCHINI: Thank you. Good morning, everyone. Welcome to Day 2 of the -- our Discretionary Committee's meeting.

I guess that was the first warning that I need to have the microphone near my face.

So we're starting day 2, but I think for Committee members and organizational representatives you found some beads on your desk. I think although this is not New Orleans, it's not Louisiana -- the weather is better there, it's warmer, and it is Mardi Gras weekend. So just want everybody to have a little taste of some Mardi Gras beads and to recognize that this is our count of significant celebration, and for many in New Orleans it has been going on for at least a month. So it's a little touch of Shrove Tuesday and all the celebrations leading up to it.

So our first item of business is roll call, so I'll call for the Committee members first, and then the organizational representatives. So

Don Bailey?

MEMBER BAILEY: Yes.

CHAIR BOCCHINI: I'm here. Jeff Botkin?

MEMBER BOTKIN: Here.

CHAIR BOCCHINI: Coleen Boyle?

MEMBER BOYLE: I'm here.

CHAIR BOCCHINI: Iris Mabry-Hernandez is representing AHRQ today. Not here yet. Charlie Homer? Fred. Michael Lu?

MEMBER LU: Here.

CHAIR BOCCHINI: Steve McDonough?

MEMBER McDONOUGH: Nice to be experiencing North Dakota spring-like weather today, here.

(Laughter)

CHAIR BOCCHINI: So this is your spring holiday? Dieter Matern?

MEMBER MATERN: Same here.

CHAIR BOCCHINI: Alexis Thompson?

MEMBER THOMPSON: I'm here.

CHAIR BOCCHINI: Okay. Thank you.

Cathy Wicklund?

MEMBER WICKLUND: Here.

CHAIR BOCCHINI: Andrea Williams?

MEMBER WILLIAMS: Here.

CHAIR BOCCHINI: And Debi Sarkar?

MS. SARKAR: Here.

CHAIR BOCCHINI: Okay.

MEMBER PARISI: You skipped NIH. I'm here, though. Melissa Parisi.

CHAIR BOCCHINI: All right. And so the organizational representatives, Freddie Chen?

DR. CHEN: Here.

CHAIR BOCCHINI: Beth Tarini?

DR. TARINI: Here.

CHAIR BOCCHINI: Michael Watson, Nancy Rose, Debbie Badawi.

DR. BADAWI: Here.

CHAIR BOCCHINI: Susan Tanksley.

DR. TANKSLEY: Here.

CHAIR BOCCHINI: Chris Kus, Adam Kannis?

DR. KANNIS: Here.

CHAIR BOCCHINI: Natasha Bonhomme?

MS. BONHOMME: Here.

CHAIR BOCCHINI: Siobhan Dolan?

MS. DOLAN: Here.

CHAIR BOCCHINI: Cate Walsh Vockley?

MS. VOCKLEY: Here.

CHAIR BOCCHINI: And Carol Greene. Okay.

All right. So the first item on our agenda today is public comments. After that, we're going to act on the motion that was left open yesterday, and then we'll do the final condition review for MPS I.

So first public comment on the telephone is Jenny Bailey, a parent representing families of children with congenital CMV infection. Operator, can you open Ms. Bailey's phone line?

MS. BAILEY: Hello?

CHAIR BOCCHINI: Hi. Ms. Bailey?

MS. BAILEY: Yes. Should I proceed with my remarks?

CHAIR BOCCHINI: Yes, please do.

MS. BAILEY: Okay. Chairman Bocchini, Committee members, and all, thank you for the opportunity to speak, and thank you for your service in the cause of protecting babies.

My name is Jenny Bailey, and I am a CMV mom here to speak about cytomegalovirus. Please see the written comments I submitted and those of two other CMV moms.

CMV is the most common congenital infection in the United States causing death in approximately 400 infants and permanent disabilities in approximately 8,000 newborns every year. According to the CDC, CMV causes one child to become disabled every hour in the United States.

There was a lot of discussion and action on timeliness yesterday, and time is of the essence in distinguishing between a congenital CMV infection and a CMV infection acquired after birth. If a newborn is not tested at birth, the only option is to retrieve the newborn blood spot from the state lab, if it has not already been destroyed, and have

that tested.

Medical practitioners often lack basic CMV prevention, diagnosis, and treatment knowledge. Hearing loss and other disabilities caused by CCMV are often late onset. Families experience traumatic and expensive diagnostic odysseys while CCMV continues to harm their babies. While CCMV is not rare, timely diagnosis and intervention are rare.

My family is one of the fortunate ones. My daughter Caroline is a 24-year-old symptomatic CMV survivor diagnosed in utero and treated at birth a quarter century ago with ganciclovir, which is now in the Red Book. Caroline wrote last year, the drug stopped the virus in its tracks. My parents could have -- my life could have been so different. I could have had all sorts of mental and physical disabilities like so many other babies born with CMV. Instead, I was left with only profound deafness as a marker of what I and my family went through.

I commend the Committee for adopting

recommendations on shortening the time between a baby's birth and when that baby's screening results are returned. Your action yesterday will save lives. I am also encouraged that the timeliness of condition review is being addressed with the new nine-month window.

In 2004, when the screening panel was devised by a contractor, ACMG, and all but two of the core conditions on the current RUSP were chosen, CMV was deferred for inclusion in the panel. The contractor deferred decision-making because they lacked expertise to address infectious diseases, and I commend ACMG for being honest with the Committee about that.

According to minutes from 2004, quote, Dr. Watson indicated this Committee may need to discuss how to address the inclusion of infectious diseases in a newborn screening panel. After more than a decade, it is long past time to move congenital CMV from the deferred category to inclusion on the RUSP as a core condition, and I respectfully ask the Committee to do that

immediately.

This Committee has tremendous power. Even though the Secretary did not adopt any condition for the RUSP until 2010, states and the medical community acted on the Committee's recommendation from as early as 2004. Absence of CMV from the RUSP creates the perception that CMV is not a common and devastating congenital illness that it in fact is.

Immediate inclusion of CMV on the RUSP will save lives and abilities of babies and signal obstetricians that the prevention message for pregnant women is imperative also.

Please help us. I sincerely thank you for your consideration.

CHAIR BOCCHINI: Ms. Bailey, thank you for your comments. As you are probably aware, there is a very specific way to bring a condition to nomination to this Committee, and I certainly would like you to contact HRSA and become familiar with the process, so that you can consider what needs to be put together to bring congenital CMV

infection to the Committee.

Thank you for your comments.

MS. BAILEY: Okay. Thank you. And that needs to be done even though the CMV was considered when the original RUSP was devised and it has been deferred?

CHAIR BOCCHINI: Yes, that's correct. And I think there is -- a number of things, obviously, have happened in that timeframe that studies conducted in terms of treatment, and studies conducted in terms of identifying the infection through blood spots or through saliva, and I think as a result of that a packet would need to be put together to provide that information to see if the data that is available meets the standard for review by the Committee.

MS. BAILEY: Is it possible for the Committee to issue a letter noting that CMV has been deferred for all these years? Because the perception is out there that -- because it's not on the RUSP it was not worthy of being on the RUSP. And that affects both pediatricians and frontline

obstetricians and general practitioners who don't warn women about the simple precautionary hygienic measures they can take to prevent the disease.

And also, when states are asking for new -- for CMV to be screened for at the state level, there is pushback from some organizations because CMV is not on the RUSP. And I just believe that this -- that -- I know this happened a long time ago, and there were different members of the Committee, but I feel like there should have been a contract taken out with infectious disease experts, so CMV and those other infectious diseases could have had a fair hearing at that time.

So I really believe that this is a special situation, that if the Committee with its tremendous power and influence could issue a statement of some sort immediately to signal the importance of this illness.

CHAIR BOCCHINI: Well, there's no question that this is an important illness and it is common. As you indicated, it is the most common congenital infection in infants born in the United

States, so it is an important topic.

And I think beyond the -- your initial comments, I think we need more opportunity to discuss issues with you and the current practice of the Committee in terms of bringing conditions forward. So we are more than happy to do that and can certainly do that following the completion of this meeting.

MS. BAILEY: Okay. And you referred me to HRSA?

CHAIR BOCCHINI: Well, we do have your contact, so is there --

MS. SARKAR: This is Debi Sarkar from HRSA. I have your contact information, and I will follow up with you after the meeting.

MS. BAILEY: Great. Thank you so much, and I really do appreciate all the time that the Committee members donate to the cause, and I know there are so many conditions that babies need to be saved from. And I just -- I am very fortunate that our daughter got this fantastic treatment a quarter century ago, and it is just heartbreaking

to see babies slowly waste away because they don't have the opportunity for diagnosis and early intervention in whatever form that may be.

So thank you so much for your time and your service.

CHAIR BOCCHINI: Okay. Well, thank you for your comments.

All right. Next, we have two individuals who are here in the meeting. The first is Mr. Steve Holland, as a parent, and he is representing MPS I families and the National MPS Society. Mr. Holland?

MR. HOLLAND: Hello? Okay. My name is Stephen Holland, and I'm the President Emeritus and a current Board member of the National MPS Society. And I'm here today representing 800 families touched by MPS and related diseases. I am also the father of three MPS I children, Spencer, Maddie, and Lanie. My son Spencer passed away seven years ago at the age of 18. My daughters Maddie and Lanie are 23 and 21 years of age, who live with my wife and I in Fort Worth, Texas.

While several MPS I parents wanted to speak on this very important topic, we were asked to consolidate our comments into one. So I reached out to other MPS I parents and have incorporated their comments into mine.

I stood before you two years, nine months ago, when my family -- with my family before you voted to move MPS I to the evidence-based review phase and explained the importance of your pending vote. I recall how excited we all were to hear your positive vote and dream about newborn screening becoming a reality in the relatively near future.

It has been sobering to wait two years, nine months for today's vote. The good thing about waiting such a long time is that I know you have had plenty of time to thoroughly review the evidence and to be able to conclude with confidence why it is of critical importance to move forward with a positive vote today.

I know you have thoroughly considered the science and facts and figures about the disease, so I don't feel compelled to repeat those

details here. I just feel the need to present the parents' perspective on newborn screening for MPS I.

Once your child receives a diagnosis like MPS I, a parent feels an overwhelming desire to make things right by that child, to create as equal of a playing field in life as possible for that child who obviously was born with a huge disadvantage of having a terminal genetic syndrome through no fault of their own.

One of the most important ways of doing that is by providing them with a medical treatment that will help prevent further damage by their condition and help sustain their life, whether that be stem cell transplant or weekly enzyme replacement therapy. The problem is that we, as parents, cannot begin these treatments until we know they have the disease. It often takes many months and sometimes even years between noticing there is a problem to getting a diagnosis.

During this diagnostic odyssey, irreparable harm is being done to our children that

a future treatment will not be able to reverse. This delay in diagnosis and treatment often creates parental guilt and regret for not following up sooner on these problems or for not forcing their pediatricians to follow up on these early symptoms when the pediatrician dismisses the parental concerns as complaints of an overbearing and overzealous parent.

Once it is too late, parents realize that they lost those precious time when early treatments could have forever changed their children's long-term clinical outcomes. However, with newborn screening, all of this regret, guilt, and conflict with the medical community over delayed diagnosis is eliminated.

Treatment by stem cell transplant, enzyme replacement therapy, or whatever new treatments are just around the corner can start immediately. The evidence conclusively shows that the long-term, clinical, life-limiting, and life-ending effects of MPS I can virtually be eliminated with early treatment. How huge is

that?

Early treatment gives that child the level playing field that we as parents so desperately desire and for which our children so decidedly deserve.

Now, I understand there are concerns over false positives and the resulting parental anxiety they can create. However, such anxiety is short-lived as compared to the permanent damage caused by the untreated disease in the months and often years following birth.

I predict that the recipients of false positives barely remember the event a few years following the birth of a healthy child. I know that parents dealing with a delayed diagnosis and treatment remember it and live with it for a lifetime. What would my child be like if he or she had only received treatments since birth?

Another important benefit from newborn screening would be reducing the births of affected siblings. In my family, all three of our children were affected even though those odds were one out

of four with each birth. Because our kids were born close together, and had an attenuated form of the disease, we didn't realize there was a problem while we were having children. If newborn screening had indicated my son had MPS I, we would have used the benefits of genetic counseling to prevent my daughters from also being affected.

We know many families with more than one affected child who indicate they would have done the same thing, reducing the overall prevalence of the disease and the resulting demands on society in general and on the family specifically. So, in a nutshell, it just comes down to time and options.

We are all blessed to live in the greatest country in the world where we have the ability to prevent most, if not all, of the permanent damage caused by MPS I, by providing parents with treatment options at birth. So let's just do that.

My family and I, along with other MPS families, thank you for your service today and for this opportunity to speak on this very important

subject.

CHAIR BOCCHINI: Thank you very much for your comments and for representing other parents of children with MPS I. Thank you very much. Appreciate it.

Next, we have Mr. Bill Morris, who wants to discuss education on newborn screening. Mr. Morris?

MR. MORRIS: Good morning. Thank you, Dr. Bocchini. I stand before you. Many of you know me and have heard my story before, but I'm going to go ahead and cover it real quick again.

My name is Bill Morris, and I'm the father of four boys, two of which are affected by two separate genetic recessive disorders. My 15-year-old son Seth was diagnosed in 1999 with phenylketonuria. He is a totally normal and healthy, happy 15-year-old who lives to drive the hair off of my head.

And then, in 2007, the youngest of my four boys, Grayson, was born with Krabbe disease. We lost him a week before his first birthday. So

I have both sides of the coin. I have experienced the joy and the lifesaving interventions of newborn screening and also the heartbreak of a lack of understanding the full availability of supplemental newborn screening.

I want to congratulate all the work that this body and its subcommittees have done on the advancement of newborn screening to date. I do want to remind all of us about the elephant in the room. There is a chronic lack of grassroots education of not only new expectant parents but also health care providers. All of us attending know the importance of newborn screening, but for the most part only those parents and clinicians directly affected by or know a child touched by a disorder through identification or lack of identification of that disorder have any knowledge of the existence of newborn screening.

This body suggested in 2010 that education should happen during the prenatal period. Some work has been done, wonderful websites created and added to, organizations

created, but I can tell you through work with my education foundation in memory of my son Grayson, only parents that hear the term "newborn screening" search out these websites. The majority of parents aren't hearing about it.

I suggest that more should be done through the Education and Training Subcommittee to strategize around this issue, and I strongly caution against removing this important subcommittee in the restructuring during the transition back to the SACHDNC.

My suggestion of a possible way of dealing with this issue is a possible partnership with the many eager advocacy parent groups and the SACHDNC to develop an organized, uniform education plan. I can testify to the fact that there is no one more passionate about newborn screening education than those parents that have been affected by it. Together we can save lives and prevent injury in children.

Thank you very much.

CHAIR BOCCHINI: Thank you, Mr.

Morris, for your comments. And thank you for your continuing contributions to the Education and Training Subcommittee. We appreciate your work.

Thank you.

Next item, we are going to put up a slide that has the language of Steve McDonough's motion yesterday, and we have modified it to be sure that it represents the roll of the Committee and the recommendations that we can make as a Committee.

So next slide.

These are the -- this was the -- what we divided as the second motion, and it has the substance that was in Steve's motion. But the language has been modified to -- as I mentioned, to meet the requirements of how the Committee can move forward with recommendations or suggestions rather than requirements.

So here is the motion as it stands, and after I read it I'll ask Steve to concur, and then Don, who seconded the motion, as well.

So the Committee encourages states to track their progress, and this is a -- would be in

the letter to the Secretary. The Committee encourages states to track their progress in achieving each recommendation and supports strategies that show progress in a transparent way.

In order to support states with limited budgets, the Committee also encourages the Secretary to develop a grant program to further assist states in meeting the Committee's recommendations. And, third, the states are encouraged to have 95 percent or more of newborns meeting the timeliness goals by 2017 and to communicate their progress to a national data resource to be determined by DHHS.

So, first, to Dr. McDonough.

MEMBER McDONOUGH: Yes, that's great. Thanks.

CHAIR BOCCHINI: Thank you, Steve.

And then Don.

MEMBER BAILEY: Yes. So I still second this.

CHAIR BOCCHINI: Okay. Good. So now it's open for discussion. Andrea?

MEMBER WILLIAMS: So I thought Dieter had -- I thought you had added something to this regarding the laboratory reporting. Did you still want that in there?

MEMBER MATERN: I think it's probably captured in the progress in a transparent way, which doesn't specify anymore what is actually being communicated to the public or anyone else. I guess that is the lingo that is used.

What I wonder, though, is about the second one about grant programs. Grant programs are, as far as I know, or in my experience, time-limited. And I think what we uncovered is that laboratories have to be open over the weekend, and samples have to be submitted overnight. So if you give a grant for five years, that's nice for five years, but what are they supposed to do afterwards?

CHAIR BOCCHINI: Cathy, and then Charlie?

MEMBER WICKLUND: Yes. This is Cathy Wicklund, and I guess -- I wonder how this is going

to affect the states that really have a geographical issue. And I don't know if money and -- can overcome some of the obstacles that they have in trying to get samples to a laboratory, if there truly is a geographical problem. And so I guess -- I don't know -- are we setting those states up to just fail? They will -- I'm just -- I mean -- I'm concerned about that.

CHAIR BOCCHINI: Charlie?

MEMBER HOMER: A couple of things. I guess to the latter point, I feel like our previous statement about timelines stands. So, you know, there are challenges with distance, but our Committee feels that the dates -- the times are the standards, and that we need to have them met. So I'm very comfortable with that.

I guess I wonder if we can make this a little stronger, and I don't know about it, but, for example, there is I believe -- I don't have the right language, but it's even called for in the legislation, the Interagency Task Force on Newborn Screening. I think we could ask the Secretary to

convene that group and charge that group with identifying a variety of mechanisms that the Federal Government could use to -- I mean, it's a little bit on -- it's a little stronger.

It says, you know, progress through national research to be determined by DHHS. I mean, I think it could be a little more directive of saying, you know, convene the interagency task force. Charge them with identifying appropriate vehicles to both encourage -- you know, encourage public reporting. So there are a variety of things like that.

I also think -- the grants to me is more about technical assistance in -- you know, this is a classic problem of flow. This is something that, for example, a lean consultant would love to go out to each of these states and help them look at issues related to flow and those kind of things. So that's the kind of technical assistance that I would see a grant program do as opposed to ongoing maintenance of the states' infrastructure, which is not -- so, anyway, I know we have to vote. There

is a motion on the floor.

I'm not proposing -- I don't have specific language for an amendment, so I'm not sure from a process. But it would be -- maybe the specific language is, convene and charge the interagency task force with developing mechanisms to both encourage and support state action consistent with these goals.

CHAIR BOCCHINI: Okay. Well, before we go to -- we need to kind of go around the table a bit. So let's follow up on Charlie's comment about whether the kind of changes that he is -- that he is proposing strengthen the recommendation and provide more direction to the Secretary and a better mechanism for solving a problem.

So how do people feel about that? And, Steve, of course, as well, defining better -- any comments related to that? And then we'll get to the others. So Melissa first, and then Jeff.

MEMBER PARISI: This is Melissa Parisi. I guess my concern is it's a little prescriptive to say a grant program specifically,

because I don't think any of us knows right now, as Charlie mentions, what the best strategies are to encourage states to be able to comply with these recommendations. So --

CHAIR BOCCHINI: Go right ahead. Sorry.

MEMBER PARISI: So I was just saying that I feel a little concerned about the second recommendation about a grant program because that's very -- relatively specific and may not necessarily meet the needs of trying to provide assistance. I don't know whether invoking the ICC is a better strategy or not, but it's a consideration.

And I also just want to say that, you know, having had experience in trying to provide genetic services to some of the more remote regions of Alaska and some other states where there are geographic limitations, I sort of echo what Cathy has said about setting them -- some of those states and some of those programs up for failure if they are unable to comply because of some very real

barriers.

CHAIR BOCCHINI: Jeff?

MEMBER BOTKIN: Yes. This is Jeff Botkin. I certainly support the intent and most of the language here. I would say we just had a Utah Advisory Committee meeting a week or so ago, and I was very impressed to see what folks in Utah have done. And I think they have been called out for some significant progress here. And Utah, remarkably, is one of the most urban states in the country. They've got everybody living in the urban area and then the rest of it is practically frontier.

So there is a lot of small hospital and birthing centers, and the hospital association has just been very active in picking up -- this up as a priority and made the resources available to start mailing things in a prompt manner without the batching. And so the costs were covered in some fashion that I couldn't describe to you, but without the need for federal grants.

So there may be mechanisms here that can

fund this sort of activity short of additional federal dollars, because probably the other thing that seems evident to me is so frequently with the kit fee, which is how most programs are funded, there is always talk about, you know, incremental dollars for new tests, but relatively rarely are there incremental dollars for patient education or other sorts of infrastructure things. And newborn screening is just a tremendous deal with the amount of money per kit fee.

So there may -- but the point is there may be other mechanisms that would be more state-centric to cover the cost of a more efficient system.

CHAIR BOCCHINI: Andrea, and then Don.

MEMBER WILLIAMS: So I just also wanted to -- maybe you could explain this, about what the limited budget is, because most states would argue that they have a limited budget. So maybe that part doesn't need to be in there, and maybe we can just say, develop a mechanism to further assist. Maybe that helps the language.

CHAIR BOCCHINI: Don?

MEMBER BAILEY: This is Don Bailey. This is, in essence, what I was going to recommend. So the second bullet we could just say, the Committee encourages the Secretary to develop a comprehensive program to support states in meeting the Committee's recommendation. That doesn't limit it just to grants, but it's very clear that we want -- that we need to support all states and it's not -- as you were saying, not just the limited one. So maybe just to further suggest that as a possible wording.

CHAIR BOCCHINI: And that does expand from funding to technical assistance, as Charlie indicated, and so that would be potentially beneficial. So --

MEMBER McDONOUGH: Yes. I support that change to the language in paragraph 2.

CHAIR BOCCHINI: Okay. So we have the -- so the language is, in order to support states, the Committee also encourages the Secretary to develop a comprehensive program to further assist

states in meeting the Committee's recommendations.

Okay. All right. Other comments from -- thank you. Great. So Carol, and then who? Okay. Go ahead.

DR. GREENE: Well, it was beautifully done. My comment is actually grammatical. For Bullet 1, I think that there is a problem with it. I think the intent is to say, you are not achieving support strategies that show progress. So if you parse it, I think the intent is to say, to track their progress in achieving each recommendation in implementing support strategies. And then there needs to be -- there needs to be some commas. And, anyway, there is a grammatical problem with the first sentence.

DR. TARINI: Regarding the Committee discussion on grant programs, I want to draw the Committee's attention to the recent grant notice from HRSA, 15-098, Improving the Timeliness of Newborn Screening Diagnosis, which is a $1.8 million program that -- because the Secretary may come back with this. The purpose of this

initiative is to improve the time and diagnosis and treatment for babies undergoing newborn screening.

The initiative will fund one organization to facilitate and coordinate collaborative learning in QI activities by newborn screening programs using strategies that improve newborn screening timeliness. So I think we should be aware of that as we prepare this recommendation.

CHAIR BOCCHINI: All right. Any other comments or -- hearing none, then let's proceed with the vote. And so the vote for this is to -- you know, to accept these additions to the recommendations, so that they would be included in the letter to the Secretary.

So in deference to Don, we're going to start on the -- alphabetically with Andrea Williams and move up. So, Andrea?

MEMBER WILLIAMS: Approve.

CHAIR BOCCHINI: Approve. Okay. Cathy Wicklund?

MEMBER WICKLUND: Approve.

CHAIR BOCCHINI: Alexis Thompson?

MEMBER THOMPSON: I approve.

CHAIR BOCCHINI: Melissa Parisi?

MEMBER PARISI: Approve.

CHAIR BOCCHINI: Dieter Matern?

MEMBER MATERN: Approve.

CHAIR BOCCHINI: Steve McDonough?

MEMBER McDONOUGH: Aye.

CHAIR BOCCHINI: Michael Lu?

MEMBER LU: Approve.

CHAIR BOCCHINI: Fred Lorey?

MEMBER LOREY: Approve.

CHAIR BOCCHINI: Charlie Homer?

MEMBER HOMER: Approve.

CHAIR BOCCHINI: And Kellie Kelm has not yet arrived. Denise Dougherty? Well, I guess Iris is here for Denise.

MEMBER MABRY-HERNANDEZ: Approve.

CHAIR BOCCHINI: Coleen Boyle?

MEMBER BOYLE: Approve.

CHAIR BOCCHINI: Jeff Botkin?

MEMBER BOTKIN: Approve.

CHAIR BOCCHINI: I approve. And Don Bailey?

MEMBER BAILEY: Approve.

CHAIR BOCCHINI: All right. Thank you all very much. Appreciate that, and appreciate your input, Dr. McDonough.

All right. Next item of business is the beginning of our discussion on the final condition review of mucopolysaccharidosis I, MPS I. And we are first going to hear from Alex Kemper and the Condition Review Work Group presentation on their findings. This presentation will begin now. We will interrupt it at about 10:30 for a short break, and then we'll come back and have Alex complete the presentation with time for discussion, questions, and comments.

So, Alex.

DR. KEMPER: Thank you very much, Dr. Bocchini. And although you said I wouldn't be interrupted until later, I would encourage members of the Advisory Committee, if you -- if I hit a point where you need some clarification, to stop me,

because we're going to really be talking about a lot of information. And I want to make sure that this is as transparent and as understandable as possible.

So I'm very lucky to work with a large team of very bright and dedicated people whose names are listed here. And I'd also like to publicly thank Dr. Lam, who is listed here as the project leader, but has been really tremendous in helping put all of this together. And she was able to come to the meeting today.

I'm breaking the rule again. I'm like standing too close to the microphone, no matter how far away I go.

And I'd also like to thank Dr. Botkin and Dr. McDonough for their work in serving as the Committee representatives to the Condition Review Work Group for this project. And they will be making comments later to help guide the Advisory Committee through its decision-making process.

So my plan for the next little bit is to highlight key findings from the systematic

evidence review. There is a draft of the document from which this all comes in your briefing book, although I know it's quite thick. Next, we are going to describe the balance of benefit and harm based on findings from the systematic evidence review. This is work that is coordinated by Dr. Lisa Prosser at the University of Michigan. She was not able to be here today, and I'm going to be summarizing that work.

And then, finally, to summarize the capability of state newborn screening programs to offer comprehensive screening for MPS I. That's the so-called public health impact assessment, and Jelili Ojodu from APHL will be presenting that work.

So let's go ahead and begin to talk about MPS I. So as we have described to the Advisory Committee previously, it's an autosomal recessive lysosomal storage disorder caused by a deficiency of active IDUA enzyme. It a progressive, multi-system disorder.

Like most of the other conditions that

we evaluate it has variable clinical symptoms, and there is really a range or a continuum of disease severity, which I am going to be illustrating in a subsequent slide.

Now, there is this traditional classification where it could be broken down into the severity of the attenuated or the Hurler, Hurler-Scheie, or Scheie, but what I really want you to remember is that this is a continuum with overlap across.

Overall, the estimated incidence based on various studies that are out there implied that the overall incidence of all forms is somewhere between 0.54 and 1.15 per 100,000 individuals. So this is the slide that I was telling you about where I was going to describe the spectrum of disorder. There is the -- again, as I mentioned, the severe form and the attenuated form.

From the studies throughout there -- and, again, I'm going to be showing some of these in a little bit -- the severe form predominates. But even with the attenuated classification, there

is the Hurler-Scheie and the Scheie. The Hurler-Scheie, which is the more severely affected form, probably appears in a ratio of about two to one Hurler-Scheie to Scheie. So, again, the disease spectrum is skewed towards the more severe end of things.

The severe form has onset by the first year of life. It is rapidly progressive. It has multi-system organ involvement. But one of the key things is the significant involvement of the central nervous system, the CNS system, as opposed to the attenuated forms which have less CNS involvement.

The untreated to severe form has -- is associated with death in early childhood. And as you would expect from the name, the attenuated version or attenuated form has death later in life. It could be in the teens, the twenties, or later.

Again, when you talk to the experts, they do talk about these more effective Hurler-Scheie's that appear more like the Hurler's who can -- that can be associated with mortality

earlier in childhood.

Again, so I just want to make sure everyone is with me in terms of the nature of -- this is, you know, a continuous disease that is more weighted towards the severe form.

This slide describes the life course of individuals affected with MPS I that is drawn from the MPS I registry. This is a report from 2012, and you can see the numbers of individuals in the registry, you can see that the severely affected form, the Hurler syndrome, has onset around six months of life, with the median time of diagnosis during that first year, treatment initiation beginning about one and a half years of life, and then death around four years of life. And you can see how it changes as you go into the attenuated form.

There has been a more recent report from the MPS I registry that focused on the disease onset and diagnosis, and it is fairly similar to what was previously reported. They didn't update the issues in treatments or mortality in that report.

So with that background, in terms of the disease course, I'd like to now talk about screening. So screening is based on the detection of low IDUA enzyme activity in dried-blood spots. I'll tell you that there are competing methods of screening. There is a tandem mass spec approach that, you know, it can't be run at the same time as your traditional, you know, metabolic tandem mass spec that we have spoken about before, but really requires different instrumentation and some work that is done ahead of time. And some of that will come out a little bit later when Mr. Ojodu talks about the public health impact assessment.

But there are different protocols that are out there. There is one that is -- has a kit that is under review by the FDA, but there is also an approach that uses digital microfluidics, the so-called lab on the chip. There has been changes in the company that offers that. It is now Baebies with the -- with that mysterious E in it. Guess Babies without an E was taken.

So in terms of establishing the MPS I

diagnosis, it follows an algorithm. So, first, one needs to confirm that the IDUA enzyme activity is actually low, and that could be measured in a variety of sources but typically in blood. And the IDUA enzyme activity with MPS I is less than one percent of normal.

But the enzyme activity alone doesn't predict the phenotype. So in terms of the evaluation, there is a pseudodeficiency, and so the -- in addition to measuring the IDUA enzyme activity, one needs to look at glocosaminoglycans in the urine. Okay? If the so-called GAGs are normal, then that suggests that the infant has pseudodeficiency. If the levels are elevated and there is a low IDUA enzyme activity level, then that means that the child is going to be affected.

At the same time the GAG levels are measured, it is typical that babies will get genotyped. And it can help predict the course if it reveals one of the known mutations. But there are many private mutations which makes prediction difficult.

And then, in addition to these laboratory tests, clinical assessment is used. And there are a variety of different signs or symptoms that you can find in infancy that would point you towards it being a severe cases versus one of the attenuated courses. And I'll show you how these numbers play out in a little bit in terms of where the uncertainty is.

So as I mentioned before, there are a lot of known mutations. There are more than 100 of them that have been described, but there are seven to nine commonly recurring mutations that can be associated with specific phenotypes. And those cover, you know, around 80 percent or so of the mutations.

So, you know, prediction can be made in those -- in most of the children with phenotype, and then that, combined with clinical findings, can help define what the next steps are in treatment.

As I mentioned before, there are these pseudodeficiency mutations. So, again, to remind you all, pseudodeficiency is not associated with

any disease. It's probably just an artifact of how the enzyme activity level is measured. But for all intents and purposes, these babies are going to go on and be fine.

When you look at the published literature, it suggests that pseudodeficiency is rare. However, it turns out that it's more common than was expected. And when we talk about the screening data that have come from Missouri, you'll see that. But it turns out that it's higher especially among African-Americans.

There is a lot of work going on in terms of genotype-phenotype correlation, especially in these private mutations, to be able to predict onset of disease. But, again, you know, this is a difficult thing to do, because the birth prevalence of the condition is one in 100,000. So it just takes a long time to accrue enough cases to be able to evaluate. And that's -- this challenge of the rarity of the disorder is going to come up again and again as I talk about the studies that have been done.

In terms of treatment strategies, as was mentioned earlier, there is really two things that are done. So stem cell transplantation is used for the severely affected individuals. It allows the production of endogenous enzyme, and that is particularly important because with enzyme replacement therapy, although that can be affected outside of the CNS, it doesn't cross the blood-brain barrier. So the idea with stem cell transplantation is you're able to get enzyme into the CNS.

So there are established guidelines for treatment with stem cell transplantation. So individuals with MPS I who are below the age of two with normal to moderate cognition -- so an IQ above 70, for example -- is what is often used. And that's because in some of the earlier studies children who were older than two or who had -- who were profoundly affected had poorer outcomes with transplantation.

There is some work being done where enzyme replacement therapy is combined with stem

cell transplantation as a bridge to when the individual begins to produce enough active enzyme. I'm going to be showing you one particular study that has been done that makes it seem like it's -- that's a very reasonable and good thing to do.

And then the other treatment, as I have alluded to, is the enzyme replacement therapy, which can potentially benefit all forms of the disease. It doesn't cross the blood-brain barrier, as I mentioned, so you can't just give an infusion and have it have a beneficial affect there.

There are reports of delivering enzyme replacement therapy intrathecally, so injecting it into the cerebral spinal fluid. But there is, you know, not sufficient evidence out there to really discuss it in a meaningful way, although it did seem like it was effective in terms of reducing the metabolites, the GAGs that you would expect to benefit in those cases.

So this is our -- you know, our typical slide that shows the flow of literature. We

restricted to studies that were published in 2003 and later, because that is when enzyme replacement therapy became available. And it's also when outcomes of transplantation began to appear to be, you know, much better as well.

The thing, though, is that even by restricting to studies that were published in 2003 and later, because there are so few -- you know, relatively so few cases, those same cases from earlier years were still reported. And you'll see that when I discuss some of the outcome studies, especially around the neurocognitive benefit of transplantation.

So unless anyone wants to discuss that, this slide in great detail, we ended up with 170 articles that were reviewed.

But, you know, these are active areas of investigation, and so we were lucky enough to be able to interview experts in the field whose names are listed here, had a number of different meetings, but to help inform the evidence review process as well as the modeling that Dr. Prosser

coordinated.

And, in addition, we held a number of expert interviews, either by telephone or by -- or getting written answers, including our very own Dr. Matern.

So moving back to the evidence review, what I'd like to do is just illustrate a typical flow for how newborn screening works. So the blood spot would go to the lab. The IDUA enzyme activity level would be measured, and it would either be low or within the normal range.

If it was in low, it could be repeated on that same dried-blood spot in duplicate or triplicate, depending upon how the specific newborn screening laboratory does things. For those babies that had low enzyme activity levels on repeat testing, would then go out for the confirmatory testing and -- or I should really say the diagnostic testing, which would include repeat measure of IDUA on a new sample looking at the GAG levels in the urine, and of course examining the baby and looking for any other signs of early onset

of MPS I. And then, while that is in process, also genotyping the sample to see if it was one of the new -- you know, a private mutation or one of the existing mutations.

So a lot of stuff sort of happens at once, but all of those pieces of data are needed to make an informed decision about whether or not the infant actually has MPS I as well as, you know, what the next approach to treatment would be.

So in terms of screening, the most informative data come from Missouri with their newborn screening pilot work, and so I'd like to thank the folk in Missouri for responding to our many, many phone calls and emails. I'm starting to wonder if they would, like, recognize my name on the phone and not answer me, but --

(Laughter)

DR. KEMPER: -- they were really, really quite helpful in understanding what is a very nuanced issue. So they began what they call a full population pilot screening. And so they are screening everyone, but the reason it's considered

pilot screening is that there are no live reports and whatever -- their information system. And so the data that I'm showing you are from January 2013 through December 2014.

They used the digital microfluidics approach that I discussed before. So they have screened about 150,000 newborns, and as was alluded to yesterday, there are always more samples than newborns because of, you know, additional samples being sent in for a variety of reasons. But what I would focus on is the 149,500 number.

Now, when they first began this project, they had a threshold set for positive, so that they wouldn't miss potential cases. And as a result, they had a lot of false positives because they are willing to accept false positives to make sure that they were sort of narrowing in on the right window for true cases.

Over time what they have done is they have dialed down the threshold to decrease false positives. So that's why there are two columns here. The first one is the actual, and then the

second is if you went back with what the current thresholds are what numbers you would get. So of those about 150,000 babies that were screened, there has been one case of confirmed MPS I, which was severe.

There were three carriers with the -- you know, before they dialed things down, too, with the current one. I'm just -- for ease of walking you through the slide, I'm just going to focus on where things are now -- 11 false positives, 21 cases of pseudodeficiency, there were seven cases that are still pending evaluation, and one that would -- that was lost to follow up.

There were 42 in-house repeats before things were repeated out, and I have the percentage there if you're interested in that. The overall false positive rate is about .03 percent. And because of all these cases with pseudodeficiency, and so forth, you can see that the overall positive predicted value is 2.4 percent.

Now -- yes?

MEMBER MATERN: Dieter Matern. Quick

question about the pending ones. You put them into the false positive rate at this point. What makes you do that?

DR. KEMPER: Let's see. Let me double check my math. You know, we could --

MEMBER MATERN: 21?

DR. KEMPER: Hold on. Let me just like -- it's always hard to redo my math sitting in front of you. But, yes, so they were in the false positive -- I mean, they were in the false positive group.

Is there anyone from Missouri here today? I'm looking around. I don't see Patrick Hopkins or Shirley here. So we could certainly take them out and it would look -- make things look higher. I mean, you know, lower.

MEMBER MATERN: I don't suggest you have to take them out. I just think you need to maybe explain what does it mean "pending"? How long are these patients hanging out there until they know whether they are affected or not?

DR. KEMPER: Yes. I can't answer that

question right now. I mean, because I don't know at what point those babies were identified through the screening.

Well, let me go through this and then we can try to resolve some of this, too. And I'm looking at K.K., too, if you know the answer to that off the top of your head. Come to the microphone.

DR. LAM: Hi. As far as I understand, when we followed up asking about the pendings, those were ones who -- they are just awaiting results from the -- at some stage of confirmation or kind of -- you know, of a -- they were repeated or recalled, and so they're at some stage of awaiting results that they are not able to give it a category so to speak.

I suspect that the -- I might have even done it, and I apologize, I might have accidentally included the pendings in the false positives. So I would take them out.

DR. KEMPER: Yes, yes.

DR. LAM: Because I think that's --

DR. KEMPER: I think that was just an

oversight when we were putting the slides together.

DR. LAM: Yes.

DR. KEMPER: But in terms of your question, in terms of how long it takes for those pendings to get resolved, too, I can't answer that question.

So moving along, we have data as well from Illinois, but they are really just in the start of their screening work. They are using a tandem mass spec system, but they have only screened about 17,000 children. They have not -- or newborns. They have not identified any cases yet.

And so I think this is helpful in the degree to which we can get a sense that the tandem mass spec could work as a high-throughput system for newborn screening. But I can't really comment on, you know, how this is going to play out in terms of cases detected, and so forth.

The one other study that I want to highlight is -- was done at the University of Washington, and it's screening based on essentially 100,000 anonymous dried-blood spots.

This is not the same as prospective screening with actual newborns, because, you know, there is no confirmation. Everything is based on genotype alone. But I thought for ease of this presentation that I would present these numbers here.

So using this tandem mass spec system, there were nine positive screens. There were three mutations that were consistent with MPS I , although they have gone back and reanalyzed those mutations and it could be that one of these three cases is actually pseudodeficiency; one carrier, too, that had problems because of the quality of the dried-blood spot; three with no identified nucleotide change.

And you can see that the positive predicted value here is about 33 percent, assuming that those three cases were all actually a case. So -- yes?

DR. TARINI: Beth Tarini, AAP. I may have missed it. Can you explain what pseudodeficiency is briefly? And is it ultimately categorized as a false positive, or is it -- like

how is that communicated? Maybe not how it's communicated to family, but like what bucket does it eventually go in?

DR. KEMPER: Yes. So I would consider pseudodeficiency to be false positive. So these babies, although it looks in the assay like they have low enzyme activity, they are, for all intents and purposes, fine. So it's an artifact of how it's measured, you know, something about the matrix or whatever. You know, people talk about the matrix, and I just started thinking about the movie. I mean, it goes sort of beyond my knowledge about lab stuff.

And, Dr. Matern, I don't know if you want to comment any more about why pseudodeficiency shows up, other than it just being an artifact.

MEMBER MATERN: I think you have explained it nicely.

DR. TARINI: So in all the calculations --

DR. KEMPER: Because they are false positives.

DR. TARINI: Okay.

DR. KEMPER: So this slide just summarizes the studies that I talked about before. Although you could adjust up the positive predicted value, it's still, you know, going to be low in Missouri if you take out those pendings.

And you can see the estimated incidence per 100,000 babies. There have also been studies done in Taiwan and in Italy, but they don't provide as much information. This is just what we've gotten from the Missouri pilot study. So for the purposes of this presentation, I'm not focusing on those.

So what I want to summarize from the screening side of things is that there are different methods for doing the screening. There is tandem mass spec, and there are multiple protocols for doing that. There is fluorometry, which is through using digital microfluidics. So, again, that is a different platform.

The screening algorithms are still in the process of being refined to balance case

detection versus issues of false positives, including pseudodeficiency. You know, one never knows about missed cases with screening, because it is just so hard to do that case ascertainment. But it's important to note that screening appears to identify a similar number of cases that you would expect through usual case detection.

And there are still challenges, some challenges, related to predicting the form at the time of initial diagnosis.

Now, what I'd like to do is talk about treatment outcomes. And ideally what we would do when we talk about treatment outcomes is compare what would happen through newborn screening versus what would happen through usual case detection, right? So the comparison isn't newborn screening versus never detected and never treated. It's newborn screening through what might happen with usual care.

So in this slide, I just summarize that we found 17 case series focusing on treatment reports; 16 of them based on stem cell transplant

with or without enzyme replacement therapy; and one which was enzyme replacement therapy overall -- I mean, alone.

And then this slide just shows you, if you look across those small case series, I'm going to show you some what I think are more reliable data in a little bit, but the survival rate across these studies is between 63 and 100 percent in the first year, and 53 to 100 percent five years later. Then, you could -- I just listed in parentheses -- I won't read this, but this is the -- kind of the Olympic model of throwing out the high and the low, just so you can get a sense of what a better estimate of the range might be.

And you can see that the range of the median ages of treatment went from about nine months to 35 months. And let me just -- I'm going to go ahead and show this, which I think is more informative. These are data from the MPS I registry that we were able to get. These data have not been published, and we've been asked by Genzyme not to distribute these numbers publicly.

Before I talk about the -- about this slide and these data, I want you to remember that the MPS I registry is a volunteer registry. They collect just a whole host of data about treatment and outcomes. But like all of these volunteer registries, they are -- you know, there is potential for misclassification and problems with validity in some of the data elements. And I think that is going to be especially more important when we talk about the issues of cognitive outcome.

So in the left two columns -- let's see if I can get -- okay. Here we go. Do this without my hand tremor hopefully making you queasy. This is treatment that began under eight months of age and treatment that began at eight months of age and older. This is -- we asked Genzyme to dichotomize by eight months because we thought through newborn screening, you know, it would be reasonable to expect that everything would be done and treatment would begin at eight months of age.

And remember that the babies -- or not the babies but the individuals that are appearing

in the MPS I registry are not being identified through screening. So if we, you know, made the number lower, there would be nobody in that bucket.

So this is less than eight months. This is eight months and older. And this is severe and this is attenuated. Okay? So you can see that -- and these are the 199 babies -- or 199 -- I keep saying "babies," but 199 individuals that got stem cell transplantation alone. And you can see that the five-year survival was 70 percent. Okay? And the five-year survival for those babies who began treatment at eight months or later was 74 percent.

So these numbers are similar here. If you look at -- this is severe cases who were treated with enzyme replacement therapy and stem cell transplant, 86 percent and 89 percent; and these are individuals who reported to have enzyme replacement therapy, 73 percent and 97 percent.

You know, it's hard for me to comment about the individuals, you know, less than eight months, for example, who got enzyme replacement therapy alone. And I think that, you know, this

is one of those things that makes me a little worried about misclassification within the MPS I registry. And of course there are a lot of other factors that are going on in terms of the year that they were diagnosed and -- you know, because certainly interventions like transplantation have gotten much better over time. And, again, I'm going to be showing you some other published studies in a little bit.

But certainly if you -- by drawing this line at eight months, it seems like the mortality within the first five years is similar for those who got stem cell transplant or enzyme replacement therapy within stem cell transplant.

Now, again, it would be nicer to dive into these numbers with, you know, greater detail and be able to do logistic regression analysis controlling for all such other confounders. But, again, look how small these numbers are, and it becomes really difficult to do that.

But the conclusion that I draw from this is it seems like within the early years of life stem

cell transplantation is not having a big effect on mortality. But it could have effects on other things, like neurocognitive outcomes, and that's really where we're going to be focusing in a little bit.

So I sort of alluded to this before, but if you look across -- oh, I'm sorry.

MEMBER PARISI: This is Melissa Parisi. You said neurocognitive outcomes, and I was just going to ask you whether the Genzyme data set had any information about neurocognitive outcomes or on relative physical disability.

DR. KEMPER: Yes. So they do collect data on those kinds of meaningful outcomes. The problem is from talking to the individuals that maintain the registry there is probably a lot of error in the database in terms of how those numbers are reported and what particular tests were used to evaluate things.

And I don't think -- and it was confirmed by some other people -- that those data are sufficiently valid or reliable enough to make

a meaningful decision. So we've had to look at other studies. I'm going to show you those other studies later.

But as the registry stands now, I feel uncomfortable drawing those kinds of conclusions from it. We have talked within the Condition Review Work Group of trying to tease things out by looking at, you know, other things that might have been going on to figure out, you know, what was a meaningful test and what wasn't. But at this point, and with the data we have, I just don't think that it can be counted on to give you that kind of meaningful information.

Is that -- I was pretty emphatic there. Usually I'm not that emphatic.

There are a lot of issues that affect survival outcomes that one would ideally want to control for. And so what we've done in this slide is just, you know, we looked across the slides that looked at event-free survival, so that's surviving and not being -- needing mechanical ventilation.

And I don't want to go through all these

individual slides of where the numbers come from, and so forth, but what I do want you to keep in mind is just how complicated it is figuring out these issues of whether or not early intervention affects mortality. So there is things like the age at transplant, there is the type of pre-transplant conditioning, so how the transplant was done, the interval between diagnosis and transplant, whether or not unmatched -- the donor was unmatched, and how sick the individual was at the time of transplant.

So, you know, not surprisingly, if you have pneumonia or some other, you know, respiratory insufficiency at the time you are transplanted, you are likely to do worse.

One of the issues that the experts brought up repeatedly on our calls was that transplantations got sufficiently good enough that one of the advantages of doing transplantation as young as possible is you're getting them before they've had a chance to develop these other comorbidities.

But it's because of all these factors and the small numbers it's hard for me to tease things apart and say definitely that based on the data we have that, you know, mortality is not affected by the age at transplantation, and it likely is. There is just a lot of confounding factors that are going on at once.

So now let's talk about issues of cognitive outcome. And, again, these are difficult studies to do and interpret because of the small numbers. But the first thing I want to show you is this nice study that was done taking advantage of a natural experiment where a treatment center went from providing only stem cell transplant to using both enzyme replacement and stem cell transplantation.

And they looked at using a standard nerve developmental battery at 12 and 24 months post-transplant. And if you look at -- I'm going to just go to the next slide, because I think it's easier just to look at the slides.

If you look at the black line, you can

see -- my little -- these were -- hold on. Now my little thing for the black line -- my little label.

The black line -- I want to make sure that I get this right into the -- because the slides got messed up when they got formatted here. K.K. is going to come rescue me because my legend disappeared.

DR. LAM: So the main two groups within intent to treat are the blue and the red, and then in the -- with the blue line being the group that got both, the transplants with ERT. And then the red line are those under the prior protocol.

DR. KEMPER: Oh, that's right. And then the black was none. Okay. And of course it's just right here on my slide.

DR. LAM: Yes. On the left they were two deaths --

DR. KEMPER: Right.

DR. LAM: -- in that group.

DR. KEMPER: So you can see that -- so this is the first -- this is a nice illustration, in fact, that both stem cell transplantation and

the stem cell transplantation with enzyme replacement therapy were beneficial over time in terms of preserving -- or not preserving but doing better with this early learning composite, which was a summary of the cognitive metrics.

And, you know, one of the things that makes things challenging is that both the treatment groups declined. Okay? So, but there was this kind of like stabilization, and certainly they did better than the other groups. You can see in these kind of light lines tracing the individual, so there is a fair amount of variability as well. And that's going to come out again in a different study in a second.

MEMBER BOYLE: Alex?

DR. KEMPER: Yes.

MEMBER BOYLE: Could you -- I still don't get the black line, but I get the other -- I get the blue and the red. What's the black?

DR. KEMPER: So this is the individuals who didn't get -- this is like the intention to treat kind of thing. So like the individuals that

-- Scott is raising his hand. Yes? Yes. My labeling -- I had a little block here of labeling that disappeared.

DR. GROSSE: The black line took the red line and just said those that died had a cognitive score of zero.

DR. KEMPER: Right. That's what I meant by the -- by keeping in everyone that you intended to treat.

DR. GROSSE: It's not a comparison.

DR. KEMPER: Yes.

DR. GROSSE: Did Nancy want -- or what is the n for each group?

DR. KEMPER: Yes. This -- so these are all small numbers. You can see that there were 9 individuals that had the enzyme replacement therapy and the stem cell transplantation, and then 10 that got the stem cell transplantation alone.

All right. And so this table just shows you the individual numbers, and I -- just because -- yes.

DR. TARINI: Beth Tarini, AAP. Do you

have any sense of the clinical significance of the difference of these cognitive domains, of that last one, what the difference of that --

DR. KEMPER: Yes. So, again, it is hard to say, you know, what --

DR. TARINI: Okay.

DR. KEMPER: -- the functional impact of these individuals were. I mean, and, again, you know, Dr. Bailey here is, you know, is an expert in these things. But, you know, typically if you, you know, consider a hundred to be a mean and there's, you know, about 15 points in terms of the standard deviation, you can see that -- and, again, it's hard because there are all of these different tests that are being used, none of which I'm an expert in, but you can see that, for example, at baseline they are already below what you would expect, you know, for the composite to be.

And the groups did go down a little bit, okay, so that's what -- you know, that's what you see here as well. But --

DR. TARINI: In that first line?

DR. KEMPER: Yes. So they -- you know, I can't -- so you can see here's the standard deviation. So, you know, there is significant overlap. I would -- I mean, when I look at these really small studies, it's hard to know even what is statistically -- like, you know, you --

DR. TARINI: Well, it's so small that -- the variance is so large.

DR. KEMPER: Right.

DR. TARINI: So you -- in fact, it may not -- it looks like it's not statistically significant.

DR. KEMPER: Yes. So if you look at -- look at the background lines, because that shows you, you know --

DR. TARINI: The variance.

DR. KEMPER: -- the individuals. There is another study that has more numbers that I think is going to be helpful for you. Yes?

DR. GREEN: They have our back. Because, again, I think that these graphs are often very influential, you know, in this mountain of

data. So just to repeat what you said, please, the black line, these are cognitive values.

DR. KEMPER: Yes. I -- so I misstated because my little thing disappeared. So this is including the individuals who died and, you know, who would be zeroes.

DR. GREEN: And that -- the n of that is two, you said?

DR. KEMPER: No.

DR. GREEN: No, no. The n -- how many died? Two died.

DR. KEMPER: Yes.

DR. GREEN: Okay.

DR. KEMPER: So -- and I think it's going to -- yes.

DR. LAM: Can I just interrupt very briefly? So the crux of -- that was reported in this article, which was by -- the study by Eisengart, Julie Eisengart, were that the -- you know, again, small n's, but there were -- it was a significantly less decline for those who -- I want to make sure I say it right -- for those who received

ERT with the transplant.

DR. KEMPER: Right. But --

DR. LAM: So a significantly less decline, and then -- on the overall scores, and then from that table one thing they were pointing out was that by the two-year mark, at least on the visual receptive domain, which is, you know, considered fairly important and related to later cognitive function and problem-solving, there was actually an increase. So the nature of the lines started to turn for those who received ERT. It's kind of a -- you know, some promising evidence, but, yes, a small study --

DR. KEMPER: Yes. So --

DR. LAM: -- and it ended at that point.

DR. KEMPER: Yes. So -- and I just want to emphasize again what K.K. just said, that we just had to take -- I mean, these numbers are all really, really, really small. And as I go through, you're going to see that there are some non-standardized ways of measuring things.

DR. TARINI: I just want to point out,

although they are small, that doesn't excuse the fact that there will be variance because they're small. Like because it's small, and if you don't find a statistically significant finding, that's because you have -- it's small and you have a large variance. Like that doesn't excuse the -- "well, I can't find statistical significance because I don't have enough numbers." That's actually potentially a problem, but you'll show us other studies.

DR. KEMPER: Well, I --

DR. TARINI: You can see trends --

DR. KEMPER: Right.

DR. TARINI: -- certainly.

DR. KEMPER: Right. So what -- you know, so I hate to use the word "trends," and I'm going to avoid doing that because, you know, "trends" suggests some difference over time versus trends like it didn't meet some, you know, arbitrary P value. So I'm just going to try to just show you what we have, you know, as the best we can.

You can tell that there has been a lot

of internal debate about how best to present these small numbers on cognitive outcome. And what I'd like the Committee to focus on is if you look across the body there seems to be promising evidence that early intervention is beneficial for cognitive outcomes. And there are a bunch of these like really small studies, and I'm just going to highlight the ones that are key.

But the problem that, you know, none of us are going to be able to overcome is because we're talking about one baby in 100,000, to be able to accrue enough cases to be able to do, you know, the kind of prospective study that we all like is just, you know -- would just take, you know, way too long.

So here is another study that just recently came out, this year as a matter of fact, that included severely affected MPS I patients. It included -- they were able to look at 217 affected infants or -- I keep saying infected infants, but infected individuals. The median age of transplant was 16 months, and they were able to look at follow-up up to a median age of 9.2, again,

with a big range. Okay?

So before I move over to the slides on the right, they do point out in this study that there was residual disease burden in most of the patients who were transplanted. So, again, we're talking mostly about cognitive function, but I do want people to remember that there are, you know, bony involvement like kyphosis, and there were some knee problems, and some babies still had -- or some infants still had corneal clouding after transplantation. So there is some other residual involvement in most of the children.

Now, prior to stem cell transplantation, the cognitive function for these infants was -- I'm sorry. If you -- I'm like looking at my lines here.

So these dark lines right here were -- see, all of my little notes disappeared as you can see here. But -- all right. So the bottom line for this is that the -- if your pre-stem cell transplantation cognitive function was over 85, and your transplant patient was less than 16 months

of age, you ended up having superior cognitive development post-transplantation. And that's what these darker lines up here are showing.

Now, the final study that I'd like to point out again was another study that recently came out by Poe and colleagues. And this looked at severe MPS I patients who had transplantation between 1997 and 2013, again, a wide age range. I didn't talk about -- the previous study included patients from the 1980s as a matter of fact who got transplantation.

And from this, they looked at a sample of 31 individuals who had a median transplantation age of about 14 months and were followed for a little over seven years. And they had a standardized battery that was done at baseline and every six to 12 months post-transplantation.

And -- oh, I'm like all excited because my little legend managed to survive this one. So if you -- and if you -- the dark line here where patients who were treated at a median age of four months, the yellow nine to 17 -- ranged in age from

nine to 17 months with a median age of 12 months, and then the red line were babies that were treated at a median age of 26 months, again, getting to Dr. Green's comment before, I want to make sure that you pay attention to the small numbers. So six, 17, and eight. Okay?

And this is broken down into four panels here. I'm showing cognitive skills, adapted behavior, receptive language, and expressive language. And this little blue spongy line here, or filled in area, shows range of normal.

So you can see that the babies who were given treatment at the youngest age in terms of their cognitive skills were on track, as one would expect, with normally developing infants. The babies who were treated at an older age were still within this range but not doing as well. And those infants who got treated later had -- were doing the worst in terms of cognitive skills. Okay?

Now, adaptive behavior -- again, these are non-standardized scores, and, fortunately, K.K. is a psychologist, so she can help us like work

through the specific instruments if you want to go that way. I'll tell you, it's always good to work with someone who is a psychologist as well when you're reading this many papers.

So the -- but look what happens here with adaptive behavior over time, but certainly the babies that are getting the earlier treatments are doing better. Okay? Receptive language and expressive language.

So the key things that I want you to take from this study are it does look like earlier treatment leads to better outcomes across these different scores. The numbers are really small, right, so they could be swayed. And that sort of gets to the comment that Dr. Tarini mentioned.

And as a matter of fact, you can see here the track that individuals took within the cognitive development. Actually, I think this slide to me was one of the most helpful in terms of even though there is this wide spread, you can see that the few cases of earlier treated, you know, were doing better than the yellows who are the later

treated, and then the reds who are the treated latest.

Now, again, I'm going to put up the caution flags because these are all small numbers, and I spoke about all of the confounders earlier. I think that a reasonable argument could be made, though, that earlier treatment leads to better neurocognitive outcome, but there are all these issues about who is included and what kind of therapy did they get, and so forth.

CHAIR BOCCHINI: Alex?

DR. KEMPER: Yes.

MEMBER BOTKIN: Yes. Jeff Botkin. I wonder if you could clarify the confounders a little bit more. So is it the case that kids would not be transplanted prior to the development of symptoms, so that you would want to know that -- sort of which general category of MPS I they had? And might it be likely that the kids transplanted at the youngest age would be biased towards the more severely affected kids, so that in fact better outcomes here might be that much more impressive

because of the negative bias, if you will, about early onset.

DR. KEMPER: So what you're getting -- there's a sort of spectrum bias where the babies that are being detected clinically, right, are the ones that are more likely to have more severe presentation. So there's this issue with the kind of transplant they got as well that I talked about before that could affect mortality. You know, who knows? It could affect this -- you know, these issues of cognitive development and the status that the babies were in at the time that they went to treatment.

And so, you know, these are all things that one would like to -- and, you know, some of these studies did try to, you know, use modeling to get to these points. But what I'm telling you is that like, you know, I think the arguments that early intervention affect cognitive development really come from two streams.

One is the -- you know, if you look at the natural history, there's significant and rapid

involvement of the CNS with severely affected cases. And so these are children that are on the, you know, downward curve in terms of what you would expect with their ultimate cognitive outcome. And if you can get them earlier, then you can preserve more of their cognitive outcome or put them on a different trajectory, so that, you know, they don't have that decline.

So they may not end up, you know, on the trajectory going back to normal, but you could preserve some of that neurocognitive, you know, status of where they would end up being.

Again -- I'll get to you in a second, Dr. Parisi, but it's just a matter of, you know, looking at what we'd expect in the natural history as well as these, you know, admittedly small studies.

Dr. Parisi?

MEMBER PARISI: Yes. Melissa Parisi. So this study and the prior study did not have a combination of enzyme replacement with transplantation, or is that not clear from --

DR. KEMPER: This is -- okay. I want to make sure that I don't misstate this, because --

DR. LAM: Can I interrupt just briefly? So this study was a little bit unique. I don't know offhand about the enzyme replacement, but --

DR. KEMPER: Yes. I don't think they mentioned it in their --

DR. LAM: Yes. What they talked about having -- right, because it was a relatively more recent study, and they were building on previous findings of one of the confounds about -- and they used -- so all of these patients had umbilical --

DR. KEMPER: Right.

DR. LAM: -- cord blood transplants, and they had the conditioning, like transplant conditioning regimen that had been also found to, you know, at least in some studies have a positive effect, and also these transplant prophylactic medications. So that was what -- it was trying to build on that. So within that group.

DR. KEMPER: And I will point out, so

this -- so what K.K. said is entirely correct in terms of, you know, trying to restrict to patients who, you know, got these specific therapies. But, you know, we all know that between '97 and 2013, you know, even within their treatment, you know, has gotten significantly better.

So, I mean -- yes, Dr. Greene?

DR. GREENE: So small numbers and also not terribly long follow up. And I know some of the follow up is nine years, which is great. I mean, the follow up is as long as it can be. And I want to preface this by saying we all know that there are advances coming, including things like gene therapy that is being worked on.

So slowing the progress of the disease, if you can keep somebody's function within the range of something that a child and a family will enjoy, and then hoping for something better, is what we end up talking about a lot in our clinics. But in addition to small numbers, what I think we don't know -- and we've seen this in other disorders -- and the second slide got a little bit more to

this, but the slide that just showed the -- a couple of slides back. So your develop -- your outcome is better two or three years later, but what's the trajectory? What is happening in the brain is something that I think we will need another 15 or 20 years to know.

That's what we found with cystinosis where when we did renal transplants and saved everybody's lives, and we know beyond a shadow of a certainty of doubt, because I was taught it as a fellow, this was the one -- one of the few lysosomal storage disorders that did not affect the brain. But once they survive their kidney transplant in their twenties and thirties, they actually have a progressive brain disease.

So what we don't know is whether we functionally converted MPS I severe form to basically Sanfilippo with a slow version. And I'm not saying that to be negative in the sense that that means we shouldn't go forward, because if we convert it to something slower and then we come up with better therapies, that still gives people a

chance. But I just want to say it's not just small numbers, it's in the context of how this disease -- these diseases work. It's a very short time.

DR. KEMPER: And, unfortunately, when we did our evidence review, we can't predict what the -- you know, what is coming out in the future, although maybe we'll budget for a crystal ball.

But I do think that the issue that you bring up -- and I think tangentially, again, I just want to raise this again is that, you know, these infants did develop other, you know, systemic problems associated with MPS I , so it didn't -- the transplant didn't completely resolve, you know, the other organ involvement associated with MPS I .

Now, I think Dr. Grosse probably has some comments on the neurocognitive outcomes. He has done a lot of work on that.

DR. GROSSE: Just to clarify the ERT. I talked -- asked Dr. Escolar, the senior author of the Poe, et al. study, and ERT was not part of their protocol. As far as I'm aware, the Eisengart

study is the only study that has looked at ERT.

DR. KEMPER: Yes. So the Eisengart was the one, like, natural history study where they did that. I didn't -- I mean, I can't -- I don't know beyond what you just said about the ERT and the Escolar study. So I guess, Dr. Boyle, and then back to --

MEMBER BOYLE: Just to follow up on Dr. Botkin's -- everybody is doctor around the table here -- and that is on the Poe study, and it says in the discussion that family history actually contributed to the identification of asymptomatic individuals who were treated. So some of those treated early were actually based on family history. So that would work in the opposite direction of what you were saying.

DR. KEMPER: Yes. It's just so hard, because they're inconsistent in how they report where cases came from.

Can I make another point? You reminded, Dr. Boyle, and I should have said this earlier, one of the challenges that I have in

interpreting these data is because it's such a rare disorder and so much stuff comes from either the same treatment centers or the MPS I registry that we talked about before, I have no doubt that some of the same individuals are coming up over and over and over again in different studies. And we are just talking about them repeatedly.

It would be nice if we could disentangle that, but it's just -- just impossible. But you know based on the prevalence of the disorder it has to be that we're talking about the same babies multiple times.

Dr. Tarini?

DR. TARINI: That was my point.

DR. KEMPER: Which one, about the -- oh, the family?

DR. TARINI: That the bias can be in the other direction.

DR. KEMPER: Yes, yes. I just don't -- again, I want to be very cautious in how I present this. But I think from a biological standpoint you could make a good argument that early intervention

is going to help preserve neurocognitive outcome. And I think that with all the flaws in these studies I think that, you know, there is an argument that can be made. The challenge is going to be of course to the degree to which you feel certain about this.

Let's see. Oh, so I just want to just finish highlighting some of this, although these came out -- up in our Q&A session here, which is that recent advances do seem to improve survival. And certainly if you look at what has happened with the more recent transplants compared to the older transplants, it does look like they've gotten better. And, you know, for those of you who are clinicians and deal with this, I think you would agree with that.

But it does look like just relying on things like the registry that in these early years that we're looking, it's not the mortality effect, and who knows what is going to happen later. And sort of Dr. Greene was getting into this a little bit as well.

The other thing is we, you know, don't

have any evidence regarding transplantation in completely asymptomatic infants, and those -- because, you know, moving to transplantation is associated with finding any, you know, sign or symptom associated with MPS I . We're just a little bit limited in that, although I'm using air quotes here for the asymptomatic. Or actually I'm using physical quotes, because you can see them, around asymptomatic.

It does look like from the Eisengart work that I showed a little bit ago that ERT in transplantation, you know, potentially are better than transplantation alone, and that earlier age -- and I put nine months -- I mean, you could quibble about where to put this nine months -- does seem to lead to more normal developmental trajectories.

We didn't talk a lot about attenuated MPS I , and we're happy to do that. But because -- well, let me -- can I -- go ahead. Dr. Wicklund?

MEMBER WICKLUND: This is Cathy. Just before you go to that one, so I just want to ask and be very specific -- and you probably said this

-- but, so is there any -- like is it very clear who needs to be transplanted? Like so if you diagnose or are they having difficulties with the newborn screen where they diagnose somebody, is it clear who needs to be transplanted and who does not?

DR. KEMPER: So if you talk with the experts, they feel very comfortable in moving babies to transplantation if they have, you know, confirmed low enzyme activity level, if they have elevated urine GAGs, you know, again, getting rid of the pseudodeficiency, if they have a mutation that is associated with what they think would be the late onset disease, and if they have any early sign or symptom of severe MPS I .

And, of course, this, you know, gets into the realm of clinical judgment, and I think that there may be, you know, some disagreement about the degree of involvement that you would need before you get to MPS I .

You know, in terms of this prospective screening activity in the United States, there has only been one baby that was identified. That baby

had severe MPS I . I don't believe that case report has been published, but I can tell you that this is a family that opted not to go to transplantation early for a variety of different social reasons, and the baby did die as a result of the transplantation due to CMV infection.

So, you know, I wouldn't want that one case, though, to drive everything again, because these are, you know, small numbers. But this is like a long way to answer your question, that from the experts that we have spoken to, they feel comfortable about when to move babies to transplantation.

The question will always come up, you know, is there a possibility that a baby might get transplanted who turned out not to have severe MPS I , right? This has come up with every condition that we have looked at where transplantation is the treatment, and that's -- I mean, I just can't answer that easily, and, you know, things change when they move into the clinical venue.

But the experts feel very strongly that

they'd be able to separate out those babies that ought to have transplantation versus those who don't. And for those of you -- actually, Dr. Greene is raising her hand, and she is -- you know, actively deals with transplantation, so I'd be interested in your comments.

DR. GREENE: Well, very little -- very little transplantation, but speaking as the liaison from the SIMD for the clinical community, and not as somebody who would identify myself as an expert -- there is a reason I wasn't on that expert panel -- I feel -- and also, if you go back one slide, or maybe more than one, the slide that said -- yes, no evidence regarding transplant in asymptomatic infants. That's because nobody would or should transplant an asymptomatic infant with what we know currently, and that's the concern that was just so eloquently described about, you know, is there a possibility.

Speaking as -- in this respect at least, an average ordinary metabolic doc, I feel comfortable that I could identify whether a child

has symptoms at birth on a good -- combination of good physical examination, ophthalmology examination, and an X-ray. And I'm not an expert in MPS I , and I feel comfortable that I could distinguish. And I think that -- and I've got a lot of experience, even though I'm not a very specific MPS I doc, and I think even a metabolic geneticist with less experience who might not be completely sure could talk with one of these experts.

So I think it's -- there's the small risk of somebody being transplanted who shouldn't, but, yes, I think it's possible to tell who is clinically affected by the severe form and needs to have a transplant. And if they don't look like that early on, you monitor. So I feel comfortable with that.

DR. KEMPER: And unlike, you know, Pompe disease, what we know about the epidemiology is that most cases that come to attention are going to be the severe form and not the attenuated form.

Let me just -- okay. So we didn't --

I didn't talk a lot about the attenuated form, because I just didn't think that it was going to be what would drive this conversation today. But, you know, there is a lot -- you know, many studies, including a trial, that shows that enzyme replacement therapy does lead to improved outcomes in symptomatic individuals with attenuated disease.

There are also two case reports of siblings that suggest that early use of enzyme replacement therapy in asymptomatic children can limit disease progression. But, you know, it's -- you know, these are case reports. Enzyme replacement therapy, you know, of course is associated with the need for weekly infusions. There's, you know, the likely -- there's a chance of developing antibodies to enzyme replacement therapy.

I can't tell you how often that is or the degree to which that interferes with the treatment, just given the lack of studies that are out there.

CHAIR BOCCHINI: Dr. Greene?

DR. GREENE: The second bullet, again, speaking as the SIMD liaison, but in this case speaking for myself as the author of a paper with Mimi Blitzer many, many years ago. Two case reports of sibling sets, I have two case reports of sibling gets, Sanfilippo and Hurler. Spectacularly disparate clinical course in the two kids in each sibling set.

So just because the second child, the younger child who got ERT is doing well, that doesn't mean that the child wouldn't have been doing equally well without the ERT. The case report was long before we had ERT and wildly disparate presentation.

DR. KEMPER: I appreciate you saying that, and I, you know, agree with the caution whenever we present these little teeny case reports.

All right. So Dr. Prosser -- oh, I'm sorry --

CHAIR BOCCHINI: Since we're going

into modeling, this is a good time to take a break and then get you back on the podium in 15 minutes.

DR. KEMPER: All right. I will -- and I can even stay around for questions.

CHAIR BOCCHINI: Oh, yes, you will.

DR. KEMPER: I mean, during the break.

CHAIR BOCCHINI: Okay. All right. Okay.

DR. KUS: FYI, Chris Kus joined, too.

CHAIR BOCCHINI: Thank you, Chris. Good to have you.

DR. KUS: Okay. I've been on for a while.

CHAIR BOCCHINI: All right. Great.

So we're going to take a 15-minute break, and then we're going to get back at 11:15.

Thank you.

(Whereupon, the above-entitled matter went off the record at 10:55 a.m. and resumed at 11:19 a.m.)

CHAIR BOCCHINI: All right. If everyone will take their seats?

DR. KEMPER: All right. So welcome

back for Part 2.

Before I return to the slides, a number of people came up and asked me questions, and I'd like to just share some of the key points that came up where I might have been inarticulate in describing things, and I just want to make sure that we're all on the same page. And it is a very complicated story. I apologize for that.

And one of the things I'd like to acknowledge as well, that folks brought up to me, is it's remarkable how the studies of cognitive outcome primarily came out within the last year or so. So had we completed this even a year ago, I think we would have been in a lot of trouble in terms of not having any cognitive data to stand on.

So some of the key issues that folks came up to me about was, one, clarifying the spectrum of the disorder. So most cases are going to be the severe form. This is going to come out in some of the modeling that Dr. Prosser did, but most cases are the severe. And even among the so-called attenuated form, it's -- the

epidemiology, the studies that are out there, suggest that it's two to one in terms of being the more severe Hurler-Scheie compared to the Scheie. So the spectrum of the disorder is very much skewed towards the more severe range.

The second issue that some people asked me to comment on is to review again the workup, what transpires after a baby has a positive screen. So bear with me as I go through that again, but I think it's really important to understand this.

So at the time that a positive screen is reported out from the state laboratory, so they've done whatever repeat testing that might occur on the dried-blood spot, then the child is recalled for another sample to confirm that the IDUA enzyme activity level is low. The urine is assessed to measure GAG levels, the so-called glycosaminoglycan levels. Those will be high in the cases of MPS I and be normal in the case of pseudodeficiency.

Genotyping occurs, I believe. At the Missouri pilot study, that work is -- the

genotyping is done at the Greenwood Genetic Clinic. Correct me if I'm wrong about that. And then, the baby is examined by specialists knowledgeable in MPS I.

And at that point, the child would not move on to transplant until it is confirmed that the child is severe. And severe, again, would be low IDUA levels, elevated GAG levels in the urine, genotype suggestive of the severe kind, or at least of the unknown kind in combination with a finding on clinical exam. And when we spoke to the clinical experts, the range of findings could include even the bony changes that can be seen on X-rays. So, again, that's in the realm of clinical expertise.

Now, how long that process takes, especially if other states were to adopt, you know, depends upon the availability of specialists and how long it would take for the laboratory studies, including the genotyping, to occur. And I can't -- again, because of the experiences -- really, the only data that we have to go from, I can't really

generalize and say how long that process is going to take.

If a child turns out to have the -- not the severe form but, you know, the attenuated form, then that is a child that would have to be followed regularly, with the frequency determined based on the -- you know, what the expert thinks based on all of the available data, and a decision would also have to be made about whether or not to begin enzyme replacement therapy in an otherwise asymptomatic individual. Again, most of the cases are going to be severe, so most newborns would be expected to move on to transplantation.

So that's the story. Is that more clear? Do people have questions about that?

So the final thing that I wanted to bring up that I don't think that I did a good job of explaining is the -- there are these different screening modalities that are out there. There's the systems that are based on the tandem mass spec platforms, and then there's the digital microfluidics lab on the chip. The tandem mass

spec platforms and the digital microfluidics are all really designed to test multiple LSDs.

So, you know, this body recommended some time ago that Pompe disease be added to the RUSP. If states were already screening for Pompe disease, then adding on screening for MPS I is an incremental addition into screening for Pompe disease. But if you're not screening for lysosomal storage disorder, that really means adopting a new platform.

Now, Dr. Matern has done a lot of work around screening, and so I warned him ahead of time that I was going to ask him if he had any other comments about what I just said or if he thought I -- thinks I captured it adequately.

MEMBER MATERN: I was a little distracted, but there are -- I mean, you have shown the data from Missouri and from Washington, from -- I mean, there are other tests that have been proposed but are not been tested in newborn screening.

There is looking at

glycosaminoglycans, as was suggested by Dr. Tomatsu, but there is no study ongoing at this point. Then, there is the Luminex platform looking not at activity but at presence or absence of iduronidase. Again, that was included in our study, and we hope to finalize it by this summer to look at least at the four conditions that we've done on all three platforms.

But to date, the -- what I can say from our study, the only surprise I had was the number of cases that we identified with low enzyme activity and mutations that are not consistent, to date, with pseudodeficiency or polymorphism.

So variants of uncertain significance, and we at this point would consider to have a variant of MPS I, and we found one in about 6,000, which is much more than anyone else. I don't know why.

Apparently, in Washington, however, and in Missouri, the incidence is also higher, as is expected based on previous thoughts, which however is of course nothing new in newborn

screening, but it suggests that the ratio that you showed of about 60 or so percent being MPS I Hurler versus the rest being the attenuated form is probably going to flip and you will have more attenuated picked up by newborn screening than the Hurler ones.

And then the question becomes -- is, really, can you differentiate those early in life with the tools that we have?

DR. KEMPER: Okay. So that's an important nuance from your experience.

Now, before I move on and talk about some of the modeling work, and then the public health system impact assessment, would it be helpful if I recapped this very confusing cognitive data that I presented? Would anybody like me to do that, or just keep marching on?

MEMBER BAILEY: I'd like to comment on it.

DR. KEMPER: Okay. Why don't you comment, and then I'll try to rescue myself.

MEMBER BAILEY: Go back to the slide

that shows the individual trajectories in the last study. It was like four or five slides back, the other arrow.

DR. KEMPER: Yes. This is the back. This one?

MEMBER BAILEY: Yes, that one. Yes.

So, I mean, the other studies that you presented showed -- suggested that -- you know, trend towards earlier being better than later. But in those studies the earlier was I think 18 months before and after, and so that wasn't very compelling.

I mean, it was compelling to know that earlier is better than later, but, you know, if the average age of clinical diagnosis -- I think you said is around six months of age -- then why -- you know, it doesn't make a strong argument for newborn screening.

This is the one we are really now looking at a group where treatment starts earlier, so in the two- to eight-month range. So on the one hand, you know, you say this is a very small,

extremely small sample, and what can we learn from this, but I like to look at variability, and so this is why this slide is very interesting to me.

So the one thing that jumps out of course is that in the blue group there is very little variability. So if we had, you know, two or three of the blue group going down, then you start worrying about the kind of consistency of effect. But everybody in the blue group is within the normal -- is within normal.

So that's a very -- even though it's just six children. So for me the main question then, is there -- and this was raised earlier -- is there something different about those six children besides the fact that they got earlier treatment? And so as long as we can, you know, say pretty confidently that they're about the same as the other kids, they just got treated earlier, then this is to me very powerful, even though it's with a small sample.

Having said that, there are a lot of yellow kids that are pretty close to that same

trajectory. And so -- and most of them are within -- in the light blue. The shaded area is the 95th percentile, is that what you said?

DR. KEMPER: Yes. And the dark line is the average.

MEMBER BAILEY: I mean, red is clearly not good, and so I would want to know what is it about within that yellow group, who is doing better and who is doing worse. Is it the kids who are getting around nine or ten months of age that are doing better than the 17 months? That's a big difference in age, actually. And so, you know, you always want to get into -- dig into these individual cases, but I think if we had some understanding about the comparability of the groups in every other way, then I would find this very compelling data, despite the small sample.

DR. KEMPER: So, actually, that was a much better summary than I could have given. All I can say in terms of the comparability is the -- you know, what's listed on the top of the slide.

And for me, you know, the sort of

biological argument that, you know, being exposed, you know, until you get treatment, and, you know, where you end up with your trajectory, which -- you know, I hate as a kind of evidence guy to rely on, you know, sort of this biological possibility. But I think that between the two of those that's why -- how I come to it.

I see Dr. Grosse standing back there, and he --

DR. GROSSE: I just want to clarify a couple of points. On the Aldenhoven study that is pooled across European and North American centers, 16 months, but in the text they also said they did analysis stratified by 12 months, but that's not mentioned in the table or figures. So I sent an email --

DR. KEMPER: Yes.

DR. GROSSE: -- have not gotten the clarification yet.

DR. KEMPER: You know, it's interesting. They -- you know, they built generalized linear models to look at things, and

they used age as a continuous variable, and they said for the ease of presentation they dichotomized things this way. And it would be interesting to know like, you know, what the lower cutoff would have been in the model. But I don't know how many -- like what the -- you know, the sample size was in there to --

DR. GROSSE: I also wanted to clarify that the data in the Poe study was not included in the Aldenhoven study. That was a deliberate decision, so there is -- those are independent samples.

DR. KEMPER: All right. So with those nuances added into the mix, Dr. Prosser is on the line, and I don't know if the operator can open her -- open up her line.

I am going to go ahead and just talk very briefly about her presentation. And the key thing is that, again, she focuses on the decision analysis, which is a way to synthesize the evidence using simulation with explicit assumptions.

So -- and she developed a computer

simulation that compared newborn screening for MPS I compared to what might be expected with clinical identification and held, in conjunction with us, a number of expert panels.

And we were most interested in the number of cases that would be identified through newborn screening compared to usual case detection, the number of deaths averted by five years of age, and the number of cases with improved cognitive outcomes.

But, you know, if you look at the registry data, you know, there wasn't a compelling argument that there was a mortality difference. And then you'll not be surprised, based on the cognitive outcome data, that it just didn't -- you know, there was no meaningful way to model differences in cognitive outcome through newborn screening versus usual case detection.

You know, I didn't emphasize this before -- maybe I did, but I want to say it again, which is, you know, our data, like from the MPS I registry, when I showed you the no differences in

mortality, was really, you know, within this early childhood period. So it may be that things diverge afterwards, so most of the stuff that we're talking about is in early childhood.

So in the interest of time, I just want to show you that -- Dr. Prosser is smart and came up with these slightly complicated models and looked at the number of severe cases identified by three years of life.

And we assumed that if you have a -- if you have severe MPS I, by three years of life you're going to have that clinically detected because of the rapid decline that those individuals have. And so the assumption that we -- that they would come to attention. We also -- she also assumed that all cases of MPS I identified through a newborn screening would be eligible and would continue to get transplantation, and because of small numbers we were unable to separately model ERT with stem cell transplantation.

So again, the modeling in this particular case is not going to help us get out of

these issues related to differences in cognitive outcome, but I do think that this slide is helpful in terms of just putting the number of severe cases in -- you know, in perspective.

So of the four million babies born in the United States each year, there would be 29 with severe MPS I that would eventually get detected by clinical identification or through newborn screening that -- again, these cases of attenuated that would be identified through newborn screening. And then, there is this group of unknown phenotype who may not have clinical signs that would need to be followed, which, again, is a -- you know, a relatively small number compared to the -- you know, to the population of the United States.

Again, what we can't predict as well is in the future when, you know, if more screening activity were to happen and the numbers, you know, would diverge from what we've learned from Missouri.

So, yes?

MEMBER BAILEY: This is my cognitive limitations myself I'm sure, but why would you identify more attenuated through clinical identification than through newborn screening?

DR. KEMPER: So these are -- again, I'm going to see if Dr. Prosser is on before I answer her question --

DR. PROSSER: Yes.

DR. KEMPER: -- for her. Do you want to take that, or would you like me? We can hear you, Lisa.

DR. PROSSER: Can you hear me, Alex?

DR. KEMPER: Yes.

DR. PROSSER: Hi. This is Lisa Prosser. Thanks for letting me join by phone.

So there was a lot of discussion about this within the expert panel, and the reason there is just because of the timing, that here we're looking at outcomes within the first three years of life.

So over time many of those that, at the time of newborn screening or shortly thereafter,

would be classified as unknown phenotype would eventually turn out to be classified as attenuated. But just at the time that we're using for the modeling here they would be classified as unknown phenotype.

DR. KEMPER: Perfect.

And I think, Dr. Greene, did you have a question, or was it the same question?

DR. GREENE: It was related. So half my question was answered. In the clinical identification, I take it that this is -- clinical identification is going up to three years of life, and the newborn screening would be identified at the -- in the newborn period?

DR. PROSSER: Yes, that's correct.

DR. GREENE: Thank you.

DR. KEMPER: And Dr. Homer has got a question for you.

MEMBER HOMER: Yes.

DR. KEMPER: I like this part where I can just --

MEMBER HOMER: How much earlier? I

mean, what is the median age of diagnosis in the clinical identification of the severe cases, and how much earlier is it through newborn screening?

DR. KEMPER: Did you hear that question, Lisa?

DR. PROSSER: So, I'm sorry, could you repeat that?

DR. KEMPER: Newborn screening would lead to detection how much earlier than clinical detection?

DR. PROSSER: So this is assuming that the same number of cases would be identified within the first three years of life, that for newborn screening those would all be identified within the first six months or so of life. And then I believe that the median age from the study that we used here was 16.7 months of age for clinical diagnosis.

DR. KEMPER: So it does bring the clock back -- I mean, bringing it to the point that Dr. Bailey was making about the cognitive outcomes. It brings things back to a time when you could get treated to be in that yellow zone.

The average age of symptom developments and diagnosis was six months, and then it took, you know, some time to move on to treatment, but remember the international guidelines were that babies should be transplanted by two or two and a half years of age, as long as your expected IQ or DQ is 70.

MEMBER HOMER: I'm sorry. There's some inconsistency in what you said.

So you said they come to clinical diagnosis by six months, and you also said that's when your newborn screening clarifies diagnosis at six months. And you just said current treatment guidelines suggest that people start -- because of current treatment programs, people are starting to treat it at 16 months, but that's different.

In other words, if the treatment recommendations change that says as soon as you make a clinical diagnosis of severe disease -- the MPS I severe disease, go to transplant, then you're still dealing with --

DR. KEMPER: Then, they could -- right.

MEMBER HOMER: -- six months of --

DR. KEMPER: Right. So there are two issues, right? So one is moving the clock earlier from screening, the other is just changing how clinical care is delivered so that you can reduce this gap from diagnosis to treatment initiation. So --

DR. PROSSER: Right, and can I jump in there?

This was a point that was discussed at length within the expert panels, and one of the points that came up is that there is a range of opinion about how early it would be possible to identify a symptomatic case within the newborn period, that there is a range of -- you know, that may be anywhere from very early on, during the newborn screening period, but may actually take several months or maybe six months or more until it was possible to diagnose that clinically.

DR. KEMPER: Yes, and beyond that, too, we are talking -- you know, these numbers are so small, and it has not been until, you know, fairly

recently that people have felt more comfortable with these, you know, transplants in very young babies. And so I can't tell you what the trend over time has been between diagnosis and when treatment has been initiated, but I think that might be a confounding issue.

Did that make any sense, what I just said? Should I say that again?

The registry has babies, you know, or individuals going back, you know, like the >80s.

MEMBER HOMER: No, it makes sense. I'm just trying to project to our decision-making. Our decision-making should be based on, are people identified earlier through screening leading to earlier treatment, which results in improved outcome? And so --

DR. KEMPER: Correct.

MEMBER HOMER: -- if at the very first step we're not clear that newborn screening identifies individuals earlier than clinical diagnosis, we have a problem. That's all we're saying.

DR. KEMPER: Right. But I think that what -- so it certainly takes, you know, some time to do that clinical evaluation I was talking about, but I think that that time is certainly shorter than the six months it would take for those babies to come to attention clinically. You know, for those -- you know, the laboratory evaluation and that kind of thing.

DR. PROSSER: That was certainly the consensus on the expert panel -- where there was a range of opinion -- was exactly at what age that was likely to be.

DR. KEMPER: So, Dr. Botkin, and then Dr. Greene.

MEMBER BOTKIN: Yes. Jeff Botkin. I wonder if you could go back to the table we were just looking at?

And I'm looking at the 44 versus the 40, and I guess I hadn't thought about the prospect of newborn screening identifying children who would never become symptomatic. Is that part of our discussion here? Is it likely that we're going to

be creating a certain class of children who carry the diagnosis but yet would never have been destined to be symptomatic?

DR. PROSSER: So that is where -- that is partly an artifact of the timeline for the decision modeling, that we're modeling out to a three-year endpoint. So the assumption there is that there would be some children that would be identified within that three-year period, under newborn screening, that would not be picked up until after the three-year period under clinical identification.

MEMBER BOTKIN: Yes, but do we think that there is potentially a class of children who would be by biochemical measurement affected, but by phenotype be unaffected for a lifetime?

I mean, there are certain newborn conditions where that seems to be a phenomenon. Does this condition, do we think, raise that --

DR. KEMPER: I mean, I can't answer that without, you know, a bigger sample of babies that have been screened and then followed over

their life. It is the sense based on the mutations that have been described and just the, you know, expected epidemiology out there that -- I feel like I'm repeating myself, hopefully I'm adding.

Is that, you know, most cases are severe, and then of the ones that are attenuated it mostly skews more towards the Hurler-Scheie than the Scheie. But that's based on, you know, what has been reported in the evidence so far and not -- I mean, this is just limited screening, right? This is a very rare condition, and, really, Missouri is providing most of the data that we have.

But that doesn't -- I mean, based on the -- you know, the cohort of children that have been screened in Missouri, it doesn't look like that's the case, but, you know, Dr. Matern, you know, comments, you know, are that, you know, maybe that will change over time.

DR. PROSSER: And within the modeling simulation, we did include a projection that there could be anywhere from zero to 20 percent additional cases identified to include that as a

possibility, but that's where the consensus of the expert panel was, that this was really unknown at this point.

DR. GREENE: So if you could go back to that earlier slide, and also I think I have a further clarification to Dr. Botkin's question.

I think the answer is, no, we don't expect -- and, again, I'm not an MPS expert, I'm just a biochemical doc. Okay?

DR. KEMPER: Are you talking about this slide?

DR. GREENE: Yes. That slide.

DR. KEMPER: Okay.

DR. GREENE: But first, a little bit more. I think you can be more definite in response to Dr. Botkin's question.

If -- so there will be people identified with the attenuated form, but we're talking attenuated. So then the discussion should include that we might be finding people on newborn screening who would have adult onset disease, but we're eliminating the people who have no

glycosaminoglycans excretion in the urine. So the pseudodeficiencies, the people who will never get the disease are, in my understanding --

DR. KEMPER: Right. No, that's 100 percent correct.

DR. GREENE: -- as a clinical metabolic geneticist.

DR. KEMPER: Right. So --

DR. GREENE: There is not going to be anybody who never gets sick. They might get hit by a bus young enough that they never got the symptoms of Scheie, but --

DR. KEMPER: Right. Well, I'm going to be --

DR. GREENE: -- were taking out the non --

DR. KEMPER: I'm going to be a little bit more wimpy than you are, right? So the pseudodeficiency -- I'm not worried about that. They are taken out. But we know that when you start doing mass population screening you find things that you weren't expecting.

So there is the possibility that you could find a class of children who have, you know, low levels of IDUA but probably enough functioning IDUA that they do okay and may develop, you know, problems, you know, many years down the road.

But who knows? I mean, I can't -- that's not like a -- you know, there is no evidence to suggest that that's going to be a big problem, but it could happen. I mean, it certainly -- you know, drawing analogy from other conditions.

DR. GREENE: Right. And so I wanted to come back -- the reason I had my hand up originally is to come back to that. And so I completely agree with what Dr. Kemper just said, just speaking as a clinical metabolic geneticist.

DR. KEMPER: Let the record reflect.

DR. GREENE: Yes. Absolutely. So there are certainly going to be people who would live long enough that they never have any meaningful symptoms, that they have a little bit of a thickening of a valve that doesn't affect them or a little bit of stiffness of fingers, so that

they might not have any meaningful clinical symptoms, but the people who truly would never develop anything would be, at least as far as we know, screened out, except that we don't know what we're going to find.

What I wanted to come back to this slide for is there seemed to be a little confusion that somebody said average age of diagnosis a year and a half, but it's average age of diagnosis a year and -- average age a year and a half for treatment initiation. It's average age of diagnosis, about seven or eight months for diagnosis in the severe form. And that's the -- and I really don't think it will take anybody six months to sort out, do you have the severe form or the mild form?

So I think what we're doing is probably comparing something like between one and two months age of diagnosis after a positive newborn screen, an average eight months -- average eight months-ish diagnosis clinically, with a huge spread.

And some of that spread, some of the zeroes are probably are siblings. And some of the

zeroes reflect the fact that whatever else -- not to detract from the discussion of newborn screening, but when that eight-month-old or that 23-1/2-month-old is diagnosed, I have never met -- and I just at the break got to talk with a parent, and he has never met a parent who didn't complain of symptoms for some period of time before the pediatrician finally said, yes, there is something there.

So when that diagnosis is made at eight months, the family has often been saying since a month or two there is something weird about the back. So there's --

DR. KEMPER: So I would -- I think you're right, you know, anecdotally, but I just want to make sure that -- you know, so we don't have any evidence that says that, but drawing from analogy for other conditions, I'm sure that's true.

I mean, just finish one quick thought too, which is remember to, when you look at the registry that these are -- you know, this is a voluntary registry system. It is not the same as,

you know, population level epidemiology. So I don't want to, you know, put too much weight on like particular numbers, but I think it gives a good flavor to how things are. Does that make sense?

So, Dr. Bocchini, I don't know if I'm allowed to call on someone from the audience or not. Somebody from the audience had a question. I'm not sure if I'm allowed to -- what the rules are.

MR. HOLLAND: Yes. I would just like to make one comment. And I'm not -- it sounds like this is the Missouri study and maybe not. So I'm speaking more broadly and based on my knowing these families and seeing them.

But the typical -- unless it's a sibling where they're able to identify the disease very early and transplant very early, and in such small populations maybe that's skewing this data.

The typical family does not know anywhere close to six months of age. They are not diagnosed that early. The typical scenario is that by the time they are finally diagnosed they are pushing 24 months, in which case the transplant

center may or may not even transplant their child because it has been diagnosed so late.

So that's just sort of the reality of the world. Don't know how it is impacting your numbers, but there is a strong, strong, pervasive -- you know, of what happens.

DR. KEMPER: So I think the point that you're making sort of underscores what I said before, which is, you know, the data from the MPS I registry are all, you know, voluntary, self-reported, may not reflect the, you know, experience of any particular families. And, again, sort of the pathway to the registry, you know, is not there for everyone.

Yes?

MEMBER WICKLUND: This is Cathy Wicklund. So if you take out the siblings of that calculation of age of diagnosis, what do you get?

DR. KEMPER: I can't do that from the registry data.

MEMBER WICKLUND: Oh, you can't do it from the registry data.

DR. KEMPER: I mean, I'm sure it could be done, but I can't.

All right. So I'm going to -- you are going to have a welcome transition, I'm sure, to my good friend and colleague. But I'll be back.

MR. OJODU: He will be back.

Good afternoon, everyone. Big shout out to a number of folks that made this happen. Elizabeth Jones, APHL staff, the CRW Work Group, and then most especially to the state newborn screening programs for providing the information that I'm going to present to you this morning -- or afternoon.

So let's see, how do you -- so I'm going to give a brief overview of the public health system's background, how we got here, our role in completing and providing this information to you all, methods, how we collected the information, disseminated the information to state newborn screening programs, and then talk a little bit about the results and a summary of the data that we have here.

You probably do have in your packets the 23-page report that includes the summary of the public health system impact, as well as the survey tool and the fact sheet that we developed to send out to state newborn screening programs to get a better sense -- or to have them get a better sense of MPS I.

So I don't think I need to spend too much time talking about this. We know that this is an additional important component of the evidence base, to add a new condition to the recommended screening panel.

And as noted a number of times, these recommendations are based on the certainty of net benefit and the -- in moving forward, obviously, the feasibility and readiness of implementing comprehensive screening. And I'm going to define both feasibility and readiness in the coming slides. But, you know, combine both of those, we would get a good sense of the public health -- at least try to get a good sense of the public health impact on newborn screening programs, to add a new

condition to RUSP.

So you've seen this a number of times, but it's important to highlight the part of the public health impact that I'm going to be -- that this survey focused on. It's the one with the red bar at the top there, feasibility and readiness.

So I'll leave it at that. Sorry about the formatting there. It looked better on my slide. I'll leave this up for another five seconds.

So our role. We were tasked by the CRW to work with DACHDNC -- that's how you pronounce it. SACHDNC and DACHDNC. With DACHDNC, condition review work group, to improve and streamline the process of the public health impact.

We have been working -- we had a meeting in the middle of last year, brought a number of experts together to help us redefine and better streamline the process of assessing public health impact. The result of all of that work led to what we put together over the last five months or so in conducting the public health system's impact and

assessment, evaluating states' newborn screening programs' capability to implement MPS I.

I don't think I need to spend too much time talking about the importance of why we are doing this assessment, but certainly it's to inform you all as you make those final decisions, to add a new condition to the recommended uniform screening panel. But it's to also provide you with real newborn screening walled barrier/facilitators related to newborn screening -- call it issues, challenges, and also successes as well, because I think we have learned a great deal from, you know, the two states that are currently screening -- or the three states -- or two states that are screening and the other state that will be screening for MPS I in the future, and I'll talk a little bit about that later.

We wanted to get a sense of the opportunity costs, and ultimately share practices that can improve on implementation strategies. I think this is a key aspect of the survey that we sent out to the state newborn screening programs

to get those practices, what they have in place for those who were screened and those that are not screening, what they need to put in place.

So I do have something to read here. So for the past couple of years, we have worked to improve and streamline on the processes related to the public health impact. And the survey that we sent out to the state newborn screening programs was mainly to one designated contact in every state that was responsible for spreading the gospel of this particular survey around to all of the newborn screening program system -- stakeholders in the newborn screening system. Whether it was lab follow up, you know, the specialist, the medical home, we wanted to get a good sense of what it will take from screening to long-term follow up.

So we surveyed 53 states -- no, 50 states and three territories, plus the District of Columbia. And we also got detailed phone interviews in the form of a phone dialogue and question-and-answer kind of session between these three states that have either -- that has

population screening for Pompe, a pilot for Pompe, or had recommended -- I'm sorry, MPS I, for the MPS I activities. Sorry about that.

So I'll just go back and say that again for the record. We conducted interviews, phone interviews with three states and newborn screening programs directly related to how they are implementing or will be implementing newborn screening for MPS I, in the form of phone interviews.

We also developed a fact sheet, and I'll talk a little bit about that later. This is also part of your packet. This fact sheet was to give state newborn screening programs that were completing this survey, you know, a good sense of the background information related to MPS I: incidence, laboratory methodologies, treatment options, and you can find that in -- as part of your package as well.

And then we had outreach --- webinar outreach to a number of folks in the newborn screening community. We reached out to state

newborn screening programs directly. We reached out to regional collaboratives and collecting information and making sure that they know the importance of this particular public health systems impact survey for MPS I, and then provided a webinar for all of them to provide any questions that they may have in completing the survey.

So we defined feasibility with these four bullet points here, feasibility of adding a new condition to the recommended uniform screening panel. One, an established and available screening test, a clear approach to diagnostic confirmation, an acceptable treatment plan, and an established approach to long-term follow-up plans. That's how we defined public health impact for MPS I to state newborn screening programs.

Please.

MEMBER MATERN: Dieter Matern. How do you define established screening test?

MR. OJODU: So we went back and used -- looked at what states that were currently screening for MPS I were -- the kinds of tests that they were

using. Obviously, that's what we had to work with there.

For readiness, we had three categories State newborn screening programs were ready and could implement within a year, developmental readiness, which we focused on -- which focuses on state newborn screening programs could implement the addition of a new condition to the recommended uniform screening panel within one to three years, and then unprepared. As it notes there, most state newborn screening programs will take more than three years to implement the new condition.

All right. So let's talk about the interview results here. Remember, these are phone interviews that we conducted with the states that either have a legislative mandate, state pilot, or other pilot, for MPS I. And as you can see there, there were three of them that we reached out to.

Some of the results are as follows. In reference to interviews that we conducted, when asked of the considerations during implementation process, the states that are currently -- have

currently implemented or plan to implement MPS I noted that they met with their state advisory committees or boards. They certainly had to consider obtaining the equipment that they are going to use for testing.

Choosing and validating the screening methodology, developing clinical protocols, which is no small task, resolving database and LIMS reporting out systems, collaborating with not only just the medical specialist but pretty much everyone in the newborn screening systems, and in some cases conducting pre-pilots.

And these are for the three states that are -- that we did the phone interviews with. The next several slides will focus on those results that we got from those phone interviews in-depth.

So barriers to implementation. Cost, and I'll talk a little bit about this later, but certainly the cost and time involved in obtaining new equipment. Whether it's new equipment that they don't currently have in their lab or they need to get new upgrades to the lab infrastructure,

hiring the competent staff for testing, dealing with a high number of false positives and pseudodeficiencies, and, as noted earlier, the low incidence of the disorder.

Continuing on with the barriers to implementation, their -- the states that we talked to noted the difficulty in creating algorithms in reference to treatment for MPS I, the uncertainty regarding age of onset and how to handle cases of unknown phenotypes. The burden -- and I will define this a little bit later in my slides -- on the complete medical system and medical -- the newborn screening system as a whole, and then method validation processes. Those were some other barriers to implementation in those states that either currently screen or plan to screen.

So these are factors that will aid. As I said, we weren't just focused on the challenges. We wanted to get a sense of, you know, what are the things that will aid in implementation for this new condition.

And as noted before, some -- the states

noted that multiplexing for MPS I with other LSDs is something that certainly will help. Conducting a pilot, we heard this from those states as well as having the infrastructure, lab and other kinds of infrastructure, related to adding a new condition in place.

Developing well-defined protocols through -- you know, whether it's lab protocols, the treatment protocols, all of those have to be in place prior to the implementation. And then pretty much having a really strong relationship with -- relationship and communication with pretty much everyone in the newborn screening system, from, you know, the medical professionals, the follow-up coordinators and staff, and the laboratorians as well.

Additional challenges are as follows from the states that are currently screening or plan to screen. Time required to validate the laboratory instrument, adjusting cutoffs to reduce the high false positives that I noted earlier, not having QA/QC materials from CDC, and proficiency

testing materials as well. And in some cases we did hear that not having an FDA approved kit for MPS I was also a challenge to implementing this method.

For the three state newborn screening programs and stakeholders that we interviewed, we got a sense -- and they noted to us that they believed that it would take approximately two to three years, or three -- or more than three years to complete the entire process, from obtaining equipment to implementing statewide newborn screening -- a statewide newborn screening population project for a new condition, in this case MPS I.

Yes?

MS. BONHOMME: This is Natasha Bonhomme. For the slides that you have just presented with the different lists, are those just a general listing, or are those listed in any type of rank order from the conversations you had with the states?

MR. OJODU: That's a good question. I

want to say that they are a general listing. I don't think that they -- we weighted them any which way.

Any other questions? Okay. So we did that. Let's see here. All right.

So as I noted, funding challenge is key. For the states that we interviewed, we wanted to get a sense of how they would bring on a new condition, in this case MPS I, with, you know, some of the barriers related to the authority to screen for a condition and also the costs related to adding or implementing a newborn screening condition, in this case MPS I.

And as noted here, these were -- and these are weighted, obviously, by the different challenge, whether it's major, minor, or not a challenge. Providing the screening tests, 81 percent said that it was a major challenge. Long-term follow up for those late onset diseases or folks -- infants that are carriers, about 74 percent or 26 states noted that it was a major challenge, and then the non-trivial activity of

increasing state newborn screening program newborn screening fee.

In some states it's a -- they have to go through a legislative mandate to do that. Others have it a little bit easier, but certainly it was a major challenge for about 56 percent of the states that responded back to us.

So this is a little bit busy, and it probably is a little bit more clear on your computer screens. I wanted to highlight a couple of things on this slide -- factors for impeding or facilitating newborn screening.

I think approximately 54 percent of the states noted that it would take approximately a year or so to get a new tandem mass spec into their laboratory for screening purposes for MPS I. Thirty-nine percent of the states said that it would take approximately a year to do the same thing for the advanced liquid logic methodology that was noted earlier.

Making sure that there was enough technical staff within the lab to screen for MPS I

was also a number of other factors that were noted, including the capacity to report out on the LIMS system and making sure that they have the interface -- instrumentation interface to address that particular new condition to their newborn screening panels.

So this question dealt with other kinds of activities related to things that may hinder or will hinder implementation, may hinder, have no impact, aid, or will aid in implementation. As noted here, costs per specimen, which is calculated at least in this as the personal equipment and reagent, was something that states' newborn screening programs that completed the survey said that will hinder implementation in their programs.

Other ongoing activities related to continuous quality improvement, the extent to which the screening protocols for MPS I have demonstrated in other -- have been demonstrated in other newborn screening programs. As I noted earlier, you know, the two states that are currently screening has provided very valuable

information for other newborn screening programs on how to bring on this particular condition into their state newborn screening programs.

And then the expected cost-benefit for screening in states, and I think Scott Grosse talked a good amount about that, so I'll leave that alone.

So these are the results from the state newborn screening programs, the approximately, let's see, about 39 state newborn screening programs that responded, excluding the three that are either screening, have a pilot to screen, or plan to screen in the future.

Fifty percent of those programs noted that funding costs is -- funding and costs is associated with the most significant barrier related to implementation. Other barriers including not having MPS I on the recommended uniform screening panel, the condition not meeting the criteria for addition to the -- for screening, limited ERT capabilities, the high number of false positives, and the uncertainty with mild cases of

the disorder.

Facilitators -- our greatest facilitators -- about a quarter of the states noted that having a treatment and, you know, good clinical outcome and, you know, having evidence showing the utility of screening is one of the greatest facilitators for, you know, adding a new condition, in this case MPS I.

About a fifth of them also noted funding. That's going to be a continuous theme in this presentation. And other factors, at least facilitators that were noted, including from some states having an FDA approved kit, and the addition to the recommended uniform screening panel.

So in reference to timing for implementation activities, states noted that they needed a good amount of time, in this case a year or -- a year to two years to develop and consult with their medical staff and specialists on developing protocols related to MPS I. It takes approximately that much time to do -- hire necessary laboratory staff and follow-up staff,

and about 50 percent of the states said that it takes about a year or less.

An additional 31 percent said it takes a year to two years to have a pilot for the screening process within the state to especially complete the validation and have that in place.

So the strength of the survey. I think the outreach that we did to state newborn screening programs, among other things, the importance of making sure that state newborn screening programs understand why we are doing the public health system impact for MPS I, you know, led to a very good, in my opinion, survey response rate.

This particular survey was filtered out I think in December -- actually, no, November 18th, and we closed it I think on January 7th. So approximately six weeks with the holiday there -- holidays there.

It gave us enough time to really talk to the states, tell them the importance of completing this survey, and making sure that they understand the impact on how you will make that

final decision on adding a new condition, in this case MPS I.

Providing that webinar and fact sheet for respondents was also key. Remember, most of these states don't screen for MPS I, and so it was very important to be able to develop that fact sheet, which is part of your packet there, for state newborn screening programs to get the -- I would say more than basic or baseline on MPS I activities.

So it's also -- it was also very good to assess perceptions about implementation based on experiences with other disorders. These individuals in state newborn screening programs have added to conditions, whether as a legislative mandate or other ways, and, you know, having a sense of how those things work and the implementation strategies certainly helped in completing this survey.

And then, finally, the assessing real-world experiences is something that we cannot take for granted. I think it was very good in getting a sense of, at least for the states that

were screening and for the states that plan to screen, what it will take to screen for MPS I .

So there were the limitations. We didn't want to focus too much on the cost aspect of things, and so we assumed that a number of things were in place -- the authority to screen, and you've heard -- may have heard folks talk about that. That actually takes a while to get that legislative mandate or other ways in adding a new condition to a state newborn screening panel, and then having the funds allocated to actually do the screening.

The assumption was that both of these things were in place prior to, you know, completing the survey. And so obviously, you know, there were a number of hypotheticals which led to subjective responses. We were trying to get a sense of, you know, a good number of states that aren't screening for MPS I , what it would take for them, and using a survey tool that we continue to revise to get the best information related to the public health impact for MPS I .

And then, the limited data on screening

for MPS I in states. I think Alex did a great job of presenting the evidence of what we know about MPS I and the states that are currently screening. I think one has been screening for 23 months, and the other has been screening for three months at the moment. You know, having -- providing a little bit more information about how screening is done in those states would have been a little bit more helpful.

So approximately four-fifths, 80 percent of the states, believe that it would take approximately one to three years, given that they have the authority to screen and they have the funds allocated to do the screening, to implement screening for MPS I.

And from the decision matrix that I provided earlier, we would categorize the responses and slot the states' collective responses as development or ready. I can go back to that slide, but I think you all remember that. I just passed it.

Additional conclusions -- funding and

cost-related challenges. There were a number of states that stressed the uncertainty about the pseudodeficiency mutations and mutations of unknown significance, as well as the long-term follow up for infants with MPS I. And for the states -- we learned a good deal from the states that are currently screening for MPS I, and detecting a large number of false positives, you know, remain an important challenge for those states that are actually screening.

And so I'm going to pass this back to Alex.

DR. KEMPER: So I think everyone might be happy to know this is our last slide. And I appreciate you staying with us so far.

There is really a lot of nuance to all of this, and, you know, I just want to go through and like highlight some of the lessons that I have learned. And, you know, it's interesting that I got a note from Anne Comeau as I was sitting here as well is that, you know, she wanted me to emphasize that a lot of the data that we're talking

about come from small numbers, and we're looking at, you know, disparate, you know, developmental outcomes, and only within, you know, a relatively limited period of time in terms of follow up.

And, again, the things -- you know, you discover things when you begin to screen in states like Missouri. So, you know, there are issues of uncertainty, and what we tried to do is do our best at pulling the threads together. But, again, a lot of this is based on small numbers.

And at the risk of sounding like a broken record, when we look at things like the registry, there is, you know, data, and it is incomplete, and it's hard to tell from the studies exactly how people came in. And, of course, you know, there are just changes going on all the time.

So to highlight some things that I take away from it is the birth prevalence is about one in 100,000. Best we can tell, most cases are severe. Dr. Matern pointed out, though, with mass screening that in fact you may begin to find other more mildly affected individuals.

Screening can identify infants with MPS I, and it has been implemented in Missouri and Illinois. And, you know, the one case of severe MPS I has been detected, as I mentioned earlier.

It is still unclear which screening methods are best. So without getting into the nuance, there is competing tandem mass spec platforms, and there is the digital microfluidics. All require adoption of new methods for states that aren't screening yet for the lysosomal storage disorder. So this group has already recommended to the Secretary that Pompe disease be added.

So if you were screening for Pompe disease, which is lysosomal storage disorder, then there is this, you know, smaller incremental addition for adding MPS I , although the fact that it's an incremental addition alone shouldn't be the reason for adding a condition. But I do want to point out that for states that aren't screening for any lysosomal storage disorders, you know, there is a lot of work that needs to go -- be put in, as Jelili mentioned.

The expected number of false positives related to pseudodeficiency is greater than was initially anticipated. Early detection of MPS I compared to clinical detection may not improve survival, at least in those first early years of life.

Early treatment, and so moving the clock back to earlier than nine or 16 months, depending upon how you look at the studies, may lead to improved developmental trajectories for cognitive outcomes. But, again, the caution is that these are based on small numbers.

And I raised the issue about confounding before, or whether or not there are other predictors of better or worse developmental outcomes. And, again, the challenge is both in the ways that the studies have been reported but also the fact that case accrual is slow, because fortunately it is a rare disorder.

In terms of attenuated MPS I, the age at which symptoms develop cannot be predicted. There is no direct evidence -- and by that I mean

things like trials -- that pre-symptomatic treatment can lead to better outcome than once individuals becomes symptomatic. There were those case studies of sibling pairs, but, you know, Dr. Greene did a good job of explaining, you know, the problems with generalizing from it. But, again, with such a rare disorder, that may be the best that we can get.

So, you know, there is a lot of nuance, and hopefully I've -- we've done a good job of capturing those things.

I'm going to open things up for questions. I don't know if you want to do that now, Dr. Bocchini, or let people take a mental health break. Or a biological break.

CHAIR BOCCHINI: Let's take some questions. But, first, I want to thank you both, and really -- it's really nice to see the evolution of the public health impact work that you and your colleagues have done. So really appreciate that.

So let's go ahead and take questions from the Committee.

DR. KEMPER: I saw Dr. Boyle go up first, and then --

CHAIR BOCCHINI: Okay.

MEMBER BOYLE: So could you go back to your previous slide, please? Thank you. This is Coleen Boyle. It's on your second-to-last bullet about the cognitive outcomes and the issues around unmeasured confounders, or they may be measured but not something that you have access to.

I guess I'm going to ask you to -- and your group to give some thought in the next minute about whether or not you can -- I mean, have you exhausted what you can look at with regard to that data? Or do you feel like you can go another level?

DR. KEMPER: You know, so part of me feels like, you know, you can always dig deeper.

MEMBER BOYLE: Right.

DR. KEMPER: But I'd be interested in hearing, you know, what other people say, because, you know, I may be lost in the forest right now. But when I put on my analysis hat, right, you need to have a certain number of outcomes for every

confounder that you want to consider. And I think that teasing things apart could be done, but I think it would require prospective case ascertainment.

I think there are two issues. Let me back up, right? So there's issues about what is going to happen when -- if, you know, screening were to be broadly adopted, right? And so we can predict, based on the Missouri data, which used digital microfluidics, but there are competing methods and Dr. Matern brought up his, you know, emerging experience about the degree to which you are going to pick up attenuated cases versus, you know, the more severely affected ones.

And then, there is a whole host of questions that I would like to know about what predicts outcomes in transplantation beyond just the age at transplantation. So, you know, one would guess it would have to do with, you know, the genotype and how the -- you know, the health of the baby otherwise in terms of how severely the baby is affected by the time the baby went to transplant, there are probably factors related to the

transplant itself, and I'm not an expert to comment on in terms of other involvement. You know, it would be interesting to know, you know, things like, you know, brain imaging, MRI, nerve conduction stuff, all that.

I don't think that with the -- I'm going to give you so much of a long answer here. But I don't -- I think that if you really, really want to be able to tease this out with precision you would need to do case ascertainment, which would be -- you know, I mean, the only way to really do that then would be under the context of larger pilot studies, given the rarity of the disorder.

So it all depends on -- and, again, this is a decision for you all, how certain you feel about the evidence that the benefit for early treatment exists.

So I'm sorry to be, like, so nuanced, but it's just I can't -- you know what I mean? I don't think that the existing data is going to tease all this out. So Scott is coming up, and I'd be interested to see if he agrees or disagrees. Oh,

you know what? I'm getting -- is it okay if I jump to him? Is it okay if I go to Scott before I go to the other Committee members?

CHAIR BOCCHINI: Okay.

DR. KEMPER: I'm going to have to change my flight home. Just kidding.

DR. GROSSE: There is more data; the problem is trying to dig the data out of the investigators. So the Aldenhoven article, which was published online January 26th as a -- sort of a proof, it's not final form, in the text they state -- they did a regression analysis. They have modeled the results and said that if a child with severe MPS I is transplanted before 12 months when their MDI, roughly equivalent to development quotient, is over 70, there is only a 15 percent chance they will have an IQ of below 70 after several years.

If they are transplanted late, there was a roughly 70 percent chance they will have an IQ under 70 at the end. So there's a pretty dramatic difference, according to that text.

Unfortunately, they did not report the regression results that substantiate those calculations. I sent an email to them and have not gotten a reply.

DR. KEMPER: Yeah. And they use, you know, generalized linear modeling, too, so they're going to have all sorts of power calculations, even if you were to get to those data. So I think -- you know, this is my statement, more data would always be better.

MEMBER WICKLUND: This is Cathy Wicklund. My question is a little -- not related to this topic we have right now. It's more about access. So it's about coverage for the genetic test and access to the treatment, and what conversations did you guys have about those issues for people, and would it increase disparities, or how would that play out?

DR. KEMPER: Yeah. So, you know, that's an interesting question that we talked a lot amongst our group. So if you're clinically detected versus detected through newborn screening, you're going to have to go and get --

you know, if you had the severe form, the treatment is going to be a transplant.

So, in a sense, it's not creating a service need that wasn't there already. The bigger issues are probably around the -- you know, if you have attenuated form, you know, who is going to get enzyme replacement therapy, who is not. But I would point out that, you know, I -- it's a rare number. It's a small number of babies that we're talking about.

So I think that that issue is probably, at least to me -- I mean, I hope I'm not interjecting myself in the conversation too much -- but a more addressable issue than this -- you know, than the outcomes issue.

MEMBER BOTKIN: A question for Jelili, and I guess I just want to be sure I understand what you're saying, your synthesis of the public health outreach here. And you had a slide fairly early in your slide deck where you went through our categories of ready, developmental readiness, and then unprepared, with timeframes being one year,

one to three years for developmental readiness, and then unprepared being it will take more than three years to implement. So you have scattering of data.

So your synthesis is that we are at -- the feedback, the results show developmental readiness where programs could implement -- the majority of programs could implement within one to three years.

DR. KEMPER: Yes, sir.

MR. OJODU: Yes. With the nuance that once there's funding, authority to screen, and also the allocation of costs to actually implement the screening, but --

MEMBER BOTKIN: Okay. So it's one to three years after --

MR. OJODU: Yes.

MEMBER BOTKIN: -- had been -- okay. Thank you.

MR. OJODU: Thank you.

DR. KEMPER: Dr. Mabry?

MEMBER MABRY-HERNANDEZ: Just I guess

a clarifying question. This is all new to me. I want to know, would you summarize I guess the evidence as poor quality, or is that how we -- the phase out? I don't know what --

DR. KEMPER: So the good news for me is that is a decision that I'm going to defer --

MEMBER MABRY-HERNANDEZ: Right.

DR. KEMPER: -- to you all. Yeah, yeah. I mean, part of it is just driven by the study design. So Dr. Mabry comes from the world of the task scores where, you know, you go off and have the luxury of having prospective large clinical trials.

Dr. Green has been like so intimately involved with the review of the evidence. I just want to make sure that I'm -- that I've hit the nuance correctly or if there is something that should be added to the mix.

DR. GREEN: Sure.

DR. KEMPER: You're okay? Okay. I just want to -- just want to be -- you know, again, it's complex.

Oh, you want to come? Oh, I thought that you were sure, like you were happy. But now I'm going down.

DR. GREEN: I appreciate the invitation and how difficult this is. You know, thinking about sort of the formal assessment of harms that I think has been explicit in this -- in this evaluation, I am very concerned about the ascertainment biases that have been raised, and as you've, you know, reasonably pointed out, are probably not currently assessable.

So thank you.

DR. KEMPER: Great.

MEMBER BAILEY: So just two points. Most of it has been raised already, but I think a key one for me is really, what is the typical age of diagnosis, so we've seen -- of clinical diagnosis. So in the chart it looks like you're saying six months, but we hear from the audience it's 24 months. That's a huge difference. And if it's closer to six or eight months, then it lessens the compelling nature of newborn screening. If

it's closer to 18 to 24 months, then it enhances the compelling nature of this tremendously to me.

And so I don't know if we really have clear what is the truth there. It would be really important for me to know.

And then, well, did you want to answer that question, Carol?

DR. KEMPER: Well, can I just add something to the mix, too, that one of the things that makes this complicated is that the window for transplantation over time has gotten -- the recommendations for when to transplant has gotten shorter. You know what I mean? So there's just -- there are like just multiple moving pieces.

I guess Dr. Greene, and then you get --

DR. GREENE: So I think -- I don't want to spend a lot of time adding to what was already eloquently said, that we don't have the data to answer that question. With that said, my -- I can say that that six months number owes something to the fact that there are some zeroes in there, and some of those zeroes are siblings.

So my clinical experience is that it -- there are some who are two years old, and that is a serious failure of a pediatrician, or somebody from another country who just wasn't looked at. So nobody should be two years old and undiagnosed, but it is really common to see somebody who is a year old.

So I give you, as a really, really wild clinical guess, that the real number is probably closer to nine months or a year on average with some scatter, and the scatter is probably just bad medicine. For a guess.

MEMBER BOYLE: Just going -- taking Don's scenario one step further, so -- and then thinking about the stem cell transplant, what's the preparation time again from diagnosis to -- you know, I know there's lots of things that need to happen. So what's -- what would we say, six months then?

DR. KEMPER: So the -- so there is two things, right. So one is the international guidelines, which say that by two years, assuming

that your development -- you know, how this, okay, developmental path that you should be -- get transplanted there. What I can tell you from -- and, again, this is based on expert opinion -- is that they would -- the experts felt strongly about queuing up the babies that had severely affected MPS I as soon as possible, so that if you could begin the process at two months of age, knowing that by the time you went through the matching, and so forth --

MEMBER BOYLE: That wasn't what I was asking. I was saying, you know, the way it happens now, if a baby is on average diagnosed by a year, can they get a transplant the next month? Or do they have -- is there some medical, you know, work-up that needs to be done that --

DR. KEMPER: Well, I mean, certainly, just a medical record that needs to be done as a matching. But -- and this is where, Nancy, I kind of like rely on you as well. Yeah. What --

DR. GREEN: So in a general way, about transplant and matching. So I myself am not a

transplanter, but I'm in the Division of Transplants. I work closely with them, particularly on sickle cell but other things as well. And I would say that, you know, it takes less time if you have a matched sib, right?

So the answer is it depends. If you don't have a matched sib, and you have to go into the national and, you know, by routine, international registry, and those donors have to be contacted and retested, and sometimes they pull out and things like that, I would say two to three months.

Now, the fact that you can use -- that there are data on cord blood -- oh, so there's cord blood, which helps in terms of match, although I have not heard a discussion of whether those were sibling cord blood or not. But, okay, so let's say they're unrelated. So that makes the possibility of a match much more likely. It certainly is not 100 percent.

And I'm sure we are all aware of patients, for a variety of indications, who just

simply do not have the option of transplant available to them. So I also wanted to raise that.

But to answer the questions, I would say two to three months depending on the source. And I'd be happy to hear numbers to the contrary.

MS. SCOTT: Well, no. I was just going to ask a question that I believe in the paper that just got published this last month, if I'm recalling correctly, you also want to eliminate -- particularly if you're going for siblings, you don't want to transplant with carriers. So you need to do that testing, because you're aiming to get the enzyme as high as possible after the transplant.

DR. GREEN: That's a very good point. Thank you, Joan. And also or a sibling who has a later onset. So another -- of disease. So, yeah, thanks. Which would then limit the pool.

CHAIR BOCCHINI: Thank you. Just please identify yourself, and then --

DR. WIERENGA: Yes. Klaas Wierenga. I'm the Co-Director for the Heartland

Collaborative. So I'm a clinical geneticist, and I have personally cared for five children in the last five years with a diagnosis of MPS. And I think I may be able to shed some light on what the confusion is about diagnosis, but -- is it six months or 12 months or 24 months.

So I think that what you have to understand is that these children develop problems at some time in their infant life. So when they are born, they are not symptomatic and they appear completely normal. And it takes some time for such a child to develop any problems, and typically they tend to be orthopedic or ophthalmologic in nature at first.

So the parent then goes to the pediatrician and says, "Well, my child developed a spine abnormality." The pediatrician cannot diagnose it as MPS I , and sends the child to an orthopedic surgeon, who then does some testing and may then or may not diagnose the child with MPS I .

So the child is symptomatic, at least

for a spine abnormality, which is associated with Hurler syndrome, but the diagnosis of Hurler syndrome may not be made at that time. So it takes a significant amount of time, and often the referral process -- you know, it's -- which is -- it's lifetime as well, because if you get a referral to genetics, in our situation if the referral is for microcephaly or a spine abnormality, nothing triggers that this is urgent, so then you may get a six-month delay in the appointment.

But at least the final diagnosis of Hurler syndrome is not made because the child wasn't symptomatic beforehand. It is just because the system is not very conducive to make such a diagnosis happen rather adequately and timely.

So I think you have to separate the issues where the child becomes symptomatic, which is usually around five, six, seven, eight months, at least to the conditions I -- but then the actual diagnosis of Hurler syndrome demonstrated by an IDUA activity that is zero, or a genetic test, that may take much, much longer.

DR. KEMPER: That's really helpful. Thank you, Klaas.

CHAIR BOCCHINI: If the international guidelines are transplant by age two, if you find a child that's eight months of age or 10 months of age, are you trying to get the transplant prior to age two, or are you looking for neurocognitive developmental changes that would then lead you to earlier --

DR. WIERENGA: Well, that's a very -- you know, so to my -- in my opinion, the clock starts ticking as soon as you make the diagnosis. So once you have diagnosed the kids, and you have certified the diagnosis by the appropriate test results, then the clock starts ticking, because then you need to get that child to transplant as quickly as possible, because hearing loss, valvular disease of the heart, spine abnormalities, they continue to affect the child. And the only rational therapy that we have currently is stem cell transplant.

So I think if you would make a case for newborn screening, you would gain two things.

One, you would obviously make the diagnosis much earlier, or at least allow for confirmatory diagnosis much earlier. But also, you cut out the referral process, which typically causes a lot of delay, but not typically in the newborn screening world, because once a newborn screen is abnormal, the Department of Health typically calls the specialty that has contracts to deal with that disease, and they would have put that kid ahead of -- head of the line.

So you gain two things. You gain timeliness in terms of diagnosis, but also timeliness in terms of an intervention. Or it becomes a possibility.

CHAIR BOCCHINI: All right. Carol?

DR. GREENE: I think the process was extremely well-described, and I agree.

CHAIR BOCCHINI: Fred?

MEMBER LOREY: Yeah. I just wanted to make a comment, to thank both of you for excellent presentations, but particularly Jelili. That was a really good public health assessment, and I

really appreciate it.

I think one of the big differences -- improvements with this one is somehow you got these people to talk without fear of losing their job or whatever. And I think that's what made that so much better, and I think it shows everybody in the room and the listening audience -- I know you get tired of this expression of "newborn screening is a system," but it really is.

And so, you know, once the Committee recommends something and the Secretary approves it, then it's these folks that are in the trenches working in newborn screening that have to face these barriers, and sometimes they are not allowed to talk about them, and they have to get the funding, and it's a lot of work. And I think you showed that with this, so I appreciate that.

CHAIR BOCCHINI: We have Alexis Thompson on the phone, wants to make a comment. Alexis?

MEMBER THOMPSON: Oh. Yes. It was just very briefly. When Dr. Greene was discussing

the logistics for stem cell transplant, something that I still do for other non-malignant disorders, just the timeline certainly has evolved quite a bit, such that most children will actually have an answer within 48 hours on whether or not they in fact have a donor.

So that is certainly worth noting, that it -- while there might be two to three months for the availability of a donor, if you know in 48 hours that you don't have one, obviously you are not waiting. And so certainly the ability to know whether one has a peripheral blood or marrow option, it actually is much quicker, and it is at no charge.

The other is is with umbilical cords, it is worth nothing that in most situations there is an agreement that one need not expect or need the degree of matching that you would for peripheral blood or marrow. And so for many children -- more children there will be matches for umbilical cord, especially if they are relatively small.

And the timeline for availability of that obviously is much shorter, so the notion about moving through the transplant process, I think that the -- that many things have been improved to actually facilitate that happening much faster.

CHAIR BOCCHINI: Let's see. Carla?

DR. CUTHBERT: Thank you. I just wanted to address a quick comment in the public health impact concerning the CDC quality assurance materials. We have had quality control materials for all of the LSDs for several years now, and this material is actually deficient in many of the lysosomal storage diseases.

In the past couple of months, we have been able to develop condition-specific MPS I materials. That's being -- that has been evaluated by our scientists, and we have tested it both on the microfluidics and the mass spec platform, and they perform well.

We have had informal evaluations by some of our laboratories, and we are going to actually have a round of formal evaluations of this

material. That information is going to be made available and compiled at an April meeting that we're going to be having, and it's -- the materials are then going to be able to move to our quality assurance program by the end of the year. So materials are actually going to be made available for everyone.

CHAIR BOCCHINI: Thank you. That's an important comment. Thank you.

Other questions at this time? All right. If not, it's five minutes to 1:00. We need to -- the next segment after lunch, just to remind everybody, two Committee members are assigned to each evidence review, so that Committee members can participate in a discussion to help develop the evidence review, but because of their involvement be able to start off our conversation with their assessment of the evidence and where it brings us on our -- to start the discussion.

So I think to get us a little bit more back on track, I guess we need -- well, we'll take a half hour for lunch, be back at 25 minutes after

1:00, so we can begin that part of the discussion, which will then lead to a vote.

All right. Thank you. 1:25.

(Whereupon, the above-entitled matter went off the record at 12:52 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:28 p.m.)

CHAIR BOCCHINI: Okay. Now we can start.

We're really in a time crunch. We have a couple of people who will have to leave for planes, and so hopefully we can make sure there is adequate time for every member to be here to vote.

So this presentation is by Dr. Botkin and Dr. McDonough. They are the two Committee members who were assigned to this condition review for MPS I , and so I'm just going to turn it over to Dr. Botkin.

MEMBER BOTKIN: Great. Thank you very much. It has been very interesting and educational beyond this group. So I'm going to provide a very quick presentation here of what our synthesis is of the information, and then of course open it up for discussion, understanding that a number of folks have to leave by about 2:00 or so.

As we often are, we're struggling with what is clearly an inadequate database for making comfortable decisions on these issues. So it's going to be a challenge, and I think this disease is one in which -- it has a couple of dimensions of uncertainty that we've heard quite a bit about. It's a rare condition, so we don't have many data points. It's a condition that has a fair amount of variability. It has different treatment modalities that have evolved over time, and, significantly, the outcomes we are looking at are developmental outcomes that require periodic assessments over a period of time.

So I would love to say let's allow pilot studies to run forward and collect data over the

next year or two, but it's quite clear that Missouri could screen for quite a few years before we would have enough data points to solidify some of the issues here. And so I think we are, at this point, stuck with an uncomfortable level of uncertainty.

So this is the matrix that I'll be referring back to periodically, and I'm going to sort of walk through the components being assessment of benefits, readiness, and then feasibility.

So in terms of outcomes, mortality, the data did not demonstrate a reduction in mortality from early intervention from newborn screening compared to treatment following clinical detection. So, really, the key outcome measure on which we have data to consider is cognitive function.

So with respect to severe MPS I -- and I'm going to draw here -- our report here draws from the language from the report, so rather than trying to paraphrase it, I have pulled out -- we have pulled out quotes here that we hope sort of

characterize the key findings.

So from the MPS I report, overall it's difficult to quantify the effects of early transplant on cognitive outcomes in severe MPS I. Although early treatment may improve developmental outcomes based on the results of one study by Poe, quantifying the magnitude of the benefits is difficult.

From the cognitive outcomes summary -- that was a supplemental document -- two recent analyses report that transplantation at less than age 16 months is associated with significantly better cognitive outcomes and lower risk of cognitive impairments among affected children. So I think these data are, again, less than definitive.

I was at least impressed with the fair amount of consistency, that each of the reports is showing benefit in a similar direction. I'd be much more concerned if we had three studies that showed no benefit, two studies that showed benefit, that sort of outcome. And, of course, anecdotal

data is not particularly reliable, but at least it provides us some additional data points here.

In terms of attenuated MPS I, it has been reported that mild cognitive impairment is common among children with attenuated MPS I , and, in particular, for a subset of the condition associated with the L23AQ missense mutation, cognitive outcomes and attenuated MPS I merit further attention by researchers.

So we didn't spend a lot of time with this with Alex's presentation, but our conclusion: there's no data available regarding whether early detection through newborn screening will improve cognitive outcomes for children with attenuated MPS I.

So net benefits, we want to think about risks, burdens, and harms. The low positive predicted value with current test technologies is a concern, and we have put sort of less than five percent here, although there is a scattering there. I think it seems like the general consensus is the positive predicted value is low, and, therefore,

there is a burden of managing a high number of false positive results. That's not unusual in newborn screening programs. It's not clear that that's different, particularly in this context and other newborn screening contexts. But we should be knowledgeable about it.

And I'd say -- a little bit of editorializing, we want to be cognizant of the harms and burdens, both to make this threshold decision about whether it's time to put it on the RUSP, but there is then -- the other set of considerations is, how do we understand what the harms are and burdens, so that we can reduce those as we implement programs, making the net benefit as great as we can as we move forward.

And that relates to this phenomenon of pseudodeficiency, which I think my understanding now is that that is something that can be readily determined by appropriate workup at the time. I will predict, however, that this terminology will be damaging to some kids and families. We ought to try to be creative and come up with a better term.

This suggests that the kid has pseudodeficiency when in fact it's the test that is inadequate producing this result. So some work on this potentially destructive notion of pseudodeficiency might be worthy.

Stem cell transplant creates a risk of morbidity and mortality. Of course, kids who are detected clinically get transplants, so not clear that there is a marginal increased risk here, other than this last bullet that I think we should be wary of, uncertainty about whether there might be inappropriate transplants in children who don't require a transplant.

Sounds like there is not much concern about that at the present time with the level of expertise with the current centers. Potentially, as this moves out to a more population base, and other -- many other centers potentially being brought on board with these decisions, certainly some risk needs to be noted that kids may get transplants who don't need them.

Conclusions about net benefit --

benefits of early detection via newborn screening for children with severe MPS I are not definitive due to the lack of data from newborn screening systems. However, in terms of cognitive outcomes, results of studies in other clinical contexts strongly suggest that significant benefits can be anticipated. Cognitive benefits of early interventions to children with attenuated MPS I remain to be determined.

So in our rubric here, our matrix, we are putting this level of certainty about cognitive benefits for children with severe MPS I as high.

Feasibility -- most appropriate test platform protocol for screening remains to be determined. It does seem clear that additional instrumentation will be necessary here, but that's a challenge for programs certainly, but it doesn't undermine feasibility.

Several options have been evaluated in the context of population screening, clear evidence that population screening is feasible, but additional work necessary to find the most

appropriate test platform and protocol, and of course always possible that different programs will adopt different approaches to screening.

So we consider the feasibility of newborn screening for MPS I to be high or moderate, which is the category here on our matrix.

And then, lastly, the issue of readiness, survey of public health impacts. Here is the quote. "Although most respondents reported that screening for MPS I could be implemented between one and three years after funding was made available, it is critical to recognize that obtaining funding for the screening test was seen as a major challenge by 81 percent."

So our synthesis there is that most public health departments are "unprepared" for screening, and that puts us in the A3 category here. And I think in contrast to Jelili's presentation where I think he qualified readiness as after funding was available, we are sort of considering this as now in that that whole funding cycle for many states which often takes at least a year would

be just beginning.

Our recommendations -- the Advisory Committee recommends that newborn screening for MPS I be approved under matrix category A3. Substantial work will need to be done in most states to fund, develop, and implement screening for MPS I. Therefore, states should be encouraged to implement screening within three to five years of approval for inclusion on the RUSP.

Second bullet, early adopters of newborn screening for MPS I are encouraged to obtain data in a rigorous fashion to promote continuous improvement of the evidence base regarding the risks and benefits of screening. And, in essence, this is not really pilots on the fly, but collecting data on outcomes, say, for kids in ways that will help us reassess this -- this particular program moving forward.

CHAIR BOCCHINI: Jeff, thank you very much.

MEMBER BOTKIN: I believe Dr. McDonough had, then, comments that he wanted to

pick up on.

CHAIR BOCCHINI: Steve?

MEMBER McDONOUGH: Thank you for that excellent presentation. The only thing I would like to add due to the constraints in time is I did ask the Hartman Group regional collaborative their opinion on MPS I before I came out. I usually do that when there is a vote, just to get the opinion of people in my area. And out of 24 responders, 18 or 75 percent were in favor of adding MPS I to the RUSP.

CHAIR BOCCHINI: All right. Thank you. So are there additional questions or comments from the Committee? Charlie.

MEMBER HOMER: Can you put our matrix back up there? So, first of all, that was an excellent presentation, and I greatly appreciate it. Based on the presentation this morning, our concerns about the lack of clear evidence of earlier detection from newborn screening compared to clinical discovery, it feels to me this is in the B category.

That is, I think there is -- the data -- I was relatively convinced about the data of earlier versus later transplant and its impact on developmental outcomes. But I am less confident that implementation of a screening program compared to current practice would result in a -- I mean, I guess for me I would say I like the language in B, a moderate certainty. Am I highly certain that it will result? No, I am moderately certain that it will result. I don't think that -- I don't know. So that would be my personal belief, given the data. Significant benefit but only moderate certainty that the significant benefit will go into place.

MEMBER BOTKIN: Well, maybe I could ask Dr. Bocchini a question in response to that. I'm not at all opposed to that line of thought here. And so one question perhaps might be, what are the implications of that different categorization? That may well be a better articulation of the level of certainty.

My -- our sense I think was that

screening should go forward. So if categorization into a B4, say, which is what I think would be the alternative category there, would preclude including on -- going forward on the RUSP, then that probably would be my hesitation about that categorization. So it's a little bit of a circular argument.

MEMBER HOMER: We're not supposed to think that way, right? I mean, we're supposed to think of, what is the evidence and the benefit, and, therefore what conclusions occur rather than what we think should happen and justify it based on the categorization.

MEMBER BOTKIN: Well, I agree with that, although ultimately you kind of have to put these considerations in a blender and decide whether you think it's time to go ahead.

CHAIR BOCCHINI: All right. Don?

MEMBER BAILEY: So just to remind us of a little bit of history. When we voted on the matrix a couple of years ago, I know that I think I and maybe Steve and maybe Dieter voted against

it, because I was arguing that a B ought to be recommended for the RUSP, because this does -- I do agree this should be recommended for the RUSP, but I agree it's a B in the way we've categorized things before, because we don't have high certainty.

I'm certain enough that I agree it should be added to newborn screening, but I think we have to -- if we do this and call this an A, we have to recognize we have changed the bar, we have changed the standard for what we're considering an A, and what are the implications for other conditions that we review going down the path.

I'm not opposed to accepting that recommendation. I just want to make it clear that that's why I -- I actually had a crystal ball, then, right? Because this is exactly the kind of situation that this puts us in.

CHAIR BOCCHINI: Thank you. Kellie?

MEMBER KELM: Kellie Kelm. I think we decided to not designate that certain boxes mean that it automatically goes in the RUSP and that it

would be left up to the Committee. So I think that you would have to think about that.

I agree that it's -- in my opinion, I was leaning towards B of, you know, moderate certainty. And I don't know, I hesitate whether or not a B should be recommended for screening.

CHAIR BOCCHINI: But I think it is clear that the Committee can determine that it's a B, and decide to put it on the RUSP. I think.

Well, again, this was -- we wanted this to be the -- a way to define things, but at the same time offered the Committee the latitude to make a decision by looking at all the factors together. So I don't think we precluded that you could say a B and then could not move that forward. Yeah. Isn't that -- okay. All right.

Cathy?

MEMBER WICKLUND: Cathy Wicklund. I don't have anything; I just want to echo that to me this feels B. I mean, when I'm reading the evidence, when we're hearing the presentations today, I just don't see how we can say there's high

certainty of the benefit. So I agree that it should be categorized in a B level.

CHAIR BOCCHINI: Okay. Further comments or discussion from the committee? All right.

MEMBER BAILEY: I would like further clarification on whether we can recommend a B go on the RUSP, because that would -- that would be important to know.

CHAIR BOCCHINI: As I interpret it -- and then, again, I'll go back to Debi and then to Alex as we put this -- and Coleen, I mean, I --

MEMBER BOYLE: Well, first, let me just make some -- offer another point as well. So, I mean, I think this is a perfect condition where, you know, a multi-state pilot rollout would be just appropriate to clarify all of the unknown factors, maybe not even a certainty around the evidence, but just in terms of the harms issues and all of that.

So, I mean, I know this is going in our matrix, but I'm just going to put that on the table as well.

CHAIR BOCCHINI: Well, certainly that could be stated in the recommendation to the Secretary, if we chose to recommend that it go forward.

Dieter?

MEMBER MATERN: I don't like the matrix.

(Laughter.)

For the reasons mentioned. And I think if we applied the matrix to all the conditions that came before this one, at the point it was included in the newborn screening programs, you probably would never reach an A level. For galactosemia, we don't have perfect outcomes. For other conditions, we don't really know to date how it really works. So if you want to have an A, it will be beyond our lifetimes.

CHAIR BOCCHINI: Yes.

DR. TARINI: Beth Tarini, AAP. So two comments. One, to Dieter's point, I think about past disorders, I think it's a bit of a fallacy and inappropriate to use the disorders that stand prior

to the formation of this Committee to make current judgment, even if they conflict -- unless we are going to enter a whole new world, we're going to start reviewing and taking off.

So similar to the dried-blood spots, what stood prior to the Committee should stay separate, in my opinion, and not influence the current decisions, which are based on the structure that was created. So if it's on, galactosemia was on, it wouldn't have made the cut. That was in a past era.

But to Coleen's point, to echo that and say in addition to the harms, I think that what multi-state pilot would add are the ability to see the effectiveness of the treatment when you're going to be doing the bone marrow transplant in the real world, with the real complications, with centers that may not have as much experience as others, and bone marrow transplants have -- I'm not saying one way or the other. I'm just saying they have complications that can affect the success of them. So that might also be helpful data.

CHAIR BOCCHINI: So we've gotten back to 2012 when we proposed the matrix, and we said as a general approach conditions that were A1 and 2 were recommended for addition to the RUSP; A3, 4, and B, an expedited review will occur after noted gaps are addressed by nominator; and then C, D, and L, resubmission is required for consideration to the RUSP.

So that's how we proposed the way this matrix would be used, and, again, this was the proposal, but I'm -- and, again, it's two and a half years ago, I'm fairly certain we gave some latitude to the Committee to move forward with the matrix being the approach to categorize.

MEMBER McDONOUGH: Mr. Chairman, at the time, you -- after we had that discussion, you indicated anything A3 and 4 would go forward to the Secretary for her consideration. So we didn't just stop at A1 and 2. A3 and A4 would go forward, but we should be aware of our vote.

CHAIR BOCCHINI: We'll have to go back and find the vote. This was the initial proposal,

not the conclusion. So you're right. That's important.

MEMBER BOTKIN: So, Dr. Bocchini, just --

CHAIR BOCCHINI: Yes.

MEMBER BOTKIN: -- you know, I would be probably more comfortable with our system, at least in the context of this disease, if we would consider perhaps a more nuanced approach. I mean, I do agree that the moderate degree of certainty is a more accurate characterization here.

But because we have such a dichotomous system where if it's not on the RUSP then implementation sort of is in a research mode, whereas once it's on the RUSP it's sort of part of public health mandates in many states. And what our last bullet was was to suggest that we would need more data here.

So is there a way perhaps that a B categorization would imply that this ought to be implemented in a way in which there is more data collection through some mechanism to answer these

questions? Because what we don't want is this, go ahead, implement, 15 years later everybody is still wondering, you know, gosh, was this a good idea or not, because we don't have the adequate data collection.

And I don't know what that would look like, but, you know, are there ways that we can assuage people's anxieties about this by trying to assure that we will get the data in a reasonable timeframe by approving this.

MEMBER LOREY: Joe?

CHAIR BOCCHINI: Yes.

MEMBER LOREY: I think there is, and I completely agree with what Beth said. But I'll go back a little bit, and use the SCID example because that's the one that came after, you know, Pagu. And that's sort of what happened with SCID.

SCID, compared to what we've heard today, is somewhere in the A category. I think everybody would agree. But the first time it was I believe not approved because they wanted to see more pilot work, but then they actually approved

it and then the Texas, California, New York group, Wisconsin, did the bigger pilot. So I think there is room for your suggestion.

DR. CHEN: Freddie Chen, AAFP. You know, we -- this Committee has no control over the evidence. We come to consensus around how we grade the evidence, but we do have control over our consistency, both with our past decisions and then going forward in our future decisions. And that I think was -- is important to bear in mind. Personally, and, you know, organizational reps don't have a vote, but I would think this is a B category.

CHAIR BOCCHINI: Steve?

MEMBER McDONOUGH: Yes. Mr. Chairman, one of the points made a couple of years ago is I felt that Bs should be able to go forward. And I don't know how long it is going to take to get enough data on how many kids are going to be brain damaged because they weren't treated in time.

The longer we delay in adding this to the RUSP and getting states to move forward, there

are going to be kids who are going to definitely be suffering from that. So I think that Bs, individually considered, if we have a consensus that there is enough stuff to add it to the RUSP, that we ought to do that, and we ought to change what we did two and a half years ago.

CHAIR BOCCHINI: Well, I think that the matrix was never designed to box the Committee into a position. The matrix was designed to give a framework within which we could work, but the Committee has the latitude I think to make a decision that would incorporate what you just said. I don't see a problem with that. Melissa?

MEMBER PARISI: This is Melissa Parisi. In response, Jeff, to your comments about continuing to do research for this condition, I think we have a track record, both with SCID and now that's emerging with Pompe disease, at least in terms of trying to ensure that if something is accepted for addition to the RUSP, that we do have the newborn screening translation research network and other systems in place to allow us to continue

to study the outcomes for those infants that are screened in the states that are willing to start the adoption and have the capability to add it to their newborn screening panels.

CHAIR BOCCHINI: Coleen?

MEMBER BAILEY: I don't know if it's appropriate to make a motion, but I recommend that we classify this as a B3, that we recommend that it be added to the RUSP, but that we urge, you know, extensive pilot studies to document efficacy and extensive work on reducing false positives. And those are really two high priorities over the next four to five years, that states work towards being able to implement it. That would be my recommendation.

CHAIR BOCCHINI: So this is a motion?

MEMBER McDONOUGH: Second.

CHAIR BOCCHINI: Seconded. Okay. Yes, further discussion. Yes.

MEMBER BOYLE: So I would like to actually see if we have a record of what we put forward for Pompe and what that language -- A2 --

the first time that we suggested the -- the first time where we actually suggested pilot studies.

CHAIR BOCCHINI: I think that was before the matrix was there.

MS. SARKAR: That's right. So the first time Pompe went through there was no matrix.

CHAIR BOCCHINI: Charlie?

MEMBER HOMER: Just two points. I don't have any trouble with us basically modifying the matrix, so that a B includes recommendation. Again, looking at Iris, the U.S. Preventive Service Task Force, A and B recommendations both have relatively equal force in the sense of -- so -- or do have equal force. So I think that doesn't trouble me.

I do want to point out in my role as Chair of the Long-Term Follow-Up Committee, and one of the authors of our paper on establishing mechanisms to monitor and see whether newborn screening achieves its purpose, what we're talking about here, in terms of monitoring, is something that at least our Subcommittee and essentially this

Committee has said should be in place anyway for all newborn screening, so I'm perfectly happy that we're saying, yes, in this specific case we should be monitoring.

But the point is, if we recommend anything, we should be monitoring whether in fact newborn screening is achieving its promise, and this would give further impetus to that.

CHAIR BOCCHINI: Okay. Thank you. Other comments?

Chris Kus? Chris, can you hear us? Is Chris Kus's line open? You indicated he -- okay. Chris, go ahead.

DR. KUS: You can hear me now?

CHAIR BOCCHINI: We can.

DR. KUS: Okay. Okay. I would just like to reinforce what Charlie just said. When we make these recommendations, we then say they need to be studied, but all newborn screenings should have long-term follow up to collect the information. That should be part of the project. So I would just emphasize that.

CHAIR BOCCHINI: Okay. Thank you. Other comments?

MEMBER THOMPSON: This is Alexis Thompson. Can you clarify -- so based on the most recent recommendation, so I think that was maybe from Don, you're saying that you're accepting that it's a B, but you're saying we should approve it anyway? Did I misunderstand that?

CHAIR BOCCHINI: Don?

MEMBER BAILEY: No, that's correct, Alexis. I just feel that, you know, the cost of not doing this outweighs any cost associated with doing it. I think we shouldn't be setting a precedent that everything that is classified as a B goes forward, but that gives us the option of doing that when we are -- when we have had enough discussion to think, you know, in the balance of things this is a good decision. But I don't think we should change our rules to say that all Bs would automatically go forward. Those are more nuanced decisions.

MEMBER THOMPSON: Thank you.

CHAIR BOCCHINI: Okay. Other comments? Okay.

MEMBER BOYLE: One more. Sorry.

CHAIR BOCCHINI: Yes.

MEMBER BOYLE: Just so that this isn't precedent setting, I guess I'd like a little bit more discussion about what, you know, makes this different, perhaps, from another. So one of them for me is the rarity of the condition and, you know, the ability to be able to get new data perhaps to change what the evidence currently is. But I guess I'd like something like that in there versus just us saying, oh, well, next time, you know, whatever. So, I mean, I feel like we need to build on our process. Otherwise, there won't be any order.

CHAIR BOCCHINI: Right. I think that the specifics related to this condition, I agree with you I think putting those into the letter to the Secretary as to why this decision was made I think would be very appropriate and necessary, because, you're right, I don't think -- I don't think this needs to be considered as a

precedent-setting decision.

I think this is really looking at the data, looking at all of the factors, looking at the fact that Hurler is -- if there is a gap in diagnosis it makes a difference in terms of when transplant is done, so I think that there are a lot of features that would make what -- the decision, if it's voted in, reasonable for that to happen, even as a B3.

MEMBER BAILEY: So just to -- I just feel like if we're going to have the matrix, we ought to be true to the classification descriptions. And so A is high certainty of net benefit, and we don't -- it doesn't fit that, and so we should be true to that. But if we have the flexibility to still make a recommendation for screening, then that's where we want to be, I think.

CHAIR BOCCHINI: Okay. That's well put. Okay. All right. Dr. Lu?

MEMBER LU: I guess on that point, whether we should consider separating the vote, so first to vote on the categorization, and then based on that, whether to add it to the RUSP given the

categorization.

CHAIR BOCCHINI: Okay. Okay. I think that that -- would you like to make that as a motion? Should we do that as a motion? And then -- because that would be separating the vote first to vote on category, and then -- then we have Don's motion to then move it within that category, if that's what it turns out to be, with a separate vote ahead.

MEMBER LU: So I will do my best. I move that we categorize this as a B3.

CHAIR BOCCHINI: Okay. Is there a second to that? Dr. Botkin? Okay. Further discussion? Okay. Then --

MEMBER THOMPSON: Could you repeat the motion? I would -- I couldn't hear it on the phone.

CHAIR BOCCHINI: Sure. So the motion that we are going to vote on is that we make MPS I a B3 -- put it in a B3 category in the matrix. So we're dividing the vote to first indicate the category, and then we'll have a subsequent vote to indicate the decision about whether to recommend

it to the Secretary.

MEMBER THOMPSON: Great. Thanks.

CHAIR BOCCHINI: Okay? So let's start this vote, then, with Charlie Homer. This is to determine whether this should be a B3 category.

MEMBER HOMER: Approve the B3.

CHAIR BOCCHINI: Okay. And then Fred Lorey?

MEMBER LOREY: Approve.

CHAIR BOCCHINI: Michael Lu?

MEMBER LU: Approve.

CHAIR BOCCHINI: Steve McDonough?

MEMBER McDONOUGH: Approve.

CHAIR BOCCHINI: Dieter Matern?

MEMBER MATERN: Approve.

CHAIR BOCCHINI: Melissa Parisi?

MEMBER PARISI: Approve.

CHAIR BOCCHINI: Alexis Thompson?

MEMBER THOMPSON: Approve.

CHAIR BOCCHINI: Cathy Wicklund?

MEMBER WICKLUND: Approve.

CHAIR BOCCHINI: Andrea Williams?

MEMBER WILLIAMS: Approve.

CHAIR BOCCHINI: Don Bailey?

MEMBER BAILEY: Approve.

CHAIR BOCCHINI: I approve. Jeff Botkin?

MEMBER BOTKIN: Approve.

CHAIR BOCCHINI: Coleen Boyle?

MEMBER BOYLE: Yes.

CHAIR BOCCHINI: Okay. Iris Mabry-Hernandez?

MEMBER MABRY-HERNANDEZ: Approve.

CHAIR BOCCHINI: Okay. Kellie Kelm?

MEMBER KELM: Approve.

CHAIR BOCCHINI: Okay. So this is to -- it's approved as a B3 category on our matrix. So now the second vote is on Dr. Bailey's motion that this move forward to be -- recommendation to the Secretary to add this condition, MPS I , to the RUSP. And, certainly, in the letter we will include the additional information that is required to meet what Coleen raised about providing the data as to why we made this decision to move

this forward, and then to add the additional data that was in the initial recommendation by Dr. Botkin. Yes, sir.

MEMBER BOTKIN: I think as part of this discussion what came forward was perhaps we should be more -- speak more directly to the Secretary to say we would encourage the Secretary and HHS to support additional data collection, perhaps through large-scale pilot studies or some such thing. This recommendation is really encouraging states to do that. Maybe we should encourage the HHS to play an active role there.

CHAIR BOCCHINI: And we did that with the Pompe decision as well.

MEMBER BOYLE: I would like someone to restate what we're voting on, so we're clear. I'd like someone to restate what we're voting on, so it's clear. Is that okay?

CHAIR BOCCHINI: Okay. All right. So the vote is whether to include MPS I on the RUSP. That's the vote.

MEMBER BOYLE: What's the caveat?

CHAIR BOCCHINI: Okay. Well, the caveat is it's -- since we've separated the place on the matrix versus the recommendation, so this is a recommendation to go forward. If voted yes, it would be to put this on the RUSP, and additional recommendations to the Secretary would be -- or additional information given to the Secretary would include the rationale that was discussed, and we'll pull those out from the minutes for why the Committee determined that this should go forward.

And it will also have a recommendation that the Secretary add help in organizing continued pilot studies and obtaining additional data for the evolution of -- and using the early adopting states to provide -- and make the recommendation I think that was nicely stated by Jeff that additional data from pilot studies or states doing studies be collected in such a fashion that it could be used to help inform additional recommendations for -- and that would go for the platform that might be used as well as other things. Is that -- I don't know. Okay. All right. Okay. Carol?

DR. GREENE: Almost --

CHAIR BOCCHINI: Okay.

DR. GREENE: Maybe more, you know, language and what words you choose, but I'm imaging myself as an analyst working for the Secretary, trying to decide whether she will agree or disagree. And to say, "I want it on the RUSP, but I need pilot studies" is going to be a serious red flag for anybody analyzing that.

So, you know, if it's on the RUSP but we all -- we certainly need data, if you really feel it needs to be on the RUSP, I would just suggest that you wouldn't use the word "pilot studies," but say there needs to be more work on implementation, and improvement, and quality improvement because there are still some challenges. So if you feel strongly it should be on the RUSP, then I suggest you don't use the term "pilot studies."

CHAIR BOCCHINI: Okay. Thank you. Cate?

MEMBER THOMPSON: This is Alexis Thompson. I had a question -- maybe it's a

difficult one to answer -- I think someone tried to address it earlier. If we think that there are some key pieces of information that would, for instance, allow us to move this from B to A, do we have any estimates on how long that might take? I understand that we may never have, you know, complete clarity, but if there were some minimal piece of information, how long would it take to accumulate those, do we think?

CHAIR BOCCHINI: You know, I don't know that I could answer that. Around the table, it's being considered it would take many years. Yes. Okay. Cate?

MS. VOCKLEY: I'm not sure how to integrate this into where we are now, but because we look at newborn screening as a whole system, from screening at birth through follow-up diagnosis and on, I wonder if there is some place to integrate some language about workforce issues, because that has been a big issue in the states that are doing screening for lysosomal disorders for people who are doing the -- dealing with the attenuated

patients or the false positives, just to look at how states can do that in a better way.

CHAIR BOCCHINI: Yes. I'm not sure that would be a Secretary's decision or involvement. I think that --

MS. VOCKLEY: That's what I wasn't sure.

CHAIR BOCCHINI: Yes. But I do think that the recognition that this is a three, that states are unprepared, would essentially indicate that that is a real -- that may be an issue for some states, and certainly something that might need to be addressed by particular states before they went forward. But probably not for the Secretary. Okay? But thank you for the comment.

MEMBER WILLIAMS: Dr. Bocchini, this is Andrea.

CHAIR BOCCHINI: Yes.

MEMBER WILLIAMS: So, you know, I still have a little bit of uncertainty in my heart, knowing that -- if there's any way possible for us to continue to look at the harms, unintended -- and

with the uncertainty with those treatments, and we hope it gets better, but it's not -- the access is not there -- so I don't know how to put that into, you know, what we say, but we still need to pay attention to it -- being selected. I still think it needs to be a part, you know, the way the ongoing studies happen.

CHAIR BOCCHINI: So, I'm sorry -- you broke up a bit, so I'm not sure that I got the gist of what you were asking. I know you raised a concern about having opportunity for everyone to have treatment, and what the harms might be.

MEMBER WILLIAMS: Right.

CHAIR BOCCHINI: Well, you know, again, I think since the -- for Hurler's, that the evidence is that we're probably identifying all those patients, and so there is not going to be an increased number of those patients. And the opportunity for newborn screening would be that we would be finding them earlier. I'm not sure that it would change what's going on now in terms of availability of transplant and the like. So I

don't think that's -- I think what we're doing is providing the opportunity for earlier diagnosis and potential intervention.

MEMBER WILLIAMS: Absolutely, I think that's true.

CHAIR BOCCHINI: Okay.

MEMBER WILLIAMS: And I apologize for breaking up.

CHAIR BOCCHINI: No, no. That's not your fault. Okay. Beth?

DR. TARINI: Beth Tarini, AAP. One thing I want to put out into the discussion is, if the Committee makes an approval contingent upon future data, then I think that it behooves us to make at least some attempt to formally then reassess data. Otherwise, it seems a bit of an empty recommendation, because then no one actually judges the data that we are looking to fill gaps on, especially if it has been a recommendation.

CHAIR BOCCHINI: We're not making the recommendation contingent upon that data. We're just identifying the gaps that exist. So I think

there is a difference. Fred, did you want to --

MEMBER LOREY: Yes. This may be a false assumption on my part, but I worry if we take out the word "pilot" it decreases the probability of making funding available, because, once again, if this recommendation goes through, this is going to fall on the newborn screening programs, and they are going to have to be the ones to scrape for the money and convince people. And maybe we don't have the use the word "pilot," but just word it in a way that doesn't decrease that possibility.

CHAIR BOCCHINI: Okay. I understand. Don, you had a comment? And then Dieter.

MEMBER BAILEY: No. I think I was just going to say what you said. That we're not making this contingent on this, but I think in line with Charles' point, broader point, that we should be doing a follow up on all conditions to evaluate the, you know, long-term benefit of -- once we implemented these screening and whether -- I'm not saying that we necessarily need to reevaluate them and whether they should go off the RUSP, but I do

think we ought to have a revisit of them every five years or so, every so many years, to say, "Okay. Well, are we? You know, what happened since we made that approval?"

CHAIR BOCCHINI: Right.

MEMBER BAILEY: And this is certainly one that's a clear need for that.

CHAIR BOCCHINI: Okay. Dieter?

MEMBER MATERN: I don't think it makes a difference whether we state "pilots," and I don't think why -- the Federal Government should fund, because necessarily the states are going forward anyway with screening for MPS I. They should figure out how they get the funding to do that locally I think. So I would not put in "pilot" in this recommendation.

CHAIR BOCCHINI: Okay.

MEMBER LOREY: But it doesn't work that way in every state, Dieter. It's a big battle in the majority of states.

CHAIR BOCCHINI: Okay.

MEMBER LOREY: Well, we can -- you

might be right. It may not make a difference, but just word it in a way that doesn't --

CHAIR BOCCHINI: Okay. Well, we'll be careful on that, and -- okay. All right. If there are no other comments or questions from the Committee, then, yes, sir?

MEMBER BOTKIN: Jeff Botkin. I should probably put back up the recommendations. But if we do approve it, have we approved -- we approved it under B3. So is that an explicit message to the states about the timeframe that they ought to be thinking in terms of for proceeding forward, or should we include a specific revision to say that states don't need to be thinking about trying to get this on board in the next year, that we understand that there is a period of time that they will need to get up and running on this.

CHAIR BOCCHINI: I think we will include that. I think when we made these designations we did say that if states were unprepared it would -- we would expect there would be a three- to five-year timeline for states to --

so it would be, you know, one to two, two to three, three to -- and three to five, or something like that when we did that.

So I think that's reasonable to -- to make the Secretary aware of what we believe is the developmental level or the -- where it states how much time it might take for states to become prepared. We can certainly include that. Okay. Other comments, Committee? Then, let's go ahead and vote. And I'm going to start this time with Dieter and go in a different -- opposite direction. So, Dieter Matern?

MEMBER MATERN: I approve to add MPS I to the RUSP.

CHAIR BOCCHINI: Thank you. Steve McDonough?

MEMBER McDONOUGH: I approve.

CHAIR BOCCHINI: Michael Lu?

MEMBER LU: Approve.

CHAIR BOCCHINI: Fred Lorey?

MEMBER LOREY: Approve.

CHAIR BOCCHINI: Charlie Homer?

MEMBER HOMER: Approve.

CHAIR BOCCHINI: Kellie Kelm?

MEMBER KELM: I admit I am struggling. Since we are asking for, similar to Pompe, more pilot data and the issues with certainty for treatment early on, I think at this time, I mean, I would prefer like SCID to defer until we had that data, you know, to be consistent with SCID. So I'm going to vote against.

CHAIR BOCCHINI: I think we have Iris Hernandez on the phone. All right. We'll try her again in a second. Coleen -- yes, Coleen Boyle?

MEMBER BOYLE: I'll approve.

CHAIR BOCCHINI: Jeff Botkin?

MEMBER BOTKIN: Approve.

CHAIR BOCCHINI: I approve. Don Bailey?

MEMBER BAILEY: Approve.

CHAIR BOCCHINI: Andrea Williams?

MEMBER WILLIAMS: Approve.

CHAIR BOCCHINI: Cathy Wicklund?

MEMBER WICKLUND: So I am also really

struggling with this decision, and for the reasons that Kellie already articulated I'm going to vote against.

CHAIR BOCCHINI: Okay. And then, Alexis Thompson?

MEMBER THOMPSON: I share Kellie and Cathy's concerns, and I vote no.

CHAIR BOCCHINI: And then, Tiina Urv will be voting for Melissa Parisi.

DR. URV: Yes. We approve.

CHAIR BOCCHINI: Okay. So the motion passes, and I certainly appreciate all the work that everybody has done to get us to this point, and thank everybody for their commitment to do this in the -- in the way it was done. I think that this certainly is good work by everybody involved, so thank you all very much. And I know some people have to leave -- oh, Iris, I'll give you one more chance. Are you on the phone? Okay.

All right. Now we have -- to close up we have the reports from the three subcommittees, and, Cathy, are you -- is it too late for you? Can

we -- okay. Beth will do it for you? Okay. All right. So we had changed the order because of airline requirements, but I think we have gone over, so let's start off with the Education and Training Subcommittee. And so Beth will make the report.

DR. TARINI: Okay. So to review our priorities, our first point was to review the existing projects that we had to close them out and/or provide a timeline for closure. The ones that remain are Priority A, identify heritable conditions not part of the RUSP and for which screening and treatment will most likely occur at a later point in child development.

And we chose heritable conditions that would represent a variety of clinical characteristics, age of presentation, age of diagnosis, clinical morbidity. I'm sure you could repeat the slides back to me, based on that you've seen them before.

So we had finished that assessment. That was presented previously, I believe last

meeting if not the meeting before as well. And so the next step is that now Dr. Bailey will lead an effort to write a white paper summarizing the work of the initiative, discuss the role of public health in child screening versus the role of practice guidelines. The first draft of this will be presented to the Subcommittee in May, and interested Subcommittee members will contact Dr. Bailey to help with the draft.

Priority C, to provide better guidance for advocacy groups and others regarding the nomination and review process. And I just want to also say that this priority has gone through a number of iterations in terms -- because of barriers to actually creating it and posting it in certain locations due to restrictions, and what we could actually provide based on websites available.

So, in some ways, this has been a work in progress, or in many ways. So we are now at the point of a public-friendly summary document of the Committee's process related to nominations, and

collaborating with Natasha Bonhomme from the Genetic Alliance.

And Natasha presented an overview of the purpose of the proposed project. She had agreed, since the last meeting, that she would work on this for us. She presented an overview with the target audience, key messages, and the general content taken from the submission of nomination package, all those steps going through.

And after discussion with the Committee and feedback, she will create and present specific content at the May meeting. And, once finalized, this content -- once this content is finalized, we will then determine the best way to package, present it to the public.

Priority C, develop a glossary of terms to be incorporated into the Secretary's website, the Secretary of Committee website. We discussed the glossary that Jeremy Penn and Cate Walsh Vockley are working on, are leading the charge for, and so the revised glossary was presented to the Committee for feedback. Feedback was given. It

was discussed, and Cate and Jeremy will work with Natasha to identify advocates to review what we have, and revisions will be made based on that feedback and then presented to the Subcommittee at the May meeting. That is the end. Any comments or questions?

CHAIR BOCCHINI: Thank you, Beth. Questions? Comments? Hearing none, thank you very much. Let's go to the -- next is Follow-Up and Treatment Subcommittee update, Charlie Homer.

MEMBER HOMER: So this is the report on the Long-Term Follow-Up Committee. We really have two main areas of activity that we have focused on for these last several meetings. Those include -- the first is identifying those barriers that impede access to high-quality counseling and treatment services required for long -- for effective long-term follow up -- thank you for the full screen -- and proposed policy solutions to address them. We'll discuss that further in a minute. And the second is facilitating widespread implementation of the framework for assessing outcomes from

newborn screening, which we just discussed.

So on the first one, we had a conversation in January with Dr. Lu, and that was what I was referring to, about whether this first area is an appropriate avenue of focus for our Subcommittee and for the Committee as a whole. The guidance that I believe Dr. Bocchini and I received from Dr. Lu at the time was in fact this is an appropriate area, although very much for the full Committee as much as for the Subcommittee, Subcommittee may frame it and bring it forward, but that it is a matter of topic.

But we had a specific conversation where Dr. Lu asked us to emphasize and focus on the unique and specific contribution that this Committee can do compared to, for example, the regional collaboratives or grantee organizations, such as the Catalyst Center that may be working in general in this area of the impact of health reform on access to and quality of care.

So we used that to inform our conversation that said focus on our unique

attributes. We had a wide-ranging conversation yesterday. I had a preparatory conversation with Meg Comeau about the work that she is doing at the Catalyst Center, and the work she is doing in coordination with the regional genetic collaboratives.

We focused on a number of areas. Three areas -- one, the issue of coverage, the sense of whether in fact essential health benefits address the broad needs of children and youth with special health care needs, and specifically those identified through newborn screening. And a potential policy action that could follow from that is mechanisms to incorporate input from families and providers and advocates in the upcoming mandated revision of the essential health benefits from the Secretary.

The second was simply highlighting that access, financial access and coverage -- that coverage -- that is, having an insurance card -- does not necessarily mean that you have access to the quality services that are necessary, and that

could include both limitations of the availability of workforce to meet the needs of the population and specific interest in areas around transition.

And the second was whether there are appropriate incentives and payment models such as are starting to exist for, for example, adults who have dual eligibility for Medicaid and Medicare due to the basis of their disability. And so there could be a further exploration of what kind of incentives to providers could facilitate enhanced access.

And the third element of this, again, ties to the broader question of whether there is in place a mechanism for prospective monitoring, not only to see whether recommendations -- when something gets put on the RUSP, it has the desired outcomes, but in the presence of health reform and changes -- not just -- changes in the health care delivery system writ large, can we implement a monitoring system to assess the impact on this population.

So those were topics that came up. I

think the question for us that -- and I think for the Committee -- and, again, knowing the time, we don't really have time, but I think this will be follow-up conversations with Dr. Bocchini and myself, Dr. Lu, and Debi Sarkar, is how do we take this concept forward?

You know, Dr. Lu highlighted that this really was a topic that should be addressed at the full Committee, and not necessarily contained within the Subcommittee. We wanted to bring this to the full Committee's attention. We thought perhaps we could identify appropriate experts for presentation to refine the general approach and the specific recommendations and come back to the Committee with additional background and recommendations.

So that was -- we spent most of our time yesterday discussing this issue. And, no, it does not mean we are wrapping this up within the next session, which is an area of concern. But I just wanted to highlight that.

So that was part one. Part two of our

conversations -- again, we have -- we have impressed, or soon to be impressed, or awaiting final signatures and clearances to be impressed. The framework that we have discussed, presented, this Committee has authorized, are going forward about setting up a monitoring system. Our Committee is committed to, how can we facilitate the implementation? We have a Subcommittee or work group Susan Berry and Deb Badawi are chairing.

This is -- how do we operationalize this? We have had a discussion about, can we identify exemplar states? We had the benefit of a presentation from Dr. Tarini yesterday, which had been previously shared with the Committee about two years about, but our memories were not perfect. And so it's very useful to hear it again.

Coming out of that, we -- the way those data were sliced and diced, we have sort of in the aggregate performance across states, but we can't from that data say, you know, North Dakota is the best state in the country with their systems, because that's not how the data were sliced, plus

there were ways that the survey data were collected that would make that difficult.

So, really, this is another one where, again, I'm actually looking to conversations with Dr. Bocchini about, are there strategies for how we can sort of move this forward and wrap this up? We talked about and we actually have obtained information from the regional genetics collaboratives.

We're going to go back to them, ask them to identify high performing states. We thought new steps could be helpful in this. We identified that there was a previous document on roles and responsibilities of states, the Fed's delivery system, that we could revisit. But, really, this is an area where we're looking to guidance as to what the appropriate -- our Committee is very, as I think the whole Committee, is focused on this area, but we're not sure what our best leverage is to move this forward. So I think that's -- I think that's where we are. I don't know if -- yes, that's the end. I don't know if my Subcommittee would like

to make any points, or, Dr. Bocchini? Carol?

CHAIR BOCCHINI: Okay. Carol?

DR. GREENE: A great discussion. I just wanted to add that I'm not sure that there was actually a document about roles and responsibilities. Coleen was the Chair of the Committee at the time, and I think there were some outlines of some ways it could be approached. But I'm not persuaded that -- yes, never got to a document.

MEMBER HOMER: Yes, yes. I'm sorry. Jill is saying that in fact she did find two draft documents. She had sent them to me I think last night, so we -- they weren't finalized, so they're just an early draft. Any other comments either from Committee -- Subcommittee members for clarification or response?

CHAIR BOCCHINI: Well, I think -- I certainly appreciate you working to bring us to this point. And as we discussed, I think that, given the additional responsibilities of the Committee, these really fall into some of the

expanded roles of the Committee. And I think over the next couple of months we will have conversations with each of the leaders of the Subcommittees and talk about how to incorporate what is being done into the -- into this new set of responsibilities as well as how to prioritize them. So I think this is -- this is clearly what we need to have happen. Thank you.

MEMBER HOMER: Thank you.

CHAIR BOCCHINI: Okay. Laboratory Procedures and Standards Subcommittee.

MEMBER KELM: Well, we have 30 slides, so --

(Laughter.)

So we promised to be done in 10 minutes. I'll try. We actually had a really fantastic meeting and -- we always do, but, anyway, this is our Subcommittee roster, and we had most, if not all, everyone there yesterday. And this is just our three priorities, and I do think that the great thing is, at least in terms of what we have been working on, we are finishing them up.

So our priorities were to review new enabling and instructive technologies; and B was to provide guidance to programs for lab implementation, integration, follow up, quality assurance; and C was a priority that we actually never had a project assigned to, so I'll just move along.

So here are the things that we talked about yesterday. So Stuart Shapiro gave us an update on a very long, over 10-year-running project, that I think is finally coming to a close. And we have lots of slides, but I promise I'll give you two, and that's going to be looking at data from states that do singles, a single screen and states that do routine second screens looking at their data, and they used primary CH and CAH for their analysis.

And then, APHL, along with CDC, hosted a meeting last week on MS/MS in newborn screening, including SUAC, and so that touched on the SUAC topic that we have talked about, I believe the Committee recommended nay, and then we were talking

about the next steps for the timeliness paper.

So, as has been said, Stuart at CDC provided some end use data. So they actually -- the initial idea was the study was actually going to be prospective, but IRBs wouldn't go for it, so then they were trying to get retrospective data and still it was very difficult. And they got data from states, and you can see them here, and you can see mainly most of the years were 2005 to 2007, and then Alabama gave data later.

And so -- and this is for CH. The interesting thing is -- so we had two one-screen states and five two-screen states. And, as you can see, they use a variety of algorithms. So we couldn't directly compare, for example, and apply costs from one state to another, which made it complicated. And, in the end, we had the data on how many cases were identified on the first screen in first screen states, and then the first and second screen in two-screen states, and there was a lot of analysis. And I will skip over it.

So the only significant predictor --

for those who are more likely to be detected on the second screen versus the first screen was actually race, ethnicity. And it wasn't things like even though there was a difference in mean serum TSH, that actually wasn't enough, for example, for those to be necessarily missed by different cutoffs. So that was a really intriguing result, and I believe they are finishing it up so that it would be prepared for publication so look for that.

And then, CAH -- here is just the results, and I can provide these, or we can ask Stuart for the full slide back if you want to have more time to read them. And once again, I mean, you can see that two-screen states are getting a significant number of cases on the second screen.

And, once again, their cutoffs we found out were very similar, and they used similar screening technology. So it wasn't an issue with technology or cutoffs that led to this difference. And here I actually have them separated, one screen versus two screen and the different CH types. So you can see that even in two-screen states they were

getting salt, and some of the one-screen states did targeted second screening, and you see that even on second screens they are getting salt wasters that weren't detected here on the first screen.

And so we have lots of conclusions. And the one interesting discussion that we had and that we thought we even wanted to bring back to the Committee was sort of, what is the target for screening for CAH? And we had a discussion and we didn't have much time to complete it and bring it back, but, you know, is the purpose of screening for CH actually salt wasters, or, you know, additional cases beyond that? And that's something I didn't know if we ever wanted to talk about or get your input on. And, obviously, we don't have a lot of people remaining, but, you know, what's the purpose of screening, and should we take that into consideration as we -- the states screen?

So Jelili from APHL, I stole his slides, and this is from what they call the national -- a national conversation on tandem mass spec newborn screening, and Victor de Jesus down at CDC also

helped organize the meeting. And it wasn't just on SUAC, it was on lots -- you know, I think Jelili said that wouldn't be enough for a meeting, but I do think it was a major topic of discussion.

So it was last Thursday, Friday in Atlanta, and they reached out to all of the states and I think they got 40 states represented. And he said that they mainly targeted the mass spec people in those state programs, so we had the right people there. And vendors also participated, and non-state participants, like data from Mayo.

And so I know there were small group breakout sessions and some other things trying to tackle some of the issues, and lots of interesting discussions on talking about missed cases and SUAC condition, obviously, and some other experiences for mass spec assays being used.

So these slides -- I know the proceedings will be available at APHL's website if you want to read more about that. And we just talked about finalizing at least -- our idea was to finalize the report, especially if we get any

feedback from the Committee, and start working on, you know, by the next meeting our goal is to get executive summary draft as well as hopefully a good draft of, you know, cutting down -- our report down to something that we could submit for peer review. And our work group is still active.

So that's it. We didn't -- the SCID slide deck, I think the last time we had actually worked on that was last May, and we saw that. But I think we are nicely finishing up the priorities that we have been working on.

CHAIR BOCCHINI: Thank you, Kellie. I think it's clear that your Committee is still active.

MEMBER KELM: Well, it's still -- the Timeliness Work Group is still active.

CHAIR BOCCHINI: All right. Questions or comments? I certainly think if in the future you want to put together a presentation on CAH and get some feedback from the Committee, that's certainly reasonable, and we ought to consider doing that if CDC thinks that would be

helpful, or others. So I think we'd be more than happy to take that on. And the rest, I think -- thank you, I think we're good.

MEMBER KELM: All right. Thank you.

CHAIR BOCCHINI: Other questions? Okay. Coleen?

MEMBER BOYLE: This is Coleen Boyle. Having worked with Stuart, or at least read his paper several times, I thought that CAH and -- congenital hypothyroidism and CAH were important issues to bring up to the Committee, and just the implications. So I don't know if we have -- did you just say that? I'm sorry. I'm fading.

MEMBER KELM: Yes. I think they --

MEMBER BOYLE: I had a cup of coffee at like 4:30. It was supposed to be decaf yesterday and it wasn't. So I like saw the whole night last night, but --

(Laughter.)

I don't usually drink coffee, but it was like, okay, 3:30 in the morning.

MEMBER KELM: So we -- I think what he

said was talking about the target for sample for screening for CAH. But another thing that we talked about, and I didn't present here was, as we are sort of thinking about future topics, we are also talking about sort of going back and looking at old, old methods that causes issues, which although we didn't talk about -- wouldn't touch on first screen versus two screen, one of the things that Susan talked about was, for example, with CH, the false positive rate that we have, and perhaps tackling that in the Subcommittee in the future, you know, as we think about still touching on some of the issues we have with some of the screens that we're doing and not ignoring them as we, you know, add new screens.

So I don't know if Susan wants to say more about that. Looks like she does. But that was something we thought about in terms of a Subcommittee project, if we had time in the future.

DR. TANKSLEY: Right. So we have mentioned it before, kind of just looking at old technologies and reevaluating some of those,

looking at the -- you know, are there better ways to screen for some of the things we have been screening for for years and years?

We talk about a high false positive rate for MPS I, and the data for that, I mean, if you looked at hypothyroidism and you looked at the false positive rate for hypothyroidism, you're close to one percent or higher, not .03 something. You know, so we really need to reevaluate some of the things we've been doing for 30 years or more, and so looking at the methods, looking at second tier possibility.

And then, on the question of CAH, it really becomes, you know, we have case definitions now, but what are states screening for? In Texas, we consider simple virilizers to be classical CAH, but there was a lot of discussion yesterday where states are screening for salt wasters.

And so what are we screening for? What are we supposed to be screening for? And I think it would be interesting to hear -- you know, perhaps survey the states and New Steps may already have

that information of, you know, what specifically are states looking for, and that sort of thing, but I think it's something that would be really good for the Subcommittee to explore further.

CHAIR BOCCHINI: Yes. I think that makes really good sense. And a systematic view of what is going on in individual states based on what you think are the highest priorities based on either false positive rates or not using standard definitions or -- those would all be potentially good things to follow up on. I think that would strengthen the program. Yes?

MEMBER BOYLE: And just one other thing maybe in line with that. I knew New Steps -- and HRSA and CDC are working on an MMWR, reports and recommendations around the new case definitions. So it might be a good time for the Committee to spotlight this a bit and bring attention to newborn screening and standardization issues or whatever. So just some thoughts around that.

CHAIR BOCCHINI: Carol?

DR. GREENE: Carol Greene, SIMD.

Particularly relating to the issue of hypothyroidism and to a large extent CAH, I think that discussion will be incredibly valuable and important and useful, but not to forget that technology doesn't solve all problems, because the problem with CH is physiology, is that the kids are so different. And that's the reason for the second screen. So you can certainly work on technology and maybe finding a new method, but the problem is that babies have weird thyroid hormone, and it changes.

DR. TANKSLEY: And there has been an evolution over the years where states were primarily using T4 as an initial screen and maybe reflexing to TSH. And now it appears that it's swapping, and so a lot of states are now screening TSH on that for -- as a primary screen. And so I'm talking on one specimen. So it will just be interesting to look at all of that information.

CHAIR BOCCHINI: All right. Other comments? All right. Okay. Thank you. I want to thank again the work -- the Subcommittee

leadership and the work of each of the groups. I think it has been outstanding.

So before we end today's meeting, I wanted to recognize the passing of a friend of the newborn screening community. Dr. Ken Pool, co-founder, Chief Operating Officer, and Chairman of OZ Systems died unexpectedly last month. Dr. Pool was a pioneer in technology that has transformed the world of health care. He was co-chair of the public health and emergency response at Health Level 7, HL 7, a member of integrating the health care enterprise, health information technology co-chair at the Mountain States Region Genetics, and a member of the Committee's Health Information Technology Work Group.

He worked tirelessly to integrate newborn screening into modern health information technology and to improve electronic communication between health care providers and public health. Our condolences go to his wife Terese, his children and grandchildren, and to his extended family.

And we are very sorry for your loss. He will be remembered not just for his tremendous contributions to newborn screening but also for his generosity and warm spirit. So with that -- yes, Carol.

DR. GREENE: I had discussed with Dieter before, and I know there is probably not even enough people for discussion, but the SIMD and Dieter, because he worked on it, would like to put forward for future discussion an issue that is related to one part -- the lab-developed tests -- and I think the ACMG would probably agree, though I haven't talked to Mike -- the lab-developed tests guidance is going to have profound implications for biochemical genetic testing, and, therefore, for newborn screening follow up.

There are significant -- the current definition as proposed by the FDA includes virtually all biochemical genetic tests, and even the largest laboratories do not feel they are going to be able to meet the bar that the FDA is proposing in the guidance.

All we -- I would be very happy to provide the Committee with the -- with a copy of what the SIMD submitted to the FDA to demonstrate what the problem is and respectfully request that the Committee consider addressing that in a future meeting.

CHAIR BOCCHINI: Thank you. That would be a good topic for us to look at. So, Kellie?

MEMBER KELM: I don't know if it would be -- I mean, I would just propose that we -- right now it's out in draft and comment period is already over. I don't know if it -- I realize nobody wants to wait until the final, but it probably will change a lot now before the final, and I don't know whether or not discussing it with the comment period being over now makes sense, but it's just something we want to consider as we think about the timing of having it.

CHAIR BOCCHINI: So commentaries all have been submitted. Well, comments have been submitted and now the final rule is being

promulgated? Is that --

MEMBER KELM: Yes. I believe the comment period ended the first week of February, and I know a lot of people have shared with me their public comments they submitted to the docket. And I appreciate that and all the work that -- thought that people put into a lot of the public comments they provided. So the goal, obviously, is to take all those into account. And we had a public meeting as well in January, and I don't know, I mean, how long it will take for the final guidance to come out. I can't promise that it would be any time in the near future.

CHAIR BOCCHINI: Okay. So no real suspected or expected timeline? It could vary? Or --

MEMBER KELM: I can try to keep you in the loop, but --

CHAIR BOCCHINI: That would be great, because then it would be good to really understand how it's going to have -- what kind of impact the final --

DR. GREENE: Right. And Kellie and all of the folks who work on the -- in the Federal Government understand far better, but it's very clear the comment period is closed, and that means that there now is a period of internal discussion within the agency that put forward that regulation.

And I know that because the comment period is closed, this Committee could not submit comments. But it is my understanding that any agency in that process certainly has its eyes and its ears open to anything that will help it in its deliberations and judgment.

So, again, respecting that the comment period is closed, I think that the longer we wait to have the discussion, the less chance there is of any discussion this Committee might have being used in the FDA's deliberation. And, again, it's a long time since I worked for the Federal Government, but I know that the discussion period is closed, but I'm not terribly sure that's a reason to not talk about it.

CHAIR BOCCHINI: Okay. All right.

Thank you. We'll take all those considerations. Okay. All right. If there is no other business, I want to thank everyone for their contributions. I think this has been a really good meeting, and I think we accomplished a great deal. And so this is obviously the last meeting of the Discretionary Committee. When we meet in May, we will be the Secretary's Advisory Committee again. And, again, thank you all for your participation. So we'll conclude the meeting.

(Whereupon, the above-entitled matter went off the record at 2:49 p.m.)