The Advisory Committee on Heritable Disorders in Newborns and Children

HRSA Meeting

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C O N T E N T S

PAGE

WELCOME	9
ROLL CALL	10
OPENING REMARKS	14
NOVEMBER 2017 MINUTES	14
AN OVERVIEW OF CUTOFF DETERMINATION AND RISK ASSESSMENT METHODS USED IN DRIED BLOOD SPOT NEWBORN SCREENING	23
LABORATORY STANDARDS AND PROCEDURES WORKGROUP: REVIEW OF THE OVERVIEW OF CUTOFF DETERMINATION DOCUMENT	54
COMMITTEE DISCUSSION AND VOTE	60
PUBLIC COMMENT	109
BREAK	127
NEWBORN SCREENING FOR SPINAL MUSCULAR ATROPHY (SMA): A SYSTEMATIC REVIEW OF EVIDENCE (PART 1)	127
NEWBORN SCREENING FOR SPINAL MUSCULAR ATROPHY (SMA): A SYSTEMATIC REVIEW OF EVIDENCE (PART 2)	201
COMMITTEE REPORT: NEWBORN SCREENING FOR SPINAL MUSCULAR ATROPHY (SMA)	267
COMMITTEE DISCUSSION AND VOTE ON SMA	286

FOLLOW-UP AND TREATMENT WORKGROUP REPORT: 350
THE ROLE OF QUALITY MEASURES TO PROMOTE
LONG-TERM FOLLOW-UP OF CHILDREN
IDENTIFIED BY NEWBORN SCREENING PROGRAMS
COMMITTEE DISCUSSION 355
NEW BUSINESS 356
ADJOURN 357

P R O C E E D I N G S

DR. JOSEPH A. BOCCHINI, JR.: Well, good morning, everyone. Welcome to the first meeting of the Advisory Committee on Heritable Disorders in Newborns and Children for 2018. I want to thank everybody for your patience and for understanding the changes that we needed to make to have this meeting happen today. And for the committee members, because we're so close to Mardi Gras, just a little lagniappe from Louisiana, so. Welcome, all.

The first item on the agenda is a roll call, and so we'll begin that. So, representing Agency for Healthcare Research and Quality,

Kamila Mistry?

DR. KAMILA B. MISTRY: Here.

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

DR. MEI WANG BAKER: Here.

DR. JOSEPH A. BOCCHINI, JR.: Susan Berry?

DR. SUSAN A. BERRY: Here.

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

DR. JEFFREY P. BROSCO: Here.

DR. JOSEPH A. BOCCHINI, JR.: Centers for Disease Control and Prevention, Carla Cuthbert?

DR. CARLA CUTHBERT: I'm here.

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

DR. KELLIE B. KELM: Here.

DR. JOSEPH A. BOCCHINI, JR.: Health Resources and Services Administration, Joan Scott sitting in today?

MS. JOAN SCOTT: Here.

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

DR. DIETRICH MATERN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Cynthia Powell?

DR. CYNTHIA M. POWELL: Here.

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

DR. MELISSA PARISI: Here.

DR. JOSEPH A. BOCCHINI, JR.: Annamarie has yet to appear.

Scott Shone?

DR. SCOTT M. SHONE: Here.

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

DR. BETH TARINI: Here.

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

MS. CATHERINE A. L. WICKLUND: Here.

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

DR. CATHARINE RILEY: Here.

DR. JOSEPH A. BOCCHINI, JR.: For

organizational representatives, by webcast, representing American Academy of Family Physicians, Robert Ostrander?

DR. JOSEPH A. BOCCHINI, JR.: Are the phones open for them? Okay.

And here, American Academy of Pediatrics, Debra Freedenberg?

DR. DEBRA FREEDENBERG: Here.

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

DR. MICHAEL S. WATSON: Here.

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

DR. BRITTON RINK: Here.

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

DR. KATE TULLIS: Here.

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

DR. JOSEPH A. BOCCHINI, JR.: And again,

by webcast, Association of State and Territorial Health Officials, Chris Kus?

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

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

MS. NATASHA F. BONHOMME: Here.

DR. JOSEPH A. BOCCHINI, JR.: Siobhan Dolan by webcast, March of Dimes?

DR. SIOBHAN DOLAN: Here.

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

MS. CATE WALSH VOCKLEY: Here.

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

DR. CAROL GREENE: Here.

DR. JOSEPH A. BOCCHINI, JR.: Okay. So, we'll just add -- Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

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

thank you, all.

So, next on your agenda was the minutes of the November meeting, and a number of you have put in corrections and -- and -- and -- related to the minutes, and there are enough of them that I think that it is best to delay the vote until we make those corrections and -- and -- and then send that out to the Committee members prior to the next meeting, so that we could then approve them along with the minutes from this meeting. So, we'll delay the vote on that.

So, I just want to welcome Dr. Freedenberg. Debra is the new American Academy of Pediatrics representative.

She has over 20 years of clinical experience in all aspects of genetics. She is the Medical Director of Newborn Screening and Genetics in the state of Texas and works daily in clinical care and laboratory services. She has served on multiple national, regional, and state committees related to the provision of genetic services and newborn screening.

Dr. Freedenberg has the unique position of having experience in academic, private practice, and public health aspects of newborn screening and clinical genetic services. She is board certified in clinical molecular genetics, clinical genetics, medical biochemical genetics, and pediatrics.

So, welcome to -- to the -- to the group, and I'm sure you'll continue to make great contributions to our -- our committee.

To remind everybody, next, there is a new committee website, and HRSA has created this new look for all advisory committee websites. We were the first to have the website updated. Please visit the new website at the URL on the slide if you are looking for information about the committee, about the RUSP, past recommendations, or past reports. All the same information that was on the previous website is on the new website, and we hope that this new website has made things more accessible for all who use it.

Next slide. The -- HRSA will be

announcing a call for new members -- Oh, Dieter?

DR. DIETRICH MATERN: About the website -- There's -- Where's the link to nominate a condition? Shouldn't it be more out there? And also want to un-nominate a condition, remove it, upgrade it, other stuff?

DR. JOSEPH A. BOCCHINI, JR.: You mean the conditions that were looked at in the past that were approved, or --

DR. DIETRICH MATERN: No, in the past, on the homepage, you had a link to nominate a condition, and we also had discussed whether there should be one to downgrade or upgrade a -- a core condition or a secondary target. And I don't know where that is anymore.

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

DR. CATHARINE RILEY: Thank you, Dieter. So -- This is Catharine Riley. So, again, this -- We're the first advisory committee to move over to this new platform, so we're still working on a few things.

You can find it under RUSP. There's a dropdown menu under RUSP if you click on the little arrow. We're working on making that more accessible. And so, we've -- we have had that feedback to make it more prominent how you get to previously recommended and then how to recommend a condition. And so, we'll be working to make those links more prominent on the homepage, but you can still get to them by clicking under -- on the RUSP tab.

We don't have anything yet for what -- the -- the last thing that you mentioned, as far as, are there -- is there a nomination or a -- a -- a form for nominating to take things off the RUSP, because the committee is -- I believe, has not developed that yet. So, we will -- we'll wait for that, and then we'll be able to put that on the website, as well.

DR. JOSEPH A. BOCCHINI, JR.: We certainly appreciate the feedback, because the goal is to make things more accessible. So, if they're not easily found, or all the things the

committee wants the public and others to know are not clearly obvious, we need to fix that. So, that -- those changes will need to be made. So, anybody else that has any suggestions for what we should do or how we should make things go better, please feel free to contact us. That'd be great.

All right, going forward -- HRSA will be announcing a call for new members in the Federal Register in the coming months for this committee.

Next, meetings are listed here. The next meeting is May 10th and 11th, and this is an in-person meeting. It'll be at the same location and include a webcast. And meeting dates have been set up through 2020 and can be found on the committee's website.

So, this is a brief review of the meeting topics for today. The committee will hear from the Association of Public Health Laboratories regarding the document on cutoff determinations and risk assessment methods used in dried blood spot newborn screening that the -- the APHL has been developing.

Then, we will hear a report from the Laboratory and Standards Workgroup on this document and the workgroup's deliberations and considerations for going forward by our committee.

The committee will also be considering the nomination to add SMA to the RUSP. The Evidence-based Review Group will present their final report on spinal muscular atrophy, and the committee, based on the certainty of evidence for net benefit and the readiness and feasibility for states to include the condition in newborn screening panel, will vote on whether to recommend to the Secretary of HHS that the condition be added to the Recommended Uniform Screening Panel.

Our last agenda item -- item today will be the final report from the Follow-Up and Treatment Workgroup on the role of quality measures to promote long-term follow-up of children identified by newborn screening programs. The committee will be asked to reach

consensus on the next steps for this report.

And I'm going to turn this over to Catharine Riley to go over the next set of slides. Catharine?

DR. CATHARINE RILEY: Thank you, Dr. Bocchini. Good morning, everyone, and welcome to the first advisory committee meeting of 2018. Just want to welcome all those who are joining us here in person today and all those who are attending via webcast. So, we appreciate everyone sharing and -- and being with us here today.

This advisory committee's legislative authority is found in the Newborn Screening Saves Lives Reauthorization Act of 2014. This legislation established the committee and provides the duties and scope of work for the committee. However, all committee activities are governed by the Federal Advisory Committee Act, which sets the standards for establishment, utilization, and management of all federal advisory committees. As a committee member on a federal advisory committee, you are subject to

the rules and regulations for special government employees.

I have some standard reminders to the committee that I want to go over. I want to remind the committee members that as -- as a committee, we are advisory to the Secretary of Health and Human Services, not the Congress. For anyone associated with the committee or due to your membership on the committee, if you receive inquiries about the committee, please let Dr. Bocchini and I know prior to committing to an interview.

I also must remind committee members that you must recuse yourself from participations in all particular matters likely to affect the financial interests of any organization with which you serve as an officer, director, trustee, or general partner, unless you are also an employee of the organization or unless you have received a waiver from HHS authorizing you to participate.

When a vote is scheduled or an activity

is proposed and you have a question about a potential conflict of interest, please notify me immediately.

So, all committee meetings are open to the public. If the public wishes to participate in the discussion, the procedures for doing so are published in the Federal Register and announced at the meeting. For this meeting, we do have a public comment section, and that will begin at approximately 9:50 this morning.

There was also an option to submit written comments. We did not receive any written comments ahead of time for this meeting. Any further public participation will solely be at the discretion of the Chair and the DFO.

Before I move on, are there any questions from the committee members?

DR. CATHARINE RILEY: So, just a few logistics: For the visitors that are with us here in person today, just a reminder that you only have access to the fifth floor -- that's the -- the floor that we're currently on in the building

-- the Pavilion, which is this room, the cafeteria, restrooms, and meeting areas. All other areas of the facility are restricted and do require an escort by a HRSA staff member, and there are no exceptions for this.

If you do need to leave and re-enter, you will be required to go through the security screening again and will require an escort to meet you at security to escort you back into the building. We will have HRSA escorts at the main security entrance at the -- at the break, both the break in the morning and the lunch break, for those who need to leave and return. If you have other re-entry needs, please find a HRSA staff member and let us know.

So, that's all I have this morning, so I'll turn it back over to Dr. Bocchini.

DR. JOSEPH A. BOCCHINI, JR.: Thank you, Catharine. So, our first topic is the APHL document on overview of cutoff determinations and risk assessment methods in dried blood spot screening.

Dieter?

DR. DIETRICH MATERN: Yeah, as requested, I will recuse myself from this discussion, and I will come back when you let me know. I was told I have a perceived conflict of interest because CLIR is being mentioned, which is a free-to-all newborn screening laboratories product. So, Mayo or I doesn't make any money because of it, so I don't quite understand why I have to leave given what we just heard about the recusal need, but I will do it anyway. Thank you.

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

MS. ANNAMARIE SAARINEN: I'm sorry, but I -- I really would like to go on the record on this, because I was wondering, based on our conversations at the last meeting and knowing what was on the agenda today, if this would happen. And I -- I have to say that I think Dr. Matern's opinion and expertise on this subject are germane, and I think it does the committee a disservice to not have him here listening and available for questions or comments or to weigh

in.

And I -- I really just, also, don't understand why he is being asked to leave the room given the criteria set forth. And I don't know if the Chair has any ability to sort of weigh in or overturn, but I -- I really feel very strongly about it. So, thanks for letting me share.

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

All right, let's go into this discussion. So, issues surrounding how cutoffs are established and how -- and used have been raised in the media and at previous advisory committee meetings. Risk assessment is essential to newborn screening establishing and revising cutoffs is something that state newborn screening programs do in order to determine how to best identify positive cases, while balancing that with minimizing identification of false positives.

During the past year, the committee has heard presentations and engaged in discussion on the topic of newborn screening cutoffs. APHL's

QA/QC Subcommittee has also been working on a document providing an overview on risk assessment methods and resources available to states to aid in the establishment and revision of their cutoffs. They have presented drafts of the document to the Laboratory and Standards Workgroup for discussion and feedback, and information on the document has been brought to the committee for discussion as it was being developed.

So, on behalf of APHL, Dr. Orsini is here to present, remotely from New York, this morning. He will provide an overview of the resource document that has been developed, which includes information on how states establish and reassess cutoffs for a variety of screening methods utilized in newborn screening.

Following his presentation, there will be time for questions, and then we will hear from the Laboratory and Standards Workgroup. The committee will need to then determine whether it feels additional steps are needed to address this

issue.

So, to introduce Dr. Orsini: Dr. Joe Orsini is trained in analytical chemistry and has worked at -- as Director of Operations for the New York State Newborn Screening Program since 2004. He is also Director of the Lysosomal Storage Disorder Testing Laboratory. In addition, he has worked with Dr. Melissa Wasserstein from the University Hospital for Albert Einstein College of Medicine to perform a 3-year consent to newborn screening pilot study to screen for MPS I, Gaucher, Fabry, and Niemann-Pick diseases. Dr. Orsini has been invited to lead national efforts in quality assurance and quality control to develop guidelines for LSD screening.

So, Dr. Orsini, if you are ready, we have your first slide up.

DR. JOE ORSINI: I am here, and can you hear me?

DR. JOSEPH A. BOCCHINI, JR.: We can hear you. Go right ahead. Thank you.

DR. JOE ORSINI: Okay, great. So, first,

I wish I were attending the meeting in person, and I miss the opportunity to see and meet with everybody there. Second, it's my honor to present an overview of the cutoff document, and this document was created from scratch and has had many contributors. So, thank you to all who provided input and feedback. We are very excited to have developed the document and hope it will be a living document that adds value to the NBS community.

To the next slide, please. This slide's a busy slide, largely described -- or briefly described by Dr. Bocchini already. Initially, there were media reports that drew national attention to cutoff variations across states back in December 2016. This prompted the APHL to survey all state NBS programs and gather information on how they set cutoffs and assess the use of analytical tools, such as R4S or the CLIR database that we'll discuss in this talk a little bit.

The APHL Newborn Screening QA/QC

Committee then began developing a cutoffs reference document. This was largely spun from -- you know, the -- the group itself said, Well, we certainly could use a document of this sort. We all have been working to -- to develop cutoffs and guidelines in our own labs, and there is no such guidance or document available to us other than papers that have been published.

So, in November 2017, a draft document was presented to the Lab Workgroup after the time from initiating it in July, and we solicited feedback from the NBS community in January 2018.

All of this has managed to make its way into the document in one form or another. So, the document is still in a draft form, and we have even received more comments for the document -- changes to the document just in the past couple of days.

On to the next slide, please. So, the purpose of this document, from our point of view, was, the intended audience was primarily state newborn screening programs and those of us

involved with developing tests, setting risk assessment. The assumption is, when reading this paper, is that the people would have a strong understanding of NBS laboratory methodologies and risk determination and that this would act as a -- - a -- a general reminder of all the things that may be considered in the process of doing this critical step.

Next slide, please. This document is not meant to provide detailed instructions on performing risk assessment in newborn screening -- - so, in other words, it's not an SOP -- but it does provide all historical and current approaches the laboratories rely on for risk assessment, and it also describes the factors that should be considered when establishing and evaluating a screening test and risk.

Next slide, please. For a primer or more of a -- an assessment of why laboratories do have different risk assessment methods, the APHL in -- developed a blog post, and this blog post is -- is available still and is among one of the more

frequently visited posts on the APHL site. The blog is referenced in the risk assessment methods document, so people can go to that and get a better understanding of some of the variations, why labs vary in -- in the way they set cutoffs across states.

Next slide, please. Okay, so some limitations of NBS risk assessment: NBS is not meant to establish diagnosis.

It's important to note that probably one of the main variations -- or one of the main variables in screening is actually the dried blood spot itself, primarily when laboratories -- screening laboratories would use in this -- when they're using this specimen type; it's going to be prone to have possible errors or variations that can really change the concentrations that are read. And this is a disadvantage when compared with diagnostic laboratories, where they're looking, and they're able to segregate portions of the blood to run their diagnostic tests. So, abnormal biomarker levels identified

through screening and -- and evaluated using only cutoffs, you know, may not detect all people with a disorder.

Let's go to the next slide, please. So, I would consider these standard disclaimers in any type of screening, but with -- relative to newborn screening, for symptomatic newborns or those with a family history of disease, additional diagnostic testing is necessary regardless of the NBS results, and second, regardless of the algorithm used to determine infants at high risk for a disease, newborn screening may not detect all affected newborns.

An example of this is -- a -- a prime example is cystic fibrosis, where babies with cystic fibrosis may have very normal immunoreactive trypsinogen, which is the marker used in screenings for cystic fibrosis. There are other examples that we've provided in the document, and we welcome any other examples that might be used so we can put them in the document, as well.

Next slide, please. So, here -- in -- in the paid manuscript, or in the document, we described the steps that are used to determine cutoffs. Prior to our draft document, no other document existed that described the general approach.

However, there were many published articles, and all are fairly similar in the -- the approach, and they start -- it's -- All this in the QA/QC group, when we were sitting down to draft this document, we -- we made -- it was obvious we were all running through the same general process, and that's what I will describe here and is described in the -- in the document.

The first step is to conduct a population study, whereby hundreds to thousands of specimens -- and these are generally going to be deidentified specimens and fresh -- relatively fresh in our system to make sure we're evaluating proper -- the samples as they would be received to the laboratory -- are tested through a screening test.

So, the next step and the next slide is, after having analyzed hundreds of samples to thousands of samples, the first thing we're going to be asking: Is the method adequately precise to differentiate results that are close to the cutoff? Our -- we analyze the data, determine if it has the precision and accuracy necessary to be able to -- for the test to work properly.

The sensitivity and specificity of the test will really come later, because at this point in time, we have -- you know, we haven't really thoroughly tested the process. We haven't run real positives; we haven't run live screening. So, a lot of the things that come up that would help to determine sensitivity and specificity would come up in live screening and may take years to fully understand where -- how those numbers develop and are going to be dependent on disease incidence and the screen test itself.

But after doing all this and verifying we have a good and solid assay, the next thing would

be -- based on results, would be to assign a preliminary cutoff. So, go to the next slide. So, the -- the preliminary cutoff is based on many things. We -- we would look at literature, any literature that's available. We'd do some comparisons with other states if there are other states that are -- have evaluated or are already in the mode of screening for what we're setting a screen up.

The other thing that we'll do is look at diagnostic laboratory results and how do -- how do diagnostic labs or marker concentrations vary in patients compared to -- to -- to normal or non-affected individuals. These are all active guidelines.

So, we -- we do discuss, in this manuscript, kind of, the special considerations for when you're setting up a new test, as well as comparing -- or setting up a -- a new test to your lab but been done in other states. By comparing cutoffs to population statistics in -- to other programs, then we can -- in -- as well

as the Region 4 Stork database, if -- if you're running a test that's been run extensively, then you can get a pretty good idea of how your test is running compared with how it runs to other states and set your cutoff based on -- on that information.

Okay, so the next slide -- This slide I could spend hours on and probably is the -- the crutch of what I would say the issue with setting cutoffs for newborn screening. But this off the subject of the document and isn't really included in the document, but I wanted to include it because this points to a lot of the challenges we face in setting cutoffs.

The slide -- this slide is a typical newborn's -- is for a typical newborn screen for an elevated marker concentration associated with a positive screen. So, as you go from left to right across this graph, what you would have is increasing concentration of a marker.

So, note that the more elevated the concentration of the marker, the further to the

right you are on this X-axis, the more likely you are to have a -- have disease, and the higher the values that are measured, the more likely the disease will be a classic or severe form of -- of the disease. These are all based on probabilities, and so these are general thinking and not necessarily always the case, but. So, as you go to a very elevated marker concentration, you're going to likely have the more severe form of disease.

Now, if you look, there are two profiles here. There's a normal profile and a disease profile. The first peak shows those individuals that are unaffected by disease. The shape and statistical characteristics of this peak are relatively easy to define, because we can run many, many samples from normal newborns.

Where things get a little tricky and -- is when you start looking at subpopulations within your normal population. And by that, I mean, say the premature babies, where you have a -- a much smaller group of those, were samples

that are taken from older babies, for whatever reason, where you may have a much smaller subgroup. You can imagine that you would have, actually, a similar -- a distribution that you could set to each of those population types.

So, what's shown on this -- this particular slide is for every person tested in a population. I think where -- later in the talk, we'll talk about how CLIR works. Where CLIR works, it's very well, and -- and the -- in the -- the -- what Dieter is -- was there to talk or could defend -- where CLIR works very well is, it takes these disease -- these normal profiles across the very wide range of subpopulations for both diseased and non-diseased individuals.

So, one last thing about this: The disease population profile you see, the second curve on the right, this is the curve that -- for -- that's very difficult to get in setting cutoffs in newborn screening. You could say that that -- that, very often, there's maybe three, four, five points, and if you're lucky, you know,

when you're first setting up a test, you have some real specimens that -- from -- newborn screen specimens -- fresh ones -- from affected individuals that we would go to in our archives to be able to help establish, well, where are those points going to be relative to your normal population.

So, where the -- the issue is, is, where do we set that? We want to detect all the positives, so -- and have very few false positives.

In the gray area, you see where we have borderline levels. This is an area that really does not get defined until screening has been underway for a long time.

Okay, so the next slide. Sorry, that -- that -- I wanted to talk about that quite a bit, because it really sets the picture for the rest of, probably, the morning you're going to have with these discussions.

Okay, the next slide, please. So, back to the document. We have a section called "Special

Considerations," and for this -- for this part, the first part of it is fixed cutoffs versus floating cutoffs, and we provide, in the document, where, generally, fixed cutoffs may be used versus floating cutoffs.

And the fixed cutoffs are generally used with assays that measure a marker directly, such as phenylalanine, associated with PKU testing and tandem mass spec, the reason, you know, you were actually able to measure the marker concentration in the dried blood spot. So, a fixed cutoff works very well in this case, and -- and especially where you're using -- with the mass spec test, where you have internal standard adjustments that make it easier to have less variation from instrument to instrument.

I do like to point out, at this point, that even in the same laboratory, running the same exact test, with everything being the same, one instrument can be different from a second instrument, and no matter all -- all the work you can do to make a match becomes a difficult task.

And so, we have things called relative response factors that help make us match instruments across the laboratories.

So, you can imagine trying to match instruments in a laboratory being a challenge. Now go across the country to many laboratories, with many variables, and you can see the -- the -- the problem with trying to have everybody do exactly the same thing when you're considering the use of cutoffs.

Okay, the other version is floating cutoffs. These are for assays -- functional assays, where you're not necessarily measuring the concentration directly of a -- a marker in the blood, but you're measuring how that marker either works like an enzyme function or how it -- how an antibody antigen binding reaction occurs. So, there's more variables.

And what this means is that on a daily basis, you can run the same tests, same set of samples, and see slightly different results. So, everything becomes relative. What you're looking

for is the highest or the lowest specimens from that particular day.

Let's go to the next slide, please. So, also under special considerations, we have borderline -- the borderline cutoff criteria. I won't belabor this too much, but borderline cutoffs were set up as a way for laboratories to deal with the fact that some markers, over time, will increase in concentration. So, it turns out, this -- you know, some of the pressures of actually testing specimens faster, because of the whole issue with timeliness, have made it so many of the markers that are on panels don't -- aren't at concentration levels that are as elevated as they would be if the sample was taken at a later point in time. So, what this means is, the difference between a positive and a negative becomes less clear.

So, when -- when we start getting into a borderline concentration range, then individuals will -- or laboratories will set up borderline cutoffs, and these will allow for calling back a

patient to get that patient in for a repeat specimen, and the cost of such a -- a test is -- although there is a cost associated when the family does have to go in for a repeat, there's -- the less of an issue is bringing them in as having a screen positive and trying to go through the follow-up diagnosis.

So, it's kind of a -- a tradeoff. It does add cost but doesn't cost as much as if you're doing a full diagnostic evaluation. In the -- we offer in this document the reasons where borderline cutoffs may be required.

The next slide, there's more on special considerations, and we -- we included multiple of median as a special consideration, as this is a relatively new approach to assessing a risk of a NBS screen result. And it's interesting because it's something that's been adopted from prenatal screening. So, in the prenatal screening world, we have a whole 'nother area where people are doing things, and they do it, largely, using multiple of medians, whereas in the screening

world of newborn screening, we're using fixed cutoffs and actual numbers that are related to a concentration.

So, the multiple of median is similar to a fixed cutoff, but instead of using concentrations, it uses a percent of a population median. It assumes the population median for the marker is constant. So, if you were to go and analyze, say, the phenylalanine concentration for the entire state of New York, multiple times, this result would give you -- On a given test, you would get a -- a number, and that number should remain constant, because the concentration of that phenylalanine in the population should be a constant.

The reason why it's not a constant is related to what test you may be using or changes in the test and variables in the test that can cause the -- the actual concentration to vary. So, this -- but this approach is interesting and may be applied more -- across more tests over time, because it -- it does make things easier in

comparing one lab to another or in monitoring your tests.

Okay, the next slide. This is a -- another special section, or a section in the paper, that has to do with the CLIR, the Collaborative Laboratory Integrative Report functionality. Here's where I'd like to say, that -- I want to self-disclose that I do work very closely with Dr. Piero Rinaldo and Dieter Matern. So, I have a lot of positive things to say about this, but in trying to be neutral, you know, I'm trying to present just the facts here.

Some of the things that -- attributes or functionalities: that -- that CLIR does allow for covariate adjustments, where marker or analyte concentrations for all markers that are tested through a newborn screen can be adjusted for their demographic variables -- for example, birthweight and age at sample collection. So, you can go back to the profile curves I showed you before and say -- you -- you can generate a curve that's very specific for a birthweight range or a

age and birthweight range for a given -- for a given marker slash screen.

The beauty of this is, it no longer means you have fixed cutoffs, but you have a profile of cutoffs that shows normal ranges of that marker across all birthweights and all ages. And this plane, if you will, or blanket of cutoff -- of -- that presents a profile allows you to detect the things that are more abnormal relative to that birthweight and age.

So, it's a very powerful program in the way it works, and there's way more to it than that that I don't have time in this to talk about. But it does -- the program allows for local harmonization, where we're -- everything's normalized to these scores and allows for direct comparison of data and markers across contributing labs.

The -- the real strength is, you get global contribution of diagnosed case data, so the ability to better define a profile of diseased individuals, where one state may have

three or four, another state may have ten or fifteen cases, and over time, you finally get to a thousand or two thousand or however many cases you may get, depending on the incidence of that disease. It gives a clearer picture of what that profile looks like relative to a normal profile. So, it's a large -- coming back to this, it also provides for a large database of normal profiles.

Next slide, please. This slide may be one of the more controversial ones, but anyway, I wanted to go over it, because it does [unintelligible due to phone connection interruption] some things to consider here.

Access to the tool is conditionally based, based on contribution of data to the tool, and this -- this was a way for -- that Dr. Rinaldo was trying to encourage people to get more data into the system, because the more data that he has in the system, the better he can define -- have the tools to work. The more positives and false positives that are in the system, the better it is for developing the

tools.

The next thing that's kind of thought of as a limitation or a -- a -- a consideration is the need to customize algorithms for each state. In New York, we had a -- a -- quite a bit different tandem mass spec panel than is being used in the database. What we're finding is that it'll be beneficial for us to, maybe, add some of the -- the analytes that are being -- that are in the CLIR database, and it will help us. This approach might -- you can think of it as a -- an issue, but if you wanted to match your analytes, you could do that and get them set.

The other thing is, you can -- there's issues with integrating LIMS and primarily with reporting a result. So, once you have a -- a result that comes out of the CLIR database and says something is positive, how do you mesh that with a report that you're going to put out to the public? People are used to seeing a normal range; they're used -- in concentration units, and they're used to seeing what's an abnormal result.

So, we have to, kind of, have -- think about how to report when you're using the CLIR database and the tools and the reports out of that.

I think, finally, the last thing is, really, the variability in case definitions, the cross-states, and cases coming into the CLIR database. And there's a certain amount of my case -- The cases of New York you'd want to weigh more heavily than cases in another state, because you just don't know how people have determined -- come to determine what's a real case.

And this has a -- this is really not related to just CLIR and differences and -- between states but in differences in how people define a case and points to the need for case definitions, which are things that people -- we are working on and APHL's working on and NewSTEPs are working on to make it simpler -- to simplify these things.

Okay, the next slide, please. So, back to -- a little more to the document. We have disorder-specific cutoff considerations. So, if

you were to go to the document, you would see, for all the disorders listed on this slide, how -- the approaches people have used in developing risk assessments and whether they, maybe, used floating cutoffs, fixed cutoffs, or any other approaches. So, it'd give you a better idea of how you were to implement.

If you were going to implement a new test, you could look at this list of disorders and kind of compare with, well, if -- if I'm running a new test, what is it most similar to, and it would help you to devise an approach based on reverse engineering, you know, what's being done in -- with similar tests elsewhere.

Next slide, please. Okay, so, finally, there's this last section of the document. It provides recommendations on monitoring of cutoffs and/or other risk assessment tools. These -- these recommendations apply to monitoring and evaluation of cutoffs in any other risk assessment, where, if you're in the first 6 months of evaluating a test, you'd want to --

When you're first getting started, you want to make -- be taking a close look at what your -- how your cutoffs looking; how it's working; what's your screen positive rate; for the positive cases you're picking up, how many are true positives and false positives. And you would be doing this, typically, every 6 months after routine newborn screening or less frequently as you become more familiar with the screen and the way it works.

We recommend, in the -- in the document, that you reevaluate the cutoff after kit changes, after equipment changes, modifications in testing, or if you -- One of the big ones is, if you learn of a false negative case, this would trigger reevaluating the cutoff and is there a way to detect it through the normal process of screening in your laboratory, or if you have any new information from clinical or natural history of the disease that may make -- decide to change where you set that cutoff for risk assessment.

So, under the next slide, finally, the

summary slide -- In summary, the document provides an overview of the currently used risk assessment methods in newborn screening programs. It also provides a general approach in how to set up a risk assessment and includes an extensive list of the variables that should be considered. I think that this will be a valuable reference document that can be used for experienced and inexperienced newborn screening scientists in years to come, and we hope that it'll be a living document that will be contributed to as -- over time.

So, finally, the last slide is acknowledgements. This is a group of the QA -- the QA/QC Subcommittee members who -- I appreciate everybody on this group for their valuable input into the document. For me to go through and name who did what would only do a disservice, because I'm certain to have missed somebody, but -- So, I really want to thank all the people that are on the QA/QC group with me and have contributed, as well as others that are

in the main group that have helped in developing this document. We hope that it'll prove to be beneficial and valuable for the years to come.

So, that's my talk. If there are any questions, I'm happy to take them.

DR. JOSEPH A. BOCCHINI, JR.: Dr. Orsini, thank you very much for that clear presentation. That was really excellent. You mentioned at the outset that they're still in draft form. We have -- the -- the committee's been given a -- a printout of the -- of the document. Is -- This is close to final?

DR. JOE ORSINI: I believe there -- there are, kind of, two levels of changes that have come up. There are some that are just clarification, and I want to -- things that'll -- that -- that'll make it seem more like a one-person voice since there have been so many contributors, and I've read it so many times. It's gotten to a point where we -- I think we need -- do need a final draft that would take it to -- you know, to have it all sound like it's

coming from one person, looking for typos and things of that sort. But there have also been some comments that are a little -- going to be a little trickier to handle.

So, I -- I'd say it close to final, and some of the -- the more recent comments we -- we do have to weigh with the QA/QC group and then on to the -- the -- the main group to just make sure how we want to handle them. So, I -- I don't know. I mean, I think the -- the body of it is fairly stable. There may be a -- a few sentences, paragraphs here or there that would change -- change it a bit, so. I don't know.

DR. JOSEPH A. BOCCHINI, JR.: All right. Well, thank you. So, I -- I think, next, we'll have Dr. Kelm talk about the discussions in the Laboratory and Standards and Procedures Workgroup, and then we'll open this up for both she and Dr. Orsini for further questions and -- and discussion.

DR. KELLIE B. KELM: Good morning. I'm just going to give, mainly, a refresher -- and I

know Dr. Orsini did, as well -- in terms of some of the discussions that the committee has had, as well as the Lab Workgroup. And it was tasked to us to, sort of, give some input to the APHL writing group, and then give you -- We did have a chance to have some discussion, about a week or 2 ago, in our workgroup, and I just wanted to give you a flavor of what that discussion was.

So, this is just a reminder that -- as Dr. Orsini said, that after there was some press about -- I believe it was December of 2016 -- that there were several presentations at this committee, in the past, to talk about a lot of issues around cutoffs and risk determination for newborn screening, and I've just highlighted here that we've actually had quite a breadth of different presentations and discussions here at the committee. And both in August and November, we had discussions at our workgroup meetings.

So, this is just the presentation title page from Dr. Orsini and Patricia Hunt's presentation in August to us, and -- and here's

some of the details in terms of the discussion at the workgroup.

So, in August, at our committee meeting to the workgroup, APHL's Writing Committee presented an outline. So, it was several slides with their outline for the document. And I know, at that time, we had some high-level items for them to consider as they worked to draft it.

In November, we actually had a draft document provided for review to the -- the workgroup, and we reviewed it, and we had a lot of input and feedback there on some things that we thought needed more fleshing out and some additions.

And in January, the APHL -- the group made this available to, actually, everybody in the newborn screening community, through their listserv, and it was shared amongst the workgroup, so that everybody could have an opportunity to read it. And then, we -- as I said, we had a meeting and discussion at the time, actually, without Dr. Orsini, who was out

of the country, and -- and some people sent some feedback on their own, as well as, sort of, we had, you know, some feedback that we sent to them.

So, I think most of the workgroup's suggestions, especially the ones that we provided in November, had been addressed in the document, so we were generally happy about that. And as I said, I think -- and Dr. Orsini said, we've still had some things that have come up, you know, some errors or some clarifications that a lot of the members of the workgroup have requested that be made.

So, these are the general points of our recent -- our January discussion and conclusions about the document to present to the committee at the time. So, this document does describe the scientific processes that states currently use to determine which specimens test within normal range versus out of range. And we do agree that this will be a valuable resource to state newborn screening programs that, as Dr. Orsini said, it's

the first document that sort of brings a lot of these considerations into one place.

The APHL document does not include best practices for screening for all conditions, and it does not harmonize newborn screening tests across states. And I know that that has come up in discussions as something that a lot of people wish for, although, as Dr. Orsini says, that -- there are a lot of difficulties in doing that -- states use different tests, states use different methodologies -- although there is interest, and we can have discussion in the future about activities to harmonize testing across states and -- and what that might be.

APHL intends for this to be a living document that is revised over time, so I think this was, sort of, their first attempt to try to bring a lot of these issues and discussions together. And that is something, especially with new activities, both, I'm sure, with CLIR and other things, as well as harmonization activities, that it could change and -- a lot

over time.

So, I believe that is it. That is our assessment. I -- I do think that it's valuable, but we also agree that there -- we -- you know, are these things to highlight about what this document does not do at this time, so.

DR. JOSEPH A. BOCCHINI, JR.: Thank you, Kellie. So, these presentations are now open for discussion, comment by -- and questions by committee members first.

Beth?

DR. BETH TARINI: This is Beth Tarini. I have a question about the presentation, and this is, sort of, a broad question about inter-rater reliability in this testing. Can -- can someone explain to me why, if we go -- if a patient goes to a hospital and gets a CBC, that CBC at one hospital versus another hospital versus another hospital gives the result and can be used interchangeably, but that cannot happen, it seems, at newborn -- in newborn screening? Can you -- can someone explain to me why we don't

have that inter-reliability?

DR. KELLIE B. KELM: So, I can say, in my experience -- So, there are a lot of tests that have actually, over the years, been -- been -- there's -- you can have harmonization, or you can have standardization. And there are many tests where there is standardization or working on standardization. I know we're working a lot about -- on that with vitamin D and some other things that CDC's been making an effort on. And I think that for a lot of newborn screening assays, there is not -- has not been harmonization efforts or standardization efforts.

And some of that, also, is -- You know, you have to figure out how you want to do that. Is that a reference method? Is it reference material? There's a number of ways you can do that, and usually, it does take it -- you almost have to do it method by method or analyte by analyte to do that.

And -- and Carla might be able to speak to that more since -- you know, but there's a lot

of different methods of analytes that you have to think about, and each one is different.

DR. CARLA CUTHBERT: Yeah, but part of this is that, again, as -- as -- My name is Carla Cuthbert. I am from the CDC.

Part of it is -- is that, you know, there are different methods actually being used, and we do not prescribe to states that they use a particular method or platform or anything like that. The decision to -- sorry about that -- the decision to screen for a particular marker, depending on whatever platform is used, is -- is determined by the laboratory director of the newborn screening program. And, as such, they have to work within the framework of, you know, their -- their own population to establish an appropriate cutoff, and, you know, we've gone through it with a number of different presentations why that there might be variability.

One of the things that -- that I've been mentioning that we are working towards at the CDC

is to -- I -- we have the benefit of -- as part of our -- our -- our participants give us their cutoffs as part of the proficiency testing program. It's not something that we share, but as they give us the numbers of their values, they let us know whether or not they've screened positive or negative for a particular PT sample. We do have access to those sample -- to -- to those cutoff values.

We also have the benefit of having quality control materials, and these are identical materials that we've created that have different marker levels. So, we can generate a curve. If we have assigned measurements for each of these markers, we can -- have received what they have named or -- or given as a measurement and can normalize. So, we're in the process, right now, of normalizing cutoffs, normalizing their PT values, to show, as part of proof of principle, the -- the spread that actually exists if --

DR. BETH TARINI: But that has to be --

DR. CARLA CUTHBERT: -- they were normalized.

DR. BETH TARINI: -- done to -- or according to specific analytes and specific platforms. You --

DR. CARLA CUTHBERT: Correct. So, we --

DR. BETH TARINI: -- can't cross --

DR. CARLA CUTHBERT: So --

DR. BETH TARINI: -- within a platform or within an analyte.

DR. CARLA CUTHBERT: Correct. So, you'd be -- So, it's a way of, sort of, harmonizing against different kinds of platforms, and that way, you can actually get a better idea of, you know, when I have a number here, this is what it means in another state.

We're in the process of doing that. We have some preliminary data, but we would like the opportunity to present it to the -- the workgroup in May, to show them a bit of what that would actually look like. So, we're in the process of being able to do that.

DR. SCOTT M. SHONE: I just want to add on to that, that the sample type is a -- a crucial part of this. You know, Dr. Orsini mentioned in his talk that at the level of the dried blood spot, it's very different than a -- you know, a tube of blood that's submitted to a -- a -- a clinical lab. And -- and at the heart of everything is the ability -- Regardless of the numeric cutoff, the ability to distinguish risk is crucial for the screening assay, as opposed to when you run a CBC, and you're looking to make treatment decisions.

DR. BETH TARINI: This is Beth Tarini. So, my understanding is that -- but I don't know this for a fact -- that at one point, the Gates Foundation used dried blood spots to check for HIV levels. So, -- but they, presumably, had some consistency. Also, I don't know this for a fact, but this was my understanding, that this was -- these -- this platform of dried blood spot has been used in other areas, and they may not have the same -- The question is, have they had the

same variance.

So, I agree with -- I -- Point taken that there is some bit of difference, but then, that would have to explain -- for dried blood versus -- versus whole blood -- thank you -- but that leaves, then, the discussion that all whole blood -- all dried blood testing has variance. Do you see what I mean?

DR. BETH TARINI: Correct. That's my point. Like, there is variance. I agree --

DR. KELLIE B. KELM: Yes.

DR. BETH TARINI: -- with the variance. My pushback is just to have the discussion, how special are we?

DR. KELLIE B. KELM: Sometimes, if you just want to know a yes or no, and if HIV is -- it's there or it's not, that is easier than if, like, this description of the disease versus the normal, and that actually, you know, sometimes --

DR. BETH TARINI: I thought they --

DR. KELLIE B. KELM: -- these are overlapping --

DR. BETH TARINI: -- were testing levels, but --

DR. KELLIE B. KELM: -- these are overlapping.

DR. BETH TARINI: -- I can check.

DR. KELLIE B. KELM: It's harder with blood spots to actually --

DR. BETH TARINI: Yes.

DR. KELLIE B. KELM: -- figure out whether or not you are quantitative enough to do that. And a lot of it is because of the sample type.

DR. CARLA CUTHBERT: The point is, we're not really unique in this regard. Clinical --

DR. BETH TARINI: That's the --

DR. CARLA CUTHBERT: -- testing laboratories --

DR. BETH TARINI: -- question I'm asking.

DR. CARLA CUTHBERT: -- have this same issue. So, we're not unique.

DR. JOSEPH A. BOCCHINI, JR.: Dr. Powell?

DR. CYNTHIA M. POWELL: Cynthia Powell.

Along those lines, one question I have is, is -- is it thought that there are sufficient control samples, like, standard positive controls of, you know, dried blood spots from babies with verified, you know, conditions?

I know that the CDC, you know, provides samples when states are starting to, you know, develop a -- a new screening test, but sometimes -- speaking from some personal experience in our own state, we're dependent on other states that have been screening for a while and, you know, their kindness in sending those samples.

So, do folks feel that there is a need for a better biorepository of samples like that?

DR. CARLA CUTHBERT: I'd like to take that again. My name is Carla Cuthbert from CDC.

It -- it is difficult to get good samples like that to go around to all programs. That is an acknowledged concern.

One of -- the second project that -- that we're actually interested in is being able to collect samples, true positive samples. Right

now, we're trying to focus on the borderline samples, because that gives us the greatest challenge. If it's -- if you're looking for a high or low marker, if it's really high or really low, it's -- it's glaringly obvious. I think it's the borderline samples that tend to be the greatest challenge.

So, one of the things that we're -- we are also working on right now is being able to request some of those borderline positive samples to CDC from our state programs, so that we can do the test, duplicate the sample, essentially like a -- like a photocopier, as it were, for blood spots, make multiple of those, and then send them out to state programs as part of an educational process, so that they could take note of the fact that, you know, this was identified as a positive sample in another program; please check your markers, so that, you know, if you need to make an adjustment, you -- you should, because this should actually read as a positive sample in your hands.

So, that is something that we're trying to do. I think it's wonderful if you have colleagues who have enough positive samples to be able to distribute. That is certainly something that the states do, and, you know, that's the best possible sample to do your evaluation. But in lieu of that, this is something that we're also trying to do to make it available on a regular basis for programs.

DR. JOSEPH A. BOCCHINI, JR.: Sue and then Carol Greene.

DR. SUSAN A. BERRY: The other issue that I want to make sure we -- This is Sue Berry. That's so good.

The other issue that I'd like to make sure we really do pay attention to is curation of the -- of -- of the cases identified as positive. When you're dealing in large volume and contributing data, and you're putting it in from your state, it's really, really, really essential that a -- a positive is a true positive, and that's why the case definition activity remains

so critical to accurate utility of databased -- database-based analysis.

So, I -- I -- I want to really urgently highlight the necessity for careful case definition and curation of positive cases when we are building databases for knowledge.

DR. CAROL GREENE: Carol Greene, SIMD. Three things, two are quick and one is a question for the document.

One is, we do want to be careful, when we -- we also want to remember, there's variability in the diseases. I happen to care for a child who was a true negative on newborn screen in another state and truly has the disease, and there's no way that we could go back and reset that without making a huge -- like, 20% of the population positive for that particular condition. There are some people with disorders who just have differences in their levels. And in case anybody's wondering, it's glutaric aciduria type 1 and low excretors.

And until we move to some other model,

where we have DNA that's going to find everything -- and we're a long ways away from that, but we just have to respect the variation in the disorders, as well. And -- and I also wonder whether there is -- And -- and that's a small minority, but we have to respect the fact that screening is still screening.

I wonder if there is a need for something other than the log that was described, so that -- The question Dr. Tarini asked is -- is the key question that everybody wants to know. I think it's what led to some of those papers and whether there's need for something that's more accessible to the general population that explains the answer to that question.

And my question about the document is, recognizing that there always have been borderlines and that there's always been a process of, some instances, you get a repeat -- you -- you ask for a repeat screen because you cannot truly assign somebody in risk to "okay" or "high risk, time to do diagnostic testing," and

also recognizing that as we get better at timeliness, there may be more of those.

I may have missed it -- I apologize if I did -- but was there -- I believe there needs to be some discussion in the document about the difference -- you -- you may need to approach a borderline differently if it's a critical condition and if it's not a critical condition, because just asking for a repeat on something where -- I mean, there -- there may be a need to make that very clear that it's an important element, because that may make you want to just call it positive and do the diagnostic testing, because sometimes bad things happen otherwise.

DR. JOSEPH A. BOCCHINI, JR.: Dr. Orsini, do you want to -- to just discuss that, about borderline?

DR. JOE ORSINI: Yeah, sure.

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

DR. JOE ORSINI: Hang on, I've got to turn down the computer sound. Okay, here I am. I'm back.

Yeah, in -- within -- we actually do recommend, in -- in the manuscript, that borderlines really are better -- you -- it's a better use of borderlines is for when the disease is not time critical. I -- I, even, maybe, had that as a point on my slide but missed it and didn't discuss it, so it is -- it is in there. You know, for time-critical tests where -- or disorders we're -- that we're screening for, if you're going to be developing disease within 5 days, I don't think most screening programs have a borderline result for those.

DR. JOSEPH A. BOCCHINI, JR.: Okay, thank you. Dr. Tarini?

DR. BETH TARINI: So, Carol brings up a -- a -- this is Beth Tarini, committee member -- a good point, which I have heard from my colleagues in newborn screening, which is, sometimes it's difficult to say if this case -- this diagnostic -- or this new case, if you will, represents just a unique outlier or a trend that we're missing. So, I guess my question is, what is -- and -- and

in true fact, we have 50 programs working on the same issue simultaneously.

So, I guess my question is, what do the programs do when they see these, sort of, quote/unquote, outliers, and also, what is the coordinated effort to share the information, so that the community as a whole can make a judgement? Because in Iowa -- sees a case that's, Oh, this is unusual, but it really does look like glutaric acidemia, then how does New York or Florida understand that something could be going on? So, those are my two questions.

DR. MEI WANG BAKER: This is Mei Baker, committee member. I just want to follow up what Dr. Greene and Dr. Tarini and talk about those two things. One thing I want to adding on is, the time, the sample collection, could be somewhat affected.

For example, if you have MCAD and -- minor MCAD, then for whatever reason, you have a sugar, you know, feeding, then you were. So, when each state, when they have false positive

situation, is go back and look how that occurred. Like, Beth, you said, is it really is a systematically, you know, fail, or it's because a unique situation, because the -- the -- the situation I described, you change cutoff, it doesn't change outcome at all.

So, that's -- and I do believe this has been discussed in newborn screen community, you know, short-term follow-up, how we do the best to correct the information on the false negative. I think this will be continue discuss. I -- I do believe that it'll be very, very benefitive for the community.

DR. JOSEPH A. BOCCHINI, JR.: So, um --

FEMALE SPEAKER: Sue.

DR. JOSEPH A. BOCCHINI, JR.: Oh. Sue, did you have a comment? And then Carla and then Debra.

DR. SUSAN A. BERRY: So --

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

DR. SUSAN A. BERRY: -- this is Sue Berry, committee member. There isn't any formal

mechanism by which false negatives are gathered up all over the -- by all the states. People who contribute to CLIR can contribute cases like that, but not every state has access to CLIR because of the limitations that are inherent to the system. So, that's the one place where some of this information is sort of, if you will, warehoused --

FEMALE SPEAKER: Mm-hmm.

DR. SUSAN A. BERRY: -- but that there are limits in -- in -- in access to it.

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

DR. SCOTT M. SHONE: Okay, this is Scott Shone, just real quick. Sue, the NewSTEPs data repository does collect false negatives. So, that -- that is -- that is a -- a source -- or a -- an opportunity to contribute that data.

DR. SUSAN A. BERRY: Yeah, thanks for that reminder.

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

DR. CARLA CUTHBERT: This is Carla Cuthbert. I just wanted to touch base on what

Carol Greene was mentioning, and -- and I don't know if Natasha wants to mention this, but I believe that Baby's First Test is also having -- putting together a response for some of the issues that -- that can actually make it helpful for the public to understand.

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

DR. DEBRA FREEDENBERG: I was also going to just follow on with Carol Greene's comment. We know that there is a difference in physiology in infants. And, for instance, for the fatty acid oxidation groups, we know that even if we have a borderline and the next screen is cleared that that doesn't mean that you don't treat them as if they needed diagnostic work-up. And for follow-up, it's the same algorithms, whether they fall into a borderline or a truly out-of-range test, and we're going to see that based on the physiology of the babies, as well.

DR. MICHAEL S. WATSON: I was only going to mention that I -- I think it's important to ask the question of why you want to harmonize.

One of the things it enables is inter-laboratory comparisons of performance, which, you know, inevitably, there will be some that perform really well and others that perform less well. And if done right, it actually allows quality improvement to happen to get that performance harmonization while you've got data harmonization to start with.

So, I think it's -- there's a lot of value, in rare disease detection, to have that kind of inter-laboratory comparison component available to you.

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

MS. NATASHA F. BONHOMME: Natasha Bonhomme, Genetic Alliance. Just to address Carla and Carol's points, around language that could be more accessible to the public -- This is something that we are working on with Amy Gaviglio of the Minnesota Department of Health, both based off the complexity that we've heard from the current discussion, but also really based on the tone of the article that really does

question the common sense of the science used, which, I think, is really important for us as a community to address, both the technical issue but also what the -- the image that the article that triggered a lot of this kind of puts out there about public health, and to be able to show, no, we actually think about this and take this very seriously. So, we hope to have more on that, potentially, at the May meeting.

DR. JOSEPH A. BOCCHINI, JR.: So, we have Bob Ostrander on the phone and then Annamarie.

Bob, is your line --

DR. ROBERT OSTRANDER: Yeah, actually --

DR. JOSEPH A. BOCCHINI, JR.: Okay, we -- we can --

DR. ROBERT OSTRANDER: -- I don't have any -- It's Bob Ostrander. I don't have any specific comments right now. I was just trying to sort out -- because when I signed in, it said I was mute only, or listen only, and I was just trying to do this on email. So, I appreciate you recognizing me, but I will chime in later.

DR. JOSEPH A. BOCCHINI, JR.: So, Annamarie.

MS. ANNAMARIE SAARINEN: Hi, thanks. Annamarie Saarinen with the Newborn Foundation. I started with Sharon Terry. We're here because I remember her testimony back in the day, as she'd go in front of committees and talk about the silos that existed when she first started her journey and why Genetic Alliance exists today.

And I think about that in terms of Carla's comments and NewSTEPs and the CLIR repository. Even though it's not universally used yet, it's still a robust chunk of data, particularly on these false negatives but across the board, and I wonder, does -- can anyone speak to why -- or -- or if there's a roadmap for these various places that are collecting right now to sort of merge into one place, where everything can provide the best body of evidence versus being siloed?

DR. MEI WANG BAKER: Mei Baker, committee members. I can just say a little bit about, on

the state level, how -- how this in, because the collect of false negative data is a little bit like a passive. So, you tell them. Because if they don't tell the program correctly, we will not know. So, I think we need to find a very creative way and to -- The one things we haven't implemented, but I was thinking, yes, in our state, just ask a physician, on a annual base, tell us the -- the newborn screening disorders that in their practice, their patient. Then, we compare with our data. So, this discrepancy then allowed us identify, Oh, yeah, this one is not identified through program. Then, you can go back.

So, we do have the one in Wisconsin. We do have -- A clinic will give data to the state. Then, the laboratory will have a data. So, we do the matching. So, each case not matching that, we go back and look, is it a missed or changed diagnosis?

Because, for example, CF, you have one mutation identified. Sweat test, at that time,

was normal. Then, later on, you have a sibling identified as sweat. Now, sweat test is 35. So, they went back and check older sibling. Now the sweat test is a 40.

So, you know, this -- all this kind of nuance and the detail to need sorting out, I think it -- Yeah, this is a part of a challenging.

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

DR. MELISSA PARISI: Melissa Parisi, NIH. So, I have two comments, and the first might not be perceived in quite the most positive way, but I -- I first of all want to say that I really appreciate this effort, and I think that there's been a lot of really good energy and efforts to try to clarify this issue, because it is a real challenge. I do have some concerns about the document as written, and I hope that there might be some opportunities for us to put some of our input in, as well.

In particular, I think that if we're

going to talk about limitations of a given analytic tool, we need to be balanced about talking about limitations for the other approaches to establishing cutoffs, as well. And I do think that because there is power in being able to compare different laboratories, whether using CLIR or the APHL NewSTEPs approach, that that, perhaps, needs to be highlighted a little bit more in this document. I -- but I'm also prepared to, you know, have counterarguments be made to these points.

So, I -- I would like to see there be -- at least be some balance with regard to the strengths and weaknesses of the different approaches for establishing cutoffs, not just for CLIR, in this document.

The second comment that I have is a little bit different, and I'm very impressed with the efforts to try to make this a document for the laboratories, but I do think that there needs to be something that is created for the public. And I'm pleased to hear that Genetic Alliance is

working on that. And -- and I hope that that is an effort that, you know, we may be able to see and have some input into, or at least be able to review, because this whole issue was really raised because of concerns in -- in cutoff establishment and children with missed -- missed diagnoses.

So, I think to the extent that there can be something that can be created that will be user friendly, I think, would be, really, a -- a -- a positive outcome of this. Thank you.

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

DR. JOSEPH A. BOCCHINI, JR.: So, I want to thank Kellie and -- and Dr. --

FEMALE SPEAKER: Carol.

DR. JOSEPH A. BOCCHINI, JR.: Oh, Carol, sorry.

DR. CAROL GREENE: Hi, Carol Greene, SIMD, and I -- I think -- maybe just to state, because it might be useful in the minutes, but going back to the concern that a level in State X

would have been called positive in State Y just across the border, and just to be concrete, and I think one thing that -- that has been said but may not be said in so many words is, that assumes that -- So, if it was -- a level in X was called normal, that level would have been called normal in State Y. That assumes that State Y, if they ran the sample, would have gotten the level in State X. State Y could have set its cutoff because its machinery runs a little differently, and that child could have been equally called negative across the border.

So, it's not just the level. It's the machine; it's everything about it. And so, we have a lot of work to do, and I think it's been a very rich discussion, but I -- I want to be -- I -- I think we need to be clear that it's not just, what would the level have been called, but who's -- you know, what was the humidity, and what was the column, and what's the norm for the machine, and everything about it that you have to think about. It's not just, what's the level.

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

DR. BETH TARINI: This is Beth Tarini, committee member. So, here's my question: Is the variance based on the machine type and/or -- or is it based on the fact that that machine is located in Madison, Wisconsin, in -- at this day of the year, on this type of -- I'm trying to get at, what's the --

There's always variability in nature. What's the variability, and are we in -- is the variability -- Are we using variability to explain something that it shouldn't explain? But -- like, is it a different machine? Is it the day of the week? Is it the path of the sun? Like, what -- because, again, if I go to different hospitals, I could say, the machine is different, the time of the day is different, the humidity is different.

Now, I'm not saying it doesn't -- and again, each test is different; I understand that. Each analyte is different. But what I'm trying to get at is that variance exists in all laboratory

testing to some degree, so when we come back to, it's just that it's different and the machinery is different, I'm trying to pin us down on why, just so I can understand.

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

DR. DEBRA FREEDENBERG: When states -- Debbie Freedenberg, AAP. When states set cutoffs, the -- as you heard earlier, they use the thousands of normal samples they have. Each state may also have a different ethnic population that may impact that, as well. So, when a state sets their cutoff, it's based on their population that they've been screening. And there's variability within different populations, as well as the technical aspects, as well, so it's based on that particular population.

So, what may have been the actual value may not actually matter. It's what it is in the context of that state's whole cutoff design.

DR. BETH TARINI: That makes sense, and I understand that, except that CLIR does not adjust for the state in which it comes from. So,

therefore, if we're adjusting based -- each state based on its ethnic makeup, we are not adjusting in CLIR for the data put in on its ethnic makeup. So, again, it seems conflicting.

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

DR. SUSAN A. BERRY: This is Sue Berry. I think CLIR actually has customized algorithms for each state. I'm -- someone else will need to be more specific about that. But they do work with states to help sort some of those individual characteristics out, is my understanding, so to some degree, there -- there is that element of being able to acknowledge those differences, particularly inside your state. And someone who uses on it a regular basis should comment further on that.

DR. JOSEPH A. BOCCHINI, JR.: Kellie, or maybe Joe could -- Dr. Orsini might be able to comment on that, as well. I think you did mention --

DR. JOE ORSINI: Well, I -- I do -- I can comment on it. There -- the CLIR database does

have tools that are set up for general use, that if your state is used in a -- What they'll do is actually compare your state's data to their database of -- of data and look to see that it's matching, at least. It doesn't have to match perfectly, but it needs to match statistically, in a way where it -- it at least can be normalized to the data that's used in CLIR.

DR. BETH TARINI: But, again --

DR. JOE ORSINI: So, where it gets a little different is if the --

DR. BETH TARINI: -- you can't normalize the data if you don't know what you're normalizing it against has the same distribution of ethnic diversity that you're normalizing it against. You're normalizing it against a -- a pool of data in CLIR, but you have an ethnic diversity.

So, you have to be clear that the normalization -- I would think if -- if it's based on -- if we're saying it's an -- if there's a significant factor of ethnicity, you have to

ensure that you're not just normalizing and washing away the ethnicity, but you're accounting for it.

That -- that's my, sort of, point, that -- that we can't live in both worlds. These are either factors, or they're not factors. And so, I just -- trying to drill down into, taking it into account is a very loose way, from my perspective -- and I'm not a statistician -- of -- of saying, we've addressed it.

DR. JOE ORSINI: Yeah. I think, you know, the CLIR -- the methods used are very statistically solid that -- where they'll compare your state's data to -- to what general data is in the system, and if that data looks statistic -- you know, if it's just shifted, say, one direction or the other, but all the other characteristics, such as standard deviations and things of that sort, match, they -- they have a very rigorous tool to make sure it matches. And I -- I think that if your test came in and it were different, or if your population were different,

that -- that you may end up showing -- having to have your own tool developed.

But to kind of -- I think one thing that makes a big difference between matching up hospital results for CBCs or cholesterol or anything of those sorts is, those things aren't going to have a "yes, you have disease or -- or may have disease" and "no, you may not have disease" criteria associated with it.

My cholesterol is 200, and I'm sure I could be -- you know, but thankfully, they aren't going to tell me I need to go see a doctor. They tell me to adjust my diet. So, there's a difference, I think, that we're trying to nail down, and it makes it very difficult and challenging, not that we can't get better. So, anyway, that's my two cents.

DR. BETH TARINI: This is Beth Tarini. I -- I -- I just want to push back, because A) if your platelet count comes back at 80, or your 3 lines come back low, you're going to heme-onc, and you are a possible cancer patient until

proven otherwise, and 2) we had established at the beginning that we are not diagnosing patients with the newborn screening. So, we're not saying, you have the disease. We're cutting out -- We're saying a line to a next step.

So, again, in either case, we're not diagnosing a disease, A, and B, we are making clinical judgements, beyond just surveillance, that may involve intervention at the clinical level with testing results.

DR. JOE ORSINI: All right, I guess it might have more to do with the nature of the frequency of the disease that you're looking for when you're in a -- in that situation relative to the frequency of some of these newborn screen diseases, where they're very low frequency.

DR. MICHAEL S. WATSON: So, you know, CLIR is set up to deal with -- it already has some covariates in it, and it probably hasn't collected as much ethnicity data as -- or genomic background data, whatever you want to call it -- as could be used to inform that question, but I

do -- You know, all you have in a state is, really, taking their whole population into consideration, which may be shifted to one group or another, but then having, sort of, you know, one thing that reflects that state. Now, that's not really addressing the issue of population variability.

The other part is that -- and I -- I'm glad Joe showed the slide that had that middle zone, where these tools are, really, most effective, because that's, really, where the false positives are rolling out. And it's -- it is a -- there's a lot of money and, sort of, family expense and system expense in managing that gray zone in the middle, where you've got overlap between your normal population range and your disease population. And CLIR seems to perform very well in that area to reduce that problem.

DR. JOSEPH A. BOCCHINI, JR.: Dr. Swoboda, do you want to find a microphone and make a comment?

DR. KATHRYN SWOBODA: Yeah. Hi, Kathy Swoboda. I'm a neurologist and clinical geneticist in Boston.

I just want to, again, re-engage the discussion back to where the families come from, because this document is great. We're never going to have all of rare disease in one pop. We're never going to have all of newborn screening in CLIR. We're never going to have -- I mean, it's never going to happen.

But we're not addressing the -- You know, there's always going to be false positives and negatives. And that's the main thing that families do not understand about a screen test, and that has nothing to do with this document. And it's never going to be solved. So, I -- I think that has to be in that document somewhere, even though you're describing scientific processes, because you just have to be realistic at the end of the day.

That was my comment. Thank you.

DR. JOE ORSINI: The document -- This is

Joe Orsini again. The document does make that statement.

DR. JOSEPH A. BOCCHINI, JR.: Okay. So, I want to thank everybody for a really excellent discussion and -- following an excellent presentation on -- on this document.

So, what we had put into the schedule here was a -- a -- a -- a vote by the committee to support this document as a contribution -- valuable resource for states and as a contribution to newborn screening community, but I also wanted the Laboratory and -- and Standards Committee Workgroup to consider what else needs to be done. And -- and, I think, based on the -- this discussion, it's very clear that there are additional things that need to be done.

A number of points have come up related to education of the public, to -- to trying to find ways to better keep specimens of false positives and -- and true positives, and -- and a number of things that might enhance the efforts that are being done by states and by APHL and

others to try and improve this process.

So, I think that I'd like to get a feel from the committee whether it's appropriate to, at this stage, vote to accept this document as a valuable resource for what it provides to individual states, and then turn back to the Laboratory and Standards Workgroup the opportunity to consider -- to continue discussions related to the additional issues that have been discussed to determine what else our committee needs to do to try and move this ahead.

In addition, we had already asked the Education and Training Workgroup to consider the public side of this and to -- to come up with considerations to bring back to the committee on how to help improve not only the public's understanding of screening but also the providers' understanding of screening in terms of, this is not a diagnostic test; it's screening test and requires an additional study for diagnosis.

So, with that, I'd just like to see if

the committee feels -- how the committee feels about moving ahead on both of those premises. If the committee's interested in proceeding with the vote, I will accept a --

Yes, Scott?

DR. SCOTT M. SHONE: Scott Shone. I don't -- I don't think we should proceed with the vote. I mean, I think that there's still too many questions. I mean, the -- the whole discussion, we circled around a couple of different topics, and I think Dr. Swoboda, sort of, ended it pretty succinctly in terms of what needs to be -- where the next steps are.

So, I'm not sure, especially if Genetic Alliance is working on that other piece. It's a big -- it's a big gap in what we just -- what we've talked about, and not knowing what the additions -- I mean, Dr. Orsini mentioned additional paragraphs, additional this and that. I mean, that -- you know, it might seem simple -- Grammar's one thing, but concepts are -- are a complete 'nother.

So, I -- I don't feel comfortable, necessarily, proceeding -- voting on this as it is given the discussion. It -- it was one thing, in the abstract, of, Okay, this is a good document, but given the discussion, I think it's prudent to regroup for May and see where we head as a whole package that addresses -- addresses the -- the -- the system's educational needs for cutoffs, not just the labs', as APHL was able to accomplish.

DR. JOSEPH A. BOCCHINI, JR.: Okay. So, the question is whether this document is going -- this document should or can address all the issues that have been raised or whether additional work needs to be done for other things. But I understand your point, Scott, about where this document is and some of the issues that were raised in terms of what else needs to be done to finalize this document.

So, any other comments? Cathy?

MS. CATHERINE A. L. WICKLUND: Yeah. Is -- I guess I'm also wondering if this conversation

is being framed correctly in the sense of range and cutoffs as opposed to consistent results from state to state. Does that make sense?

So, in other words, getting at, kind of, what Carol was talking about, regardless of whether or not -- whatever the cutoff is, that a baby's result will get called consistently regardless of whether it went -- Like, if you sent the sample to 10 different labs, regardless of the cutoff, it would all come back screen positive, or they would all come back screen negative.

Right? Isn't that what we're trying to get at, as opposed to, like, trying to have a standard cutoff that everybody's using the same, or am I kind of missing the point?

DR. JOSEPH A. BOCCHINI, JR.: No, I think you're very right about that, and -- and so. One document provides the -- the tools to individual states, but you're right; the rest of what needs to be considered is how to get the same result whatever methodology you're using, so.

I got Jeff and then Carla.

DR. JEFFREY P. BROSCO: Jeff Brosco, committee member. So, I think that what's been tricky in this really wonderful conversation is, what's just about the report, and what's about the -- the larger issues.

And the one comment I heard about the report, in particular, was -- was Melissa's, about if there's equal treatment of all the different approaches. So, I -- I think that -- that I would like to see that addressed before we vote on this document.

But I can certainly see, you know, Dr. Orsini and others saying, Okay, yes, the public's very important, and the question you just raised, Catherine, is really important. This is just a background document on what states do, and that's a separate issue from all the other issues we brought up.

DR. JOSEPH A. BOCCHINI, JR.: And that's how I was framing the discussion.

Carla?

DR. CARLA CUTHBERT: Carla Cuthbert, CDC. Your point is well taken, Cathy, about whether or not you would get the same results in -- in every state. And that's what proficiency testing programs all -- are all about, and all of the states participate in PT programs. So, you know, I'd like to reassure you that, yes, there -- there is a mechanism out there, and the states perform very well in that regard, and if there are issues, our scientists do check up on them.

Like I said, one of the nuances that we want to tackle are the borderline cases. And so, that's not going to change overnight. It's something that we have to prepare and create, and it will be an educational program that CDC will institute to state programs, so that there will be an opportunity for states to have samples in hand that look like those borderline samples, so that they can figure out ways that they can make sure to catch all of those tricky samples.

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

MS. ANNAMARIE SAARINEN: Annamarie

Saarinen, Newborn Foundation. Is there a way for us to articulate that -- what was said earlier, that this is a living document and that there is a pathway, whether that's through -- I -- I'd hate to wait 'til May for the workgroup or the subcommittee to give us a way to provide the input that Melissa was sort of outlining.

So, I think if you can address, maybe, those two things, that would, maybe, make it easier to vote on this document as, again, more of a -- a -- it's a background at setting the table; there's input and improvements to be made versus this is something that --

Does that make sense? I -- I'm just trying to find a way to get you to -- to a vote that makes sure that the -- the improvements and the input are -- are still available to the committee.

DR. BETH TARINI: This -- this is Beth Tarini. To follow up -- but that's an excellent point. Is this document not living, again, on APHL website? Is it living on any website right

now?

DR. BETH TARINI: So, does it have to have a committee vote to live until -- Can it not -- Can you have -- Can you have two things? Can you have it as a living document until the committee decides they want to vote on a final version; therefore, it lives, and then --

DR. KELLIE B. KELM: I mean, this is -- this is APHL's document, primarily -- sorry, this is Kellie Kelm --

DR. KELLIE B. KELM: -- and then the decision is whether or not the committee wanted to do anything to recognize the document.

DR. BETH TARINI: So, it lives, but --

DR. JOSEPH A. BOCCHINI, JR.: Yeah, it's -- Right.

DR. KELLIE B. KELM: So, it could be recognized on our site, for example, as a resource, but APHL is still intending to publish it.

DR. JOSEPH A. BOCCHINI, JR.: Right. It is not our document, and -- and they do not --

they're not waiting for our decision. The question was whether we were going to -- Whether we were going to support the document and -- and provide another opportunity for it to be found on our website as, certainly, one of the outcomes.

DR. BETH TARINI: I would motion to have the document live on APHL's website with a -- if -- if you -- can you link without -- with a link; therefore, anyone that comes, you get the traffic solution solved. And then -- then, revisions can be made, and then we can approve a later draft.

DR. JOSEPH A. BOCCHINI, JR.: And, certainly, APHL has been involved in -- in -- with us and, certainly, has heard the considerations and the recommendations made by the committee to -- with their input, as to how to consider strengthening the document, as well.

So, Beth, is that in the form of a motion?

DR. BETH TARINI: Yes.

FEMALE SPEAKER: I second.

DR. JOSEPH A. BOCCHINI, JR.: There is a

second. So, let's, then, go ahead and -- and take a vote.

DR. JEFFREY P. BROSCO: I'm sorry, can we just clarify? So, I'm not entirely sure I understand the motion.

(Laughter)

DR. BETH TARINI: So, the motion I suggested was that -- that the committee not vote at this time --

MALE SPEAKER: Oh.

DR. BETH TARINI: -- on the document, but that's not prohibit --

DR. BETH TARINI: -- the document from living.

DR. JOSEPH A. BOCCHINI, JR.: Oh, so --

DR. BETH TARINI: Like, do we have to vote on not voting, I guess, is my question.

DR. JOSEPH A. BOCCHINI, JR.: I guess I misunderstood. That doesn't have to be a motion. You could -- if you indicate that you feel the committee does not need to vote on it, and that's

the consensus around the table, I -- I think --

DR. JOSEPH A. BOCCHINI, JR.: -- we can -- That's what you were --

FEMALE SPEAKER: What she said.

DR. JOSEPH A. BOCCHINI, JR.: You were seconding what she said, okay. All right. So, if you feel we need a vote -- But I -- I think if it's the consensus around the table that we don't vote on it, then I -- I -- I think we can hold the vote until the next meeting.

DR. BETH TARINI: But the document can still live.

MALE SPEAKER: Sure.

DR. JOSEPH A. BOCCHINI, JR.: The document is going to live independently, right.

(Laughter)

DR. KELLIE B. KELM: The question is, does a link live on the Secretary's site.

DR. BETH TARINI: But a link can --

DR. KELLIE B. KELM: That's what I'm asking.

DR. BETH TARINI: Can a link live without

approval?

DR. JOSEPH A. BOCCHINI, JR.: No.

DR. BETH TARINI: Okay.

DR. JOSEPH A. BOCCHINI, JR.: No. We would not link to it.

DR. BETH TARINI: I don't know where the traffic, necessarily, goes, but certainly -- Can a link live on -- on Natasha's website?

DR. BETH TARINI: Someone else can manage the internet traffic.

MS. JOAN SCOTT: This is Joan.

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

MS. JOAN SCOTT: Yeah. I think the point is that we think it is a valuable resource, and we are -- you know, have pom-poms on for APHL to continue the work in addressing some of the gaps that have been discussed at the committee and to bring it back to us, but we certainly don't want to, in any way, inhibit what they are doing.

DR. JOSEPH A. BOCCHINI, JR.: Correct. Yeah. Oh, and there's no question that a significant effort has been made, and I think we

do have a -- a -- an excellent document that needs to be tweaked based on the input from the committee, or at least provide that back to HPL for their -- APHL for their consideration, so. But I certainly understand the committee's decision not to take a vote, at this time, until we have additional information.

At the same time, we want both the Laboratory and Standards Workgroup and the Education and Training Workgroups to continue their efforts to address other issues that this document, which is intended for the laboratories, does not address.

Okay. All right. So, we'll go on to the next topic. Can someone go ask Dr. Matern --

DR. JOSEPH A. BOCCHINI, JR.: Oh, he -- you already did? Okay. So, he's ready to come back in?

(Period of silence)

DR. JOSEPH A. BOCCHINI, JR.: So, all right, as Dr. Matern is coming back in, let's go ahead and -- and begin our public comment

section. There he is.

So, we have received requests for four -- from four individuals who would like to make public comments today.

The first up is Jill Jarecki. Dr. Jarecki is the Chief Scientific Officer with Cure SMA, and she will be speaking about the nomination of spinal muscular atrophy to the Recommended Uniform Screening Panel.

Dr. Jarecki?

DR. JILL JARECKI: Thank you. So, good afternoon, members of the advisory committee. Thank you for the opportunity to testify today. As you heard, my name is Jill Jarecki, and I'm the Chief Scientific Officer at Cure SMA, and I'm speaking today, on behalf of the SMA community, to support the nomination of SMA to the RUSP.

I want to begin by thanking the committee for carefully reviewing all of the evidence supporting SMA newborn screening over the past 9 months. During this period, multiple SMA families have testified here about the need for SMA

newborn screening.

These parents, including Elizabeth Moore, who you'll hear from today, have discussed the very positive impact of presymptomatic treatment on their children. These stories have -- these have included stories about infants who have two copies of SMN2 who are now standing and walking, which is unheard of in children with SMA type 1 and in stark contrast to the outcomes of their older siblings.

Beyond this very compelling anecdotal information, there's also significant scientific evidence to support SMA newborn screening, which I know will be summarized in detail for the committee later today. Therefore, I would like to highlight only the most critical data now.

Natural history indicates that there is a limited window for optimal intervention in SMA type 1, the most common and severe form of the disease. Dr. Kathryn Swoboda, who's here today and now at Mass General Hospital, showed, back in 2005, that type 1 infants suffer rapid and

irreversible loss of motor units in infancy, with over 90% denervation often seen by 6 months of age. Important for therapeutic efficacy, motor neurons cannot be restored once lost, so every day counts for these babies in preserving their motor neurons.

As you know, in December 2016, the FDA approved Spinraza as the first disease-modifying treatment for this devastating disease. Data from the Phase 3 trials in infants showed a statistically significant reduction in the risk of death or the need for permanent respiratory ventilation and that 51% of babies gained motor milestones compared to none in the sham group. These trial results were recently published in the New England Journal of Medicine.

Further analysis of this data shows a clear and significant correlation between time of symptom onset and drug response. Seventy-five percent of infants receiving drug prior to twelve weeks of disease onset gained motor milestones. In contrast, just 32% of babies first treated

after 12 weeks gained motor milestones.

The average age of clinical diagnosis for type 1 babies in the Cure SMA database is 4.9 months, and this is after several months of diagnostic delay. This is clearly unacceptable now that we have an effective treatment for this condition.

In addition, as you've heard from multiple families over the past months, result of Biogen's open-label study of presymptomatic infants demonstrates that many infants treated proactively before -- when free of symptoms achieve normal motor milestones, such as walking and standing. This is in contrast to the positive data from the Phase 3 trial of the symptomatic infants that I just summarized, where fewer than 10% of babies even gained the ability to sit.

To date, no presymptomatic infant treated with Spinraza in this study has died or required permanent respiratory support compared to 39% of those in the Phase 3 trials in symptomatic infants.

Importantly, the current newborn screening assays are designed to identify SMN1 gene deletions. These detect 95% of all patients, although 5% of patients have point mutations that are not detected by these assays. Dr. Prior at Ohio State University has reported that these patients have milder forms of SMA compared to those with deletions.

In addition, SMN2 copy number can be used to predict SMA with good accuracy.

Also, while there are different ages of onset for SMA, the available data collectively indicates that less than 10% of SMA patients present symptoms -- first present symptoms after 3 years of age.

In closing, our entire SMA community strongly urges the advisory committee to approve the SMA nomination now that there is a life-saving treatment for SMA, which is shown to be even more effective when delivered early and presymptomatically. Newborn screening, combined with early intervention of therapy, is the best

chance for these babies to have optimal outcomes.

I thank the committee for the opportunity to address you today and urge you to vote that SMA be added to the RUSP this afternoon. Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Thank you for your comments, Dr. Jarecki. Appreciate them.

Next, we have Ms. Elizabeth Moore. Ms. Moore is a parent of a child with SMA, and her comments will address newborn screening for SMA.

MS. ELIZABETH MOORE: I'm doing this one-handed, so. Okay. Here we go.

Good morning. My name is Elizabeth Moore, and I'm the mother of three beautiful children. Children are the reason I am here today, mine and yours. My son William is 6 years old now and living with type 1 SMA. William couldn't make the trip to see you today, although I wish he could have.

When William was diagnosed, we had never heard of SMA. We knew nothing about what it was or what it could do. William was completely

typical, with no signs of anything out of the ordinary, but when William was 30 days old, all of that changed.

It was then that he quit moving on his own, and shortly after, he quit breathing on his own. It wasn't long before SMA stole his ability to eat, to talk, and eventually to smile.

William is now bedridden. He needs saliva suctioned out of his airway often because he cannot swallow. Our house is a mini ICU, and it takes a team of people, around the clock, to help care for William. Our life with William looks a lot different than we had ever imagined. We are so proud of how hard he works every day.

William can only move his eyes today, which is, remarkably, how he speaks. He uses his eyes to control a computer, which is his only outlet to the world. William is our special blessing and has taught us so much in life, especially not to take the small things for granted.

And this little one right here is Mary.

She's our 2-year-old bundle of personality and energy. She may have already caught your eye today; it's not easy to keep her still or quiet, but -- but because we had William, we knew the dangers of what SMA could do. And so, we had her tested.

The test was positive. She has the same genetic deletion as William: SMA type 1. Fortunately, she received treatment when she was 2 weeks old, before she started declining and losing motor neurons. Alongside everything else that William has done in his life, he may have saved his little sister's life. If we didn't have him, we wouldn't have thought to check her.

Mary has not only outlived the typical life expectancy of SMA type 1 and is thriving, she walks, talks, eats, breathes, cries, screams, all on her own. She is our miracle and offers so much hope to so many in the SMA community.

But like I said before, it isn't just about all the motor milestones that she has achieved. It is the simple things in life that

overwhelm me each day. My daughter laughs when I tickle her. She dances to music. She plays mommy and takes excellent care of her baby dolls. She takes ballet classes with her peers, splashes in her bathtub, and can empty any cabinet in record time. And whenever she slows down for a minute, she asks for a hug and gives the biggest in -- in return. Then, she calls me Mama, and she tells me that she loves me.

William has never done any of those things. He doesn't get to interact with his peers or play independently. He never says "Mama" or "I love you." He has never had the ability to give a hug. Every time Mary expresses herself, like right now, I wonder what William would have been like if he had had that opportunity.

Children are the reason I am here today, mine and yours. Every day, I think about all the babies that are being born with SMA and their parents don't know, all the missed opportunities. Screening newborns for SMA is not only the difference between life and death, it is the

opportunity to give the simple blessings of life to a family who has never heard of such a horrible disease. Thank you.

(Applause)

MS. ELIZABETH MOORE: Can you say thank you?

DR. JOSEPH A. BOCCHINI, JR.: All right, thank you, Ms. Moore, and thank you for bringing your daughter.

DR. JOSEPH A. BOCCHINI, JR.: That's perfectly fine.

Next, Ms. Kristin Stephenson, Senior Vice President and Chief Policy and Community Engagement Officer with the Muscular Dystrophy Association was on the schedule to speak. She was unable to -- to -- to remain, so we're going to read in her -- her comments for the record.

So, thank you for the opportunity to address the committee. My name is Kristin Stephenson, and I serve as the Chief Policy and Community Engagement Officer for the Muscular Dystrophy Association. Pleased to be here today

at this -- as this committee prepares to vote on whether to add Spinal Muscular Atrophy to the RUSP.

I've had the privilege to address the committee as newborn screening efforts for neuromuscular disease have moved forward. Today, I'm particularly excited to be here, as I hope, before the meeting concludes, that SMA will be recommended for addition to the national panel.

As an umbrella organization representing more than 40 different disorders, MDA is committed to promoting early screening, diagnosis, and treatment for multiple diseases, including Pompe, SMA, and muscular dystrophy. We're proud to be working collaboratively with the clinician, research, and advocate community on screening efforts around these disorders and look forward to facilitating the additional -- the addition of additional neuromuscular diseases to the RUSP, as they are ready to meet the rigorous evidence review standards set out by this body.

With Pompe currently on the RUSP and with SMA hopefully being recommended for addition to the RUSP today, there is now greater opportunity than ever to ensure that lifesaving and -changing therapies and care are available to newborns nationwide.

For SMA specifically, as you are preparing today to vote, I would urge you to consider that there is a strong follow-up and long-term-care infrastructure in place to help support the SMA community through a nationwide network of more than 150 Care Centers supported by MDA, with more than 20 sites holding SMA-specific clinics.

As I shared in my comments to this body in November, the Care Center Network provides clinical care and access to support and services to families living with neuromuscular disease, including SMA. The Care Center Network, which is led by some of the most respected thought leaders in neuromuscular disease, also serve as sites for many of the clinical trials, where potential

therapies are investigated for SMA, muscular dystrophy, and other disorders.

MDA also supports a provider-entered disease registry for SMA that currently collects data at more than 25 Care Center locations across 16 states, and that is being expanded to include additional clinical sites. This disease registry collects longitudinal data to help drive therapy development and improve clinical care. The development of the MDA registry has been a community effort that has engaged multiple stakeholders and clinical experts, and insights from the registry data are being used to increase understanding of the disorder and support regulatory science.

A "yes" vote from the committee today will mean that critical data on how SMA impacts infants will be able to be understood in a broader way, and that new information will be able to inform and drive improved clinical care, as well as fuel future therapy development. With SMA's addition to the RUSP, babies will be

identified much earlier, and we will have the opportunity to better understand and appreciate the disease by early monitoring disease information collection in the clinical setting.

The same care network and disease registry also support the Duchenne's muscular dystrophy community, which is, admittedly, further behind SMA in a timeline for consideration for the RUSP but which will also be an important disorder to screen for at birth. The -- the clinic network currently provides care for the majority of individuals in the U.S. with DMD.

As you prepare for your vote today, we urge you to consider: The existence of a well-developed clinical care network, disease registry, and robust channels that flow from these systems to share information with the provider, research, and patient community are in place to support the SMA community.

This is a community working together toward a common goal of newborn screening, and we hope that, today, you will vote to recommend that

SMA be added to the list of conditions on the RUSP. And we hope that, in short order, we can come before you again and ask for a "yes" vote on including additional neuromuscular disorders on the RUSP.

Thank you for your time today, for your commitment to ensuring the best possible outcomes for babies born in the United States. And that's signed by Ms. Kristin Stephenson.

Next, we have Dr. Travis Henry. Dr. Henry is a laboratory scientist with the State Hygienic Laboratory at the University of Iowa. His remarks will address the addition of conditions to the RUSP and consideration of the responsibility of a state mandate.

DR. TRAVIS HENRY: Good morning. Thank you for the opportunity to speak today. My comments are made as an individual and do not represent my employer, my state newborn screening program, or my affiliation with this committee's Laboratory Standards Workgroup.

I would like to commend the committee on

development and use of a decision-making process and a decision matrix to assess addition of conditions to the Recommended Uniform Screening Panel. The process and matrix provides a framework for consistent evaluation of nominated conditions and also provides states with collated evidence review and published guidelines for assessment of new conditions within their programs. This was one of the functions of this committee, to provide evidence review and summary to assist states in review and addition of conditions to their state panels.

But perhaps the most important function of this committee is to reduce health care disparity through review and addition of conditions to the RUSP. The RUSP is then implemented by states in mandated newborn screening programs. If the primary goal of this committee is reduction of disparity in newborn screening, and this is carried out by states under mandate, then this committee must consider and include the legal and ethical implications of

a mandate in its decision-making process.

When a state mandates newborn screening, it is removing the right of parents to choose. The state is exercising its authority over the individual because greater harm exists by not screening every baby. In order to justify the restriction of individual freedom, the state must have unquestionable certainty of benefit. Thus, when it comes to addition of conditions to the RUSP, the only condition-readiness score which provides the certainty of benefit required by limitation of personal freedom, a mandate is A1.

As defined by this committee's decision-making process and matrix, any score other than A1 contains known gaps in feasibility and readiness. Any gaps in feasibility and readiness cannot and should not be transferred by the state onto its citizens under mandate. If a condition does not merit an A1 score, then more data should be collected prior to addition to the RUSP.

This committee has used this approach in the past for the addition of severe combined

immunodeficiency. The committee determined more data was needed and so requested additional pilot data be collected prior to addition of SCID to the RUSP. This is exactly what is required for mandated screening: unquestionable certainty of benefit prior to state restriction of individual rights.

This committee has developed an effective decision-making process and matrix for assessment and addition of conditions to the RUSP. However, the consideration of the responsibility of a mandate is missing from the decision-making process. If the intent of the RUSP is to reduce disparity in newborn screening through state-mandated screening, then this committee must consider the legal and ethical responsibilities of the state when it removes personal freedom and mandates screening. Thank you.

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

Okay, this will conclude the public comment section for the meeting, and I will now

turn the -- We're ready for our first break, and so I'm going to turn this over to Catharine for some housekeeping.

DR. CATHARINE RILEY: All right. Thank you, Dr. Bocchini, and thank you for a great morning of presentations and discussion. We'll now break for 15 minutes. We're just running just a few minutes behind, so we will begin promptly at 10:50 for the next section.

Just a reminder: You do have access to the cafeteria, restrooms. There's a little snack shop, as well, and if you do exit the building, you will need to go back through security to re-enter. So, we'll begin again at 10:50 promptly. Thank you.

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

DR. JOSEPH A. BOCCHINI, JR.: All right, so the meeting is now back in session. Next item is the Newborn Screening for Spinal Muscular Atrophy: Systematic Review of the Evidence. We're going to start this presentation before we break

for lunch and then continue it after we return.

And just as background, in February 2017, we received the nomination package submitted by Cure SMA and a multidisciplinary workgroup of clinicians, researchers, and advocacy organizations for inclusion of this condition on the RUSP. At the May 2017 meeting, the committee voted to move SMA to full evidence review, and we have received preliminary reports from Dr. Kemper and the Evidence Review Workgroup at the August and November 2017 meetings. Dr. Kemper and two of his colleagues, Dr. Prosser and Dr. Ojodu from the Evidence Review Group are with us today to present the final evidence review on spinal muscular atrophy.

Dr. Kemper and the Evidence Review Group are an independent group tasked with reviewing the evidence available on SMA. This group does not provide recommendations or participate in the committee's process to decide whether to recommend adding a condition to the RUSP.

Dr. Kemper and Dr. Prosser will present

Part 1 of the -- of the evidence review, and Mr. Ojodu will present Part 2 after return from our lunch break. After the presentations, the committee will -- of the report on SMA, the committee will then discuss and -- and vote on whether to recommend this condition to the Secretary of HHS for the Routine Uniform Screening Panel.

Dr. Kemper is a Division Chief of Ambulatory Pediatrics at Nationwide Children's Hospital, Professor of Pediatrics at the Ohio State University College of Medicine, and so we'll let you get started.

Alex?

DR. ALEX R. KEMPER: Fantastic. Thank you very much. I'm really delighted to be able to present our summary of the report. I'm just -- Oh, good, I -- I have control over it.

So, the -- the committee's been provided with the evidence report. The presentation that we're going to be making now, and then a little bit after lunch, really summarizes the salient

points from that report. Of course, we're all happy to dive in deeper as needed by members of the advisory committee.

I'd like to begin by acknowledging the Condition Review Workgroup. I couldn't ask to work with a greater group of individuals. These individuals really worked very hard over the past 9 months to prepare this work and were very thoughtful in -- in that work.

I'd also like to acknowledge two of the committee members, Dr. Tarini and Dr. Matern, who were representatives to our Condition Review Workgroup and helped to make sure that we were keying in on those issues that are most relevant for the Condition Review Workgroup. So, thank you very much to the two of you.

This work also would not be possible without the technical expert panel. The individuals listed on the screen -- I won't read all their names in the interest of time -- participated on three calls that were held in September, October, and December to discuss a

wide range of issues to make sure that we, as members of the Condition Review Workgroup, really understood as much as we could about the condition and, probably most importantly, helped us to identify other sources of data that might not come up during our usual approach to evidence review. So, I'd like to -- to, again, thank all the members of our technical expert panel.

So, again, as I go through the summary of the systematic evidence review, there's certain questions that I want you to consider, questions that I think are going to come up later, and I think it's helpful to key in on these things.

So, first of all, what's the prognostic implication of SMN2 copy number; how should that information be used?

The second is, what's the importance of detecting compound heterozygotes and carriers. That will make more sense as we talk about the screening process.

A third thing is, what's the appropriate comparator to understand the impact of newborn

screening compared to usual case detection. So, as Dr. Jarecki and others have mentioned earlier this morning, nusinersen is now the FDA-approved targeted therapy for SMA. And so, the issue is -- is, the detection of infants through newborn screening really should be compared to what would happen to usual clinical care, and that usual clinical care now would include treatment with nusinersen. So, it's not comparing newborn screening to just supportive care but newborn screening to earlier implantation of nusinersen.

And then, the final point that I would suggest you all consider is, how convincing are data that are not available in the peer-reviewed literature. So, the -- there's been great scientific and medical progress around SMA, even within the past 6 months to a year. And so, more than any other topic that we as the Condition Review Workgroup have tackled, there's -- there's definitely more unpublished data, data that appears in the -- in the so-called gray literature than -- than what we've had to manage

in the past. So, again, I'm going to bring these points up again, but I just want to put this in your mind as we go through things.

So, the final thing that I wanted to do before we really dive is to remind everyone of our process. So, I'm going to be presenting the systematic evidence review component. In our work, we really focus on the data, not on expert opinion, and so, for example, you know, the -- we -- we can't use lack of data -- we can't use expert opinion to fill in when there's a lack of data. We're really just have to rely on where the -- the data are. And, again, this is the challenging thing, because this is a quickly moving field.

The second component is going to be what Dr. Prosser is going to present. That's the modeling of the expected outcomes, so what would happen if we began screening all 4 million babies born in this country each year for SMA based, primarily, on findings from the systematic evidence review and additional information from

the technical expert panel. She will discuss that in great detail.

Here, again, we're limited to available data. So, you know, we can't put in estimates where there're just no data.

My hope is that I will complete the systematic evidence review discussion and Dr. Prosser will finish the discussion of outcomes before lunch. Then, we'll all break, and then when we come back, we'll discuss the public health system impact, which is the third puzzle piece, and that will be presented by Jelili.

And, again, it's important to remind -- to remember that this is limited to state surveys. APHL also dug into issues of the costs of -- of screening -- the screening test, as that's part of our charge, but we do not look into overall costs related to the care of individuals with SMA. So, just to say that again, we look at cost, but it's really the cost of the newborn screening test itself.

And as Dr. Bocchini mentioned, we're --

we're here to present the evidence, but we do not make recommendations. We're really here to support the work of the advisory committee in that process. So, as I go through this, if there's something that -- that needs clarity, if you have, you know, just clarifying questions, please let me know.

And then, what I think might make most sense is for the more substantive, meaty questions, if we can save that for after the -- after all three components are -- are presented, because they kind of build on each other, and I suspect some of those questions will get resolved and -- and, no doubt, other questions will -- will come up. And so, if you have a clarifying question and I don't see you, just, you know, maybe throw your beads or something.

(Laughter)

DR. ALEX R. KEMPER: So, I want to spend a little bit of time, first, talking about SMA before we get to the details of the systematic evidence review. I think this is something that -

- that's common knowledge across the advisory committee, with this, you know, being our -- our, what is it, third presentation or so -- I guess it's our second presentation on the topic -- but I just want to make sure that we're using common language and coming at this from the same place.

So, SMA is an autosomal recessive disease affecting the motor neurons in the spinal cord and the brain stem. It results in motor weakness and atrophy. It has a broad phenotype -- phenotypic spectrum, ranging from birth to adulthood, differences in severity and -- and clinical course. Most individuals affected with SMA, though, are the more severely affected children who present in earlier childhood, and we'll be talking about that in a little bit.

There are many different types of SMA. And, you know, getting back to the historical classification, which we'll be talking about, and even some of the refinements of this, the -- it's really distinguished by the maximum motor milestones that the individual achieves and the

age that that happens. And that -- that sort of links to the classification that we've -- that we'll be talking about.

So, again, here's a list of different forms of spinal muscular atrophy. You'll -- you will see that there's type 0 through type 4, and then there are also other forms that we won't be talking about. We will really be talking about those forms that are associated with the SMN1 gene, and more particularly, we're really going to be focusing on types 1, types 2, and types 3.

These are the -- the forms that are more common. These are the forms that present in childhood. There's an SMA type zero that, really, can profoundly affect fetuses, and -- and most of those fetuses will not survive to birth. And so, that's going to be less of a focus of our conversation.

So, again, it's really going to be types 1, types 2, types 3 that we're going to be talking about, and even within there, it's really type 1 that's going to drive most of our

conversation.

Okay, everybody with me? Yes? Okay.

So, you know, one of the questions, when you think about newborn screening, is the -- you know, what -- what's the current delay to therapy. So, if you were to implement newborn screening, how much would you be moving the clock back in terms of the time of diagnosis? And so, I'd like to present findings from a systematic evidence review that was published in 2015 that looked at studies from 2000 to 2014, and they looked at the -- they -- they combined studies that looked at the average age of onset of symptoms and then the age of diagnosis.

And you can see that for SMA type 1, from this review, the average age of onset was about 2-1/2 months, and the age of diagnosis was 6.3 months, so, you know, suggesting that there's this, you know, on average, 4-month delay to diagnosis. And you can see that for type 2, the delay seems greater, and then, again, you can see type 3, as well.

And so, the -- the reason that I'm showing this slide is, again, just to give you a sense of what the -- the -- the -- the process is to final diagnosis and how far back the clock could potentially be moved back through newborn screening.

We talked a little bit about the classifications of SMA. There was an international consortium, back in 1992, that further refined the -- the historic types that have been used, and I -- I think, even, for several decades, this group recommended subdividing things into, you know, 1A, 1B, 1C, so forth, and you can see that this just gives a little bit more granularity to the classification of SMA.

There are going to be some times when I'm going to refer back to 1A, 1B, 1C, and so forth, but in general, for the purposes of the conversation, especially given the -- the amount of data that we have, we're going to be looking at things, primarily, by the larger grouping. But

I just did want you to be aware of these -- this -- this more refined approach to SMA classification.

This is a figure from a publication in 2002, where they looked at -- it was around 375 individuals with SMA and then looked at their SMN2 copy numbers, and, again, this figure was taken directly from that publication. And you can see that if you have two copies of SMN2, you're more likely to have SMA 1, although there's a little bit of overlap, and that when you move up to 3 SMN2 copies, you can see that there's, really, greater overlap across the classification of SMA 1, SMA -- SMA 2, and SMA type 3, and that the same thing happens with 4 copy numbers, where there's some overlap between SMA type 2 and SMA type 3.

The reason that I point this out, again, is to just reinforce that copy number is important, but it's not entirely predictive of the type of SMA that an individual is going to go on to have.

Certainly -- and -- and this -- this, again, is from a -- a -- a study in -- in 2002, which is the same study as this one, where they -- and this was in the pre-nusinersen era, where they looked at SMN2 copy number and survival, and you can see that there -- that, you know, there -- there's a correlation there. And then, if you look at the Kaplan-Meier survival curve on the -- on the right, you can see that having more copies of SMN2 is associated with a greater likelihood of surviving longer.

So, again, one of the key points that I want to make here is that SMN2 copy number is important, and it can be predictive of outcome, but it's not 100% predictive, because there is some overlap, especially when you get beyond copy numbers of 2, so 3 and -- 3 and 4. And I can talk about, later, what current recommendations are based on SMN2 copy number, but -- but I -- I just want to provide this, kind of, overview, first, of what the issues are.

And, again, this -- this is from a -- a -

- the more -- more recent study showing, again, that for individuals with SMA type 1, the -- the figure on the left is a Kaplan-Meier curve for vent-free survival, so that means that you're alive and not ventilator dependent, and then the curve on the right is probability of survival. Again, age is on the x-axis.

There's that little blue dot, that dotted line, that we added into the figure, and that figure represents -- If you look across all the data that we've been able to find and duration of treatment, that's, kind of, how far out we go in terms of the treatment evidence. So, what I want to do here is just preview the fact that our treatment outcome data, in terms of the duration, is -- is really limited in terms of primarily being in early childhood.

Again, here's another slide from the -- the -- or another figure from the same presentation, showing that SMN2, if you subdivide by subtype of SMA, is related to outcome.

So, I put this slide together to help

frame us with how it is that -- that we're here considering SMA for the Recommended Uniform Screening Panel. So, in terms of the genetics, most cases are due to homozygous deletion of SMN1 exon 7. There are about 5% that are compound heterozygote.

So, that 5% number comes from looking across a bunch of different studies, probably low end of 2%, high end of 6%. You know, we -- because of the rarity, we really don't have good -- a good sense of the percentage of individuals who are compound heterozygotes for SMA. And then, as we've discussed, copy number of SMN2 influences outcomes.

Now -- so, we -- we understand the genetics fairly well in terms of the screening. There's -- there's a target, exon 7, in one or both alleles, and we'll be talking about that. SMA has been implemented in the United States, so there's a research project that is going on in New York. We talked about that before; I'm going to highlight that again. And then, there was also

a screening project that was done in Taiwan, in terms of diagnosis, that's based on confirming deletion of this exon in the SMN1 gene, and then looking at SMN2 copy number. And, of course, all this has to be confirmed by clinical exam.

And then, there's a specific treatment, so nusinersen, which was FDA approved for all types of SMA in December 2016. I'm going to be talking about other therapies that are out there for it, but since nusinersen is the only FDA approved treatment and because that's really where most of the evidence is around treatment outcomes, we're going to be focusing in on that. But this -- this figure -- there -- this slide, I hope, sort of encompasses where -- you know, how is it we got to where we are and -- and the kinds of things that I'm going to drill into.

There are a number of different outcome measures that are used when SMA is studied, so ventilator-free survival -- we talked about that a little bit ago. There are also two measures that are commonly used. So, there's the

Hammersmith Infant Neurological Examination, the HINE, and that's -- that's a standardized assessment tool for infants between 2- and 24 months of -- of life.

There are actually three components of it. There's a neurologic exam, an exam for developmental milestones, and then behavioral assessment. It's really the developmental milestones component of it that's been, really, the -- the -- the focus in terms of measuring outcomes of treatment for SMA.

Now, separate to this, there's also the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, or the CHOP INTEND. This is for children between the ages of 4 months and 4 years, and it's really been targeted for use in assessing SMA.

So, it's -- both -- both these tools are -- are complicated to understand, and part of it is, just with normal development, you meet more milestones. So, you know, as a -- as a child ages, they, you know -- An unaffected child would

be able to do more stuff as they -- as they age.

And so, the -- so, it's not like there's, like, one cutoff for the score. You really have to think about the score in the context of the age of the individual and then, of course, the nature of SMA, where you -- you either plateau and then begin to lose the ability to do some of these things. Understanding trajectories is really important.

So, I'm listing up here the elements of the HINE. If you add it up, you can get to a total of 34 points. Some of the publications, including the -- the Finkel publication I'm going to be talking about a lot, has an upper limit of 26. I'm not sure how they got from the 34 to the 26, but I just want you to get a sense of the range, anyway.

And so, if you look at the table that we put in here, if you have infants with no known perinatal risk, otherwise healthy children, they typically score between 24 and 34 at 12 months of age and would be up to 31 to 34 by 18 months of

age. If you go back and look at the natural history studies, between 2 and 24 months untreated infants are -- are around zero to 3, so markedly lower. And then, we're going to be talking about treatment again, but you can see that their range goes from zero to 17, but, again, on this modified 26-point scale.

I -- I'm going to leave this slide up just for a second in case you want to look at the -- at -- at how the scoring works, but -- but -- but just know that we're going to be talking about a range in here.

Okay, now I'm going to move over to the CHOP INTEND. This one's a little bit more complicated in that it has many more domains. There are 16 domains. I'm not going to read them all, but I will leave them up here, and the scoring is a little bit different in that you can get up to a score of 64. Healthy infants, like we talked about before, can go up to 50. And I have the points there, and then I have some information about treated individuals.

I actually think, for this one, it's helpful to look at the figure, where the, kind of, blue/purplish -- whatever color that is -- are -- are healthy controls, and then the reds show a typical course for affected individuals. And, again, we're going to be drilling into this again in a little bit.

So, I'm going to change gears and talk about the screening approaches. In the -- in the interest of time, and because it always makes me nervous to talk about laboratory testing depth being a non-laboratorian, I'm going to simplify this, because I -- I think the nuances aren't going to really help inform what the eventual decision that you all make is.

So, there's generally two approaches. There's the approach, for example, that's been in -- used in Taiwan, where they just ask if there's SMN1 there. That is, are there, you know -- you know, looking -- looking for deletions on both alleles of the gene.

So, using the approach that they've used

in Taiwan -- and this is similar to the approach that the -- the -- the CDC uses, which I'm going to talk about in a second -- they don't detect carriers. They only detect -- they only -- they would only detect individuals who have a deletion of the exon in both alleles of the gene. So, it's not like they don't report out carriers; they simply don't even detect carriers. That comes at the -- The -- the downside of that would be, if you were one of these compound heterozygotes, it would be missed in this process.

Now, New York has a pilot research program going on in three hospitals there, and the way to think about this is that they ask if SMN1 is there, and, if so, how does the quantity relate to other genes. The bottom line is that this approach picks up carriers, but it could also pick up compound heterozygotes.

So, again, the two ways are, you can either do it in a way where you can detect individuals who have the deletion on both copies of their SMN1 gene, or you could pick up

individuals who have deletions on both copy or just one copy -- or one allele, rather, and you would -- that would allow you to pick up carriers and compound heterozygotes in addition to those affected with deletions on both alleles.

Does that make sense? All right. Good. And I'm going to skip over so you don't ask me anything about PCR.

So, the -- the CDC has also developed an assay which, again, targets SMN1 exon 7 deletion. It doesn't pick up carriers, like we talked about. It can be multiplexed with SCID screening. So, that, you know, allows a -- a -- a large degree of efficiency there. And then, the CDC also has offered consultation, technical support, and -- and perhaps even most importantly, they have reference materials for the newborn screening lab, when to adopt this. They could -- they could evaluate how they're doing.

So, now let's move into the evidence review itself. You know, the key thing I -- I want to let you know is that, you know, we -- we

screened, through 2007, 182 articles, and from those, using -- you know, the -- the -- to be able to answer the questions that we want to talk about, there were 5 treatment studies and 2 screening pilot studies that were published that we were able to extract and -- and evaluate, and we'll be talking about that.

So, I want to put this evidence review in context of how fast the field is moving. So, four of the seven key treatment and screening articles were published during our review process, after November of 2017. A bunch of the key background articles -- so, these are articles that don't meet the criteria for evidence extraction but -- but are really key to our understanding of things -- were published after 2017, and then there are a number of different conference presentations and posters and -- and that kind of thing that -- that really helped inform this evidence review.

But the -- the -- the key thing is, this is, really -- We're -- we're relying on gray literature a lot more than we have in the past.

And, again, I think it just speaks to how fast the field is moving, which is very exciting but -- but also challenging.

So, there are really three SMA newborn screening publications. There's a publication from 2017, from Genetics in Medicine, regarding the New York state pilot study. There was one, also, in Journal of Pediatrics, about the Taiwan study, and then -- I've been waiting all day to say this -- there was a prior report -- ha, ha, ha -- published in 2010, using anonymous dried blood spots, but we're -- we're not going to focus on that study now that we have actual prospective evaluations.

So -- actually, before I circle that, you can see, at the time of publication, there were about 3,800 newborns that were screened in the New York pilot project. We, thanks to Dr. Caggana, have updated information, which I'll be showing you in a second. In Taiwan, they screened about 120,000 newborns, and we're going to be digging into that in a little bit.

Now, if you look at the New York state pilot report, they talk about the false positive rate as being zero, and that's because, in their analysis, they don't consider carrier detection as being false positives. Now, how you feel about carriers is -- you know, I don't want to -- you know, that -- that's not a decision from the Condition Review Workgroup, but we are going to tease out carriers separately and -- and -- and -- from the compound heterozygotes, because I think it's just really important to disentangle those things, because the implication in carriers is different, obviously, than -- than would be a compound heterozygote expected to go on to develop SMA.

So, here is, hot off the press, the -- the New York data, and again, I really thank Dr. Caggana and her colleagues for sharing these unpublished data with us. So, they've -- they've now screened 10,362 -- at least, as of this point -- with a false positive rate of -- of zero, that -- that -- you know, not counting carriers as

false positives. They've identified 144 carriers. So, that's, one in seventy-two of the newborns that were screened were carriers. That's 1.4% of the individuals screened.

They've identified one individual with SMA who had the traditional homozygous deletion of the -- of the exon 7, and this individual also had the -- had two copies of SMN2. This individual was diagnosed at 7 days of age and began nusinersen at 15 days of age, and by report -- again, this is not published, but -- but by report, by 1 year of age, this child is -- is doing well, not requiring mechanical ventilation, and his or her developed milestones have been met.

So, that -- that's, you know, the one case that was identified. There are, to my knowledge, no compound heterozygotes that have been identified through the screening process.

The Taiwan pilot project was done to -- was done, really, as a feasibility trial, done between November 2014 and September 2016, which

is interesting, because it was before nusinersen was widely available.

Again, in the -- in the interest of time, I'm not going to go through the details of the flow diagram on the left, but I'll just highlight that nearly all the -- the parents that were approached for screening agreed to it. They don't report any false posi -- or -- or false negatives, rather. There was a -- they had a -- a -- a two-tier testing process that ultimately led to the identification of seven with confirmed homozygous deletions, which -- which, again, is just summarized here.

So, if you look at the Taiwan data, their estimated incidence was 1 in about 17,000. Again, even with 120,000 screened -- 120,000 -- given how unusual most of the conditions that are identified through newborn screening, developing a -- a stable birth incidence or birth prevalence can sometimes be challenging.

I just want to point out that of the seven patients who were identified, the median

age of diagnosis was 8 days of life.

All right. Now let's move to treatment, unless anybody has clarifying questions around screening. I'm, like always worried when a lab person's going to ask me a clarifying question.

(Laughter)

DR. SCOTT M. SHONE: Scott Shone. I just have a question about the other eight. So, you have the seven -- you had 15 screen positive. Seven were confirmed SMA, but the other eight, were they --

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

DR. SCOTT M. SHONE: In -- in the -- in the write-up, it says 8 of the positive first-tier screens had 1 copy of SMN1. Is that the other 8, the 15 minus 7? Is that -- So, you're counting false positives as one --

DR. ALEX R. KEMPER: So -- so, they -- they -- they counted -- see, this is what I was just, like, worried about, like, showing this little diagram. But they -- they counted the -- those eight as false positives in the method that

they were using. So, there were seven cases that were identified and eight that were -- that -- that they considered to be false positives.

Okay, anything else?

DR. ALEX R. KEMPER: I'm glad I didn't have to talk about PCR or Bunsen burners or anything.

All right. So, there are three treatments that I want to discuss. This one I'm presenting you, this is really more of a historical reference, because near as I can tell, it's not being further developed. Olesoxime, which I hope I pronounced right was a -- a study that included individuals with type 2 or type 3 SMA in a -- in a randomized trial for this medicine that's supposed to affect the mitochondria.

The bottom line is that after 25 months of therapy, the -- the -- the -- there was no significant difference in -- in motor outcome. It's -- it's interesting that the P value still seems, you know, kind of low given the relatively small numbers, but I think that with the

development of nusinersen, near as I can tell in -- in -- in our looking, that there's no further development of this drug going on. I could be wrong about that, but -- but, certainly, I don't have any other information other than the fact that there was this one negative study that was published just last year.

Before I get to nusinersen, I also want to talk about the one study of gene therapy that -- that just very recently came out. So, this was a Phase 1 study that included infants with type 1 SMA and 2 copies of SMN2. They received one single-dose treatment of this gene therapy. They did, first, the low dose of the gene therapy followed by a -- a high dose.

We -- and it's -- Our -- our rating systems are described in the full report. We rated this as a moderate-quality study, not because the study itself isn't important, but we -- there was no information about who was rating motor development and whether or not they were asked how the child was doing before, where it

was going on with them. And because of the subjective nature of some of the items on the motor development scores, that lowers the overall quality of the evidence.

So, I just want to point out that children in the -- in the first cohort, it was just three subjects. There were 12 subjects in the second cohort who received the higher dose, and treatment for the lower dose began around 6 months of age. For the higher dose, it was around 3 months of age. You can see there, they both had symptom onset between 1 and 2 months of age, and you can see here the mean score on the CHOP INTEND scale.

So, again, this was a, you know, small study. Again, it's, sort of, a rare disorder. It wasn't a comparative trial, but it -- it does provide evidence about the potential benefit of gene therapy. And I know there's a lot more work going on in this domain, and this is, really, all we can comment on gene therapy itself is from this one study.

In terms of event-free for survival, there is a hundred percent at 20 months. Again, if you look back to the previous natural history studies, that compares to about 8%. All the subjects increased in their CHOP INTEND score from baseline, with a higher dose appearing better, and if you look within the highest dose group, you can see the individual motor milestones that were achieved.

And I'll just leave that for a second instead of reading it out. But you can see that, at least compared to natural history, it does seem to be a -- a -- a -- a -- a major impact in terms of survival and motor development.

I think it's helpful to see how the scores change over time, and so you can see, on the left, the -- those in the lower-dose group and on the right, and the higher-dose group. There is one -- one subject, you can see in the purple, on the right, who did not improve as much as the other subjects, whether that was due to that individual being treated late, or later, or

some other factor we can't comment on.

All right. So, I'm going to move into nusinersen if everyone's ready for that. Yeah? Okay. So, I mentioned before, nusinersen is the only FDA-approved treatment. As we talked about before, it alters splicing of the SMN2 pre-RNA, so that you get more functional SMN protein. It's a -- Well, I'll just leave it there without drilling things in.

So, there are a number of different manufacturer-funded studies, and I personally get lost in these names. And so -- And they all seem like such -- such good, positive names, too, but I just can't keep track of them. And so, what I'm going to do is, I'm going to read the names and what they're associated with, but I'm just going to -- When I go through the studies, I'm going to talk about what the studies are and try to avoid the names, the acronyms, as much as I can.

So, there's CHERISH, which was a Phase 3 trial in subjects with later-onset SMA. That's not going to be a focus of what we're talking

about today. There's ENDEAR, which was the Phase 3 trial, so this was a comparative trial of subjects with infantile-onset SMA. We're going to talk about that a lot. NURTURE, which is a Phase 2, open-label study of subjects with presymptomatic SMA, EMBRACE, which is another open-label study, and then SHINE, which is also a -- a open-label extension study.

Again -- Oops. I went too fast. For the -- what we're going to be talking about today is really ENDEAR and NURTURE, so the Phase 3 trial of infantile-onset and the Phase 2 study of -- of subjects with presymptomatic SMA that are really, I think, going to inform the -- the discussion that you have later.

So, let's first talk about the Phase 3 trial. So, in our rating system, this was -- was -- was considered to be a -- a strong study. It enrolled subjects who had symptoms before 6 months of age, and they had to complete screening for study participation by 7 months of age, and this study -- for study entry, they had to have 2

copies of SMN2.

Now, interestingly, this study was terminated early because of a dramatic difference in survival. So, there were -- at this point, there were 80 in the treatment group and 41 in the control group who received at least 1 intervention.

Now, sort of teasing apart where people were in the process of the study is a little complicated because of the way that -- that it was ended, but if you -- if you look at -- at -- you know, across subjects in the nusinersen group, there was 61% event-free survival versus 32% in the control group. Again, that's what led to the unmasking of the study.

This shows an event-free survival curve comparing nusinersen to those subjects who were randomized to control. So, you can see the -- the -- the differences in the curves, which, of course, was statistically significant.

If you drill into motor milestone response, that was also dramatically different,

with 41% in the treatment group and none in the control group, and you can see listed here some of the motor responses that were identified. Again, these all come from the -- the Finkel paper that was recently published in the New England Journal of Medicine.

So, now we're going to move into the gray literature, okay, because one of the key questions that we're interested in is, what's the benefit of presymptomatic care, right? So, if you identified a -- a -- a newborn through newborn screening, how does that compare to usual clinical case detection?

So, if you look in the gray literature, there's a -- there -- there's a comment -- and, again, we have the presentation listed here -- that if you look at individuals with total disease duration of less than, equal to, 12 weeks before treatment, compared to those who began treatment after 12 weeks, they were more likely to have better outcomes.

So, one of the things I want you to

appreciate is, this is not 12 weeks of life, but this is 12 weeks of disease duration. But it does look like if you stratify 12 weeks, there's a difference. And so, these are -- are figures from that presentation.

So, if you look at the survival curve on the top left, that has disease duration less than, equal to, 12 weeks -- the treatment group in blue and the sham-treated group, the control group, in black. Okay? The bottom slide has disease duration greater than 12 weeks -- same thing, with the treated group in blue and the -- the -- the control group in black. And so, you -- what you have to do to understand the -- directly compare the benefit of treatment before and after that 12-week mark is kind of mentally overlay those two blue lines, but you can see how they do diverge.

Same thing with that figure on the right. So, this is the HINE motor milestone responders. You can see that 75% of those treated before 12 weeks were considered to be motor milestone

responders versus 32 percent. So, again, compare those two blue bars to get a sense of what happens when you stratify at 12 weeks of disease duration.

So, in terms of treatment -- and, again, sort of focusing on where we are with the evidence -- there's no peer-review-published reports comparing presymptomatic detection to usual case -- usual clinical detection. There just isn't that head-to-head comparison that we could find.

That being said, there are multiple presentations and abstracts from the ongoing Phase 2 study of presymptomatic individuals. So, again, these are presymptomatic individuals who were being treated with nusinersen. There's no, you know, control group. Again, that -- that was ended with the Phase 3 study that I described before that -- that -- that would be considered ethical at this point.

So, here's one presentation that -- that if you look at 20 subjects who began treatment

before 6 weeks -- And you -- you would ask, you know, where these subjects came from. There were 15 siblings. Three were identified through screening, one through prenatal screening, and one because of a family member who was a known carrier. Again, these are not publications. I can't, you know, tell you exactly, you know, how they were recruited and what the process is. I can only, you know, report what we were able to dig up from the presentations.

So, if you look, of those 20, 9 of them have now -- at least, based on the presentations -- passed 1 year of life. All 9 of them are alive, and, again, the motor development appears to be a function of the SMN2 copy numbers.

So, what I want to orient you to is, the -- these bars represent the number of infants who are reaching these milestones. So, you can see that there were 6 who -- 6 with SMN2 -- with -- 6 with 2 SMN2 gene copies who achieved head control. There were 3 with 3 SMN2 gene copies, and that represents all 9 individuals. Okay?

So, all nine, at this point, had achieved head control. And so, you can follow along. All nine were able to kick and touch their toes, but the numbers fell down for rolling, sitting, crawling, cruising, and standing unaided.

We really can't, given these small numbers, do any statistical testing in here, but I think it's helpful, at least, to get a sense of the role that the SMN2 gene copy number might be playing in there.

So, I -- I'd like to end my discussion of nusinersen by talking about this figure that's been presented in a number of different meetings. Okay? So, the green line that's higher represents those children who began nusinersen therapy presymptomatically with 2 or 3 SMN2 copies. Okay? So, this -- that -- you can imagine what might happen with newborn screening. The red line -- and the -- the red line are those subjects that were treated in the Phase 3 trial. So, these are infants who were symptomatic at the beginning of therapy. The blue line represents a similar thing

with -- with symptomatic children who got nusinersen, and then the dark line, at the bottom, is the -- the -- the -- the control group from before -- essentially, the individuals who didn't have therapy.

So, again, for the purposes of understanding this, I'd recommend that you focus on the green line and focus on the red line. The y-axis here is the average total milestone score, ranging from zero to 26. We talked about the HINE-2 before.

So, one of the things that -- I'm going to just -- just circle this. There -- there are two things that make, I think, this graph difficult to interpret, okay?

So, the first is, the x-axis is not the age of the child, but it’s their scheduled visit day for therapy. So, those children who were detected presymptomatically are likely younger than the symptomatically ones. So, you can't just look and say, you know -- You -- you can't directly infer what their age of life is or how

long their disease duration was. So, it makes it hard to interpret this.

The second thing is that, again, this was the -- the mean total milestone score across these different studies, and of course, you know, normally, with -- with children, they would, you know, progress and -- and reach higher scores just because of normal development. So, because of these variations in ages, it's hard to -- You know, what K.K. and I tried to do was think about how we could put, you know, like, you know, lines on here demonstrating what normal development might be, but because of the way these figures are constructed, we just can't do this. Again, this is -- this is unpublished, and we're, kind of, restricted to what is available out there.

Another question which I can't answer is, if you look at the last green dot, so the last point in terms of motor milestone score, it looks like there's a dip down. Now, certainly, those confidence intervals overlap with the previous point, and so this could just be a statistical

fluke, and who knows what's going to happen next. But I can't tell you if this portends that there's a decrease in motor milestone score. I mean, it -- it's just -- it is what we have.

Oops, I forgot to move it over there, but I think you -- you get the -- the -- the point there. Again, this -- this could just be random noise or who knows what.

So, I -- I presented a lot of data, and I know that in the -- in the tome that we sent you, there's a lot of information. I think it's helpful to highlight some of the key take-home lessons.

So, we know that screening can detect cases of SMA in newborns. You know, there's this question about the role of compound heterozygote detection and carrier detection.

We know that treatment can modify the course of SMA, but there are really few data about presymptomatic identification. It does look like presymptomatic treatment alters the natural history -- I put that in quotes because, you

know, I've always hated the term, anyway.

The outcomes that we have are generally limited to around the first year of life. So, it would be nice if we were able to project out longer, but we just can't because, you know, it's the nature of the science and how things are developing, plus, also, what's been reported.

The magnitude of motor development changes are hard to know, right? So, we talked about, sort of, comparing scores and that kind of thing is challenging.

And I think it's fair to say that more work is needed to understand the role of SMN2 copy number for risk stratification or prognosis. Certainly, SMN2 copy number tells you a lot about what you can expect in terms of the course of the disease, but it's not, you know, locked solid.

So, there are just a couple of points that I want to make. One is that Dr. Jarecki, who addressed the advisory committee this morning, has been working hard with a number of her experts in the SMA treatment community to develop

guidelines that use the Delphi technique, with 13 voting members. It has recommendations for when you should begin treatment based on copy number and also the kind of follow-up that's needed. So, those guidelines are in development in terms of, what do you do after a positive screen.

The -- there's also -- and Dr. Swoboda, who addressed the advisory committee, has helped develop a data repository with longitudinal history data, as well as data that will be coming in from some of these investigator-initiated clinical trials, and that, ultimately, is going to go to Mike Watson and his LPDR data common. So, there are new data sources that -- that are coming forth.

Again, this is not the kind of thing that we as the Condition Review Workgroup could go in and -- and analyze, but I do want to make the advisory committee aware that there's a lot of work going on to better understand and characterize the condition and its outcomes.

So, there's lunch, but if I can indulge

the advisory committee, I think it makes a lot more sense for us to talk about the modeling right now, because the modeling is heavily weighted on the information that I talked about before. We'll go and have lunch, and then we'll talk about the public health impact assessment.

But for now, Lisa, if I can bring you up? And I -- You know, I didn't say this enough before, but while Lisa's coming up, I'm going to just say that -- that K.K. Lam has really been integral to this process, and given the 9-month timeline that we have, I don't think it -- it would have happened without her -- her expert ability to both be a taskmaster and understand this complicated information.

DR. JOSEPH A. BOCCHINI, JR.: So, most of you know Dr. Prosser, but for those of you who do not, she's a professor in the Department of Pediatrics and Communicable Diseases at the University of Michigan, also has adjunct faculty appointments at Harvard Medical School and Harvard School of Public Health. So, we agree

with Alex that we'll go forward with her presentation, because it sort of -- it fits right now, and we'll change the time for returning from lunch.

DR. LISA A. PROSSER: All right. Well, thank you. So, I have the highly coveted position of standing between you and lunch, but this will -- I think this will be about 15 minutes and leads directly from the information that Dr. Kemper just presented.

So, good morning, or almost good afternoon. In the next few slides, what I'll be doing is going through the analytic approach, as well as the results for the modeling analysis, to estimate population-level health benefits at the level of the U.S. population for the proposed screening program for SMA.

So, just in terms of background, that we integrated this approach into the Condition Review Workgroup process several years ago in order to be able to make the best available use of the data that we have. We're using decision

analysis here as a validated approach to evidence synthesis that the evidence base is typically very scarce for the conditions that we're reviewing, and traditional evidence review processes did not yield the full set of information that would be helpful for the committee to have for decision-making. And so, here, we're integrating decision modeling, especially helpful here, for this condition, where the evidence base is even more scarce in some places than for other conditions that we've addressed.

So, using simulation modeling, ranges can be estimated for population-level health benefits at the level of a U.S. birth cohort of 4 million annually. And, in particular, what we'll be doing with the decision modeling is explicitly identifying assumptions that are going into both the assessment of the evidence, the development of the model, and it allows us to identify where the key areas of uncertainty are, and that's what I'll end with at the end of this slide set.

So, the overall goal for the modeling analysis is to quantify both screening outcomes as well as health outcomes for newborn screening of SMA compared with clinical identification. And important to highlight here that the two screening strategies that we're comparing is assuming that a screening program is followed by treatment of every probable type 1 case that is identified through newborn screening.

And we'll talk about the -- the questions around the -- which infants will be likely recommended for treatment and compared with clinical identification and treatment, and that will come into play when we evaluate how the -- the evidence from the clinical trials is incorporated into the modeling analysis, because what we're comparing here is screening followed by treatment compared with clinical identification followed by treatment, not clinical identification in the absence of treatment.

The primary health outcomes are

mortality, ventilator dependence. We have not modeled motor function. Dr. Kemper just reviewed some of the challenges of evaluating those data from the clinical trial, but I'll end with some comments about how those are likely to play out in terms of the modeling.

Again, our focus here was on SMA type 1, that as with our evaluation of past conditions, we focused on the most severe forms of the condition that's being considered for screening: infantile-onset for -- typically, for other conditions and, here, focusing primarily on SMA type 1 and looking at projected health benefits over a 1-year time frame. We do quantify screening outcomes and the number of projected cases for the -- for subtypes other than type 1 and, again, focusing on 1-year endpoints.

So, in the next two slides, I'll be walking through the schematic of the simulation model that we've used to estimate the outcomes, and so walking through from the left-hand side to the right-hand side.

So, under clinical identification, that the estimated birth prevalence of approximately 1 in 11,000 can be divided into -- We've grouped here type 0 and 1, and we've done that for the newborn screening or with the model as well. Some proportion of type 0 and 1, type 2, type 3, type 4, that over half of those are expected to be type 0 and 1.

The exact probabilities are listed in the report, and we can discuss those if there are questions. For those that are identified as either type 0 or type 1, the 3 outcomes that we're modeling are: alive and non-ventilator dependent at age -- age 1, ventilator dependent at age 1, or death.

This slide shows the schematic for the newborn screening submodel. So, again, starting on the left-hand side, in the blue box, that what was happening in this model is that we are sending a hypothetical cohort of 4 million newborns that are not at -- otherwise at high risk for SMA, that after screening, they can

either experience a positive screen or a negative screen. If it's a positive screen, there's some proportion that have confirmed SMA. Again, some will be confirmed as a negative repeat screen at that point.

And then, here, we get into the key parts of the model that will drive our health outcomes. So, moving into the gray boxes, that for those confirmed cases of SMA -- and keep in mind that, here, from the two pilot screening programs, New York and Taiwan, we have eight cases that have been identified. Of those, one has been identified as symptomatic, and seven of the eight were asymptomatic at the time of confirmation. Following across the top of the screen, that the assumption is that all of those symptomatic cases will receive treatment with nusinersen, and then, at that point, you see a Circle A, which reflects the group of outcomes that we have here in gray.

So, again, turning to the -- the other gray box, asymptomatic, for those newborns that are identified with SMA but asymptomatic at the

time of confirmation, that there will be some probability of how many copies of SMN2 they -- they each have. And so, each of the arrows represented in the model represents a probability that has been derived from a -- from all the evidence that has been available to the Condition Review Workgroup, including published evidence, unpublished evidence, the gray literature, as reviewed earlier by Dr. Kemper. We've also been very lucky to have been able to collaborate with Dr. Swoboda, who -- who -- Dr. Swoboda and her team have provided some additional information that contributed to defining the ranges for many of these probabilities.

So, again, each of these probabilities is identified both by a point estimate as well as by a range. And, again, what's important when we're interpreting the results from the modeling analysis is, really, to focus on the ranges, not necessarily the point estimates, especially given the strength of the evidence behind some of these probabilities.

So, once a -- in the model, as a newborn is identified with SMA, is asymptomatic, and has a -- identified with however number of copies they have, we then make an assumption as to whether or not they will receive treatment with nusinersen or not. And there are -- there are some -- Like, there is not yet a consensus about which copy -- number of copies will receive treatment at -- once you get to 4 and 5, but our assumption for the base case for the modeling analysis is that all cases with 2 copies of SMN2, with 3 copies of SMN2, and in our base case, we assume that 4 copies of SMN2 will also be treated with nusinersen, although, as you can see from the model here, that after each of those branches that we can vary that within the model, whether they received -- some proportion receives treatment, some receives watchful waiting until they actually exhibit signs or symptoms.

We've only varied that now for 4 copies of SMN2, and we've actually varied that all the way from zero to 1, because that's where there is

the most discussion from the technical expert panel about consensus guidelines for treatment.

For 5 copies of SMN2, the base case assumes that it will be watchful waiting for that set of infants. The -- the probability of -- or the proportion of infants that falls into that category is extremely small based on the available data that we have, so that doesn't really impact the results in any large way.

So, another comment in terms of the way that the modeling analysis works is that once we have, you know, collected the proportion of infants into different copy numbers, we then have to make an estimate of whether or not these are likely to be type 1 SMA or not. And we've done that for every single category of SMN2 copy number based on available data from -- from a -- an in-press paper from Caggana and colleagues, as well as from Dr. Swoboda's data.

And we've adjusted -- we've had to adjust those data slightly to account for the incidence of birth prevalence as observed from other

studies, as observed in these studies, because there's a slightly lower report of type 1 SMA in the studies that we have available to us that have reported on both subtype and copy number.

Just a couple of comments here. So, again, we've worked closely with the technical expert panel and greatly appreciate their input in building this model, along with our liaisons to the advisory committee, and especially to Dr. Swoboda and her team for providing unpublished data for contributing to these ranges.

So, just to review a few of the key modeling assumptions, that the screening projections are based on the data from the New York pilot program. Other model inputs, again, are derived from the evidence that was just reviewed, from expert panel assumptions, and from the Taiwan pilot program data. The potential benefits of earlier treatment that are modeled are improved survival and improved respiratory function. We've not modeled improved motor function.

In terms of our estimates of treatment effectiveness, it's important to note that there are no trials that have looked specifically at treatment for a newborn screened population compared to unscreened and treated. So, what we have used here in the analysis to proxy for this potential effectiveness of treatment is looking at, within the Phase 3 clinical trial, the early- versus late-treated infants.

So, again, this was a trial of infants that were identified before 6 months of age. They have published, in poster format, a post hoc analysis of effectiveness for early treated -- less than 12 weeks -- compared with late-treated -- 12 weeks or greater. And that's what we viewed as -- as the estimate for effectiveness for symptomatic infants in the model. For asymptomatic infants, we've used the data from the single-arm trial, so the 9 out of 9 that are all doing well and are not -- are all alive and not ventilator dependent at 1 year of age.

So, this slide shows the modeling results

for a birth cohort -- a 4 million annual U.S. birth cohort, and starting from the bottom, from the very last line in the table of total SMA. So, this slide shows that under both clinical identification and newborn screening, we're anticipating that there would be the same incidence of SMA, 364 cases, with a range of 152 to as high as 764 each year.

The lower bound represents -- so, this is based, again, on range-of-birth prevalence that has been observed in the published literature, and also from the pilot programs. So, the lower rate, 152, reflects the observed incidence so far from the Taiwan pilot program, approximately 1 in 17,000, and the 764 represents a slightly higher birth prevalence of about 1 in 5,500 from the published literature.

And then, looking at the results by type -- So, of these 364 total cases of SMA identified through newborn screening, the projections are that there would be 196 cases of SMA type 1, with a range of 82 to 413, and the assumption is that

this will be the same under both clinical identification or newborn screening. But what will be different is the timing of identification.

So, looking at the next row -- So, 196 were symptomatic. Again, under clinical identification, our assumption here is that these cases are only coming to -- to light if they have had signs or symptoms. And so, the time frame, when we're looking at these two columns, is completely different. So, for clinical identification, these are symptomatic cases of type 1 that are identified at any age, whereas at newborn screening, the 45 cases symptomatic compared to 151 asymptomatic. We're -- this is at the time point of 11 days of life, which is the longest time to which it took to confirm the cases within the pilot newborn screening programs.

So, just running through the details on the newborn screening side of the table -- So, 45 would be expected, each year, to be asymptomatic.

Again, there's a very broad range here, because we have such small numbers and a very large confidence interval that we're using around that probability of symptomatic given -- given confirmed SMA. For asymptomatic, again, it ranged. The point estimate is 151, with a range of 133 to 363. For SMA type 2 -- again, we're assuming similar numbers across clinical identification, newborn screening would be identified, but of course, the timing of that identification would be different.

DR. LISA A. PROSSER: Yeah, mm-hmm, go ahead.

DR. JEFFREY P. BROSCO: Just to clarify, the --

DR. LISA A. PROSSER: Yeah.

DR. JEFFREY P. BROSCO: -- SMA type 2, is that type 2 and type 3 and type 4, or --

DR. LISA A. PROSSER: Yes --

DR. JEFFREY P. BROSCO: -- just type 2?

DR. LISA A. PROSSER: -- exactly. It's type 2 plus -- Yep, type 2 through 4. Thank you.

Any other clarifying questions at this point?

DR. LISA A. PROSSER: Okay, great. Okay. So, now, this results table focuses only on type 1 SMA, so, again, this is a break-down of, on this previous slide -- Okay, that's not helpful. So, of the -- of the ones that are -- that are identified as either symptomatic or asymptomatic, this is a breakdown.

So, under clinical identification -- and now, we are looking at 1 year of age. So, again, we can look to these to be equivalent for clinical identification, newborn screening. Again, we're focusing on type 1 SMA, assuming that all of those cases, even under clinical identification, would have come to light, would have been treated with nusinersen in the absence of screening, so that there would be 52 cases that would be ventilator dependent at age 1 of life, 36 deaths, compared with newborn screening, 4 cases expected to be ventilator dependent, with 48 averted cases under newborn screening, 33

averted deaths under newborn screening compared with clinical identification.

But, again, important to look at the ranges around those, that the ranges for cases or deaths averted go from 16 to 100 for ventilator-dependent cases, and for deaths, from 14 averted to 68. And, again, this is per year, per each year of screening. And again, to highlight here that this combines the results both for symptomatic and asymptomatic, assuming that they are both receiving treatment.

So, the overall summary for projected population-level outcomes is that 364 cases, with a range of 152 to 764, would be -- of confirmed SMA would be identified annually, that of those, 196, approximately, would be type 1 SMA cases, again with a range of 80 up to, potentially, 400. Of that, there are estimated reductions in deaths and cases of ventilator dependence for newborn screening compared with clinical identification, and this is specifically for type 1 SMA and assuming that both arms are treated with

nusinersen.

Additional benefits will likely accrue to the other subtypes, but that's not been included in the modeling, and it will be an interplay between what the treatment effectiveness is for those other subtypes compared with the timing of identification and initiation of treatment.

And important to highlight that the areas of key uncertainty for the model that would impact those results and where -- whether we're falling to the lower end of the range, 80, or upper end of the range, 400, is around how -- what proportion of cases are likely to be asymptomatic or symptomatic at the time of confirmed diagnosis, as well as the conditional probabilities of type -- of subtype given SMN2 copy number, that that's where we have some data, but we really don't know what that's going to look like until we have more data from newborn screening.

So, that's where I'll pause and open up for any clarifying questions. Anything --

additional questions, discussion, we'll hold 'til after lunch.

DR. JOSEPH A. BOCCHINI, JR.: Thank you, Lisa. So, let's limit this to any clarifying questions for either Dr. Prosser or Dr. Kemper.

Scott?

DR. SCOTT M. SHONE: Yeah, Scott Shone. I just have a quick question about prior model assumptions and how they lead into this one. So, I -- I guess my -- my question's around incidence, and so for here, the assumption was --

DR. LISA A. PROSSER: Yeah.

DR. SCOTT M. SHONE: -- that incidence was assumed to be consistent with estimates of prior, and then, if you look back at, like, the ALD model, it was almost two-thirds as much, and then MPS I was about equal, as well.

So, I just wanted to understand, sort of, you know, now that -- For those other disorders, have you gone back and looked to see how -- how -- how realistic were those estimates? And so, how does that feed into what we're seeing here in

terms of anticipating numbers?

DR. LISA A. PROSSER: So -- Yeah. So, that's a great question, and we haven't done that, and that's certainly something that we could do and would be interesting to look at. But -- but let me clarify why those -- some of those estimates differ, that, actually, we did have data from pilot programs, say, for example, for Pompe, where the incidence under screening was actually much higher than had been observed under clinical identification, and so that, we incorporate into the model.

That, we haven't seen, so far, with the pilot program. So far, it looks to be well within the confidence intervals of what's been observed through clinical identification.

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

DR. DIETRICH MATERN: Well, it's basically a comment that I would have made to -- or wanted to made, is that newborn screening has shown us, in the past, that we are usually wrong to assume the incidence based on classic cases

and that the milder or later-onset cases are usually underestimated until you screen the population.

DR. LISA A. PROSSER: Mm-hmm. Well, so say that that's a -- a very good point, and so from that perspective, this analysis would be consistent with a conservative approach that models only benefits that would be accrued if the incidence were the same.

So, what we've not included here are that if it turned out that there was a higher incidence and there was, kind of, this longer tail of much lower-severity cases of SMA, those are not included in our model. So, they're not being -- you know, this is not a cost-effectiveness model, so, you know, there would be questions there that were -- there are not costs that were be accounted for.

I think the -- the question there would be, you know, if there is this longer tail, if they have low SMN2 copy numbers and are receiving treatment, we have not modeled any potential

harms to those potential cases. That's a good point.

DR. SCOTT M. SHONE: So -- Scott Shone again.

DR. LISA A. PROSSER: Yeah.

DR. SCOTT M. SHONE: So, I -- I -- I, sort of, wanted to go with what you just said, is that not only are the incidence of SMA 1 is going to be higher, but the other subtypes could potentially be.

DR. LISA A. PROSSER: Right.

DR. SCOTT M. SHONE: And so, I -- I guess I want to -- the -- the second blue bullet of, Additional benefits will likely accrue to other subtypes, I'm not, necessarily, certain that that's -- that either Alex or -- or the model, necessarily, have shown that, and I wonder -- That's, actually, in my opinion, an unknown. It -- it, sort of, is an uncertainty of long-term outcomes for SMA 1 plus all of the other subtypes. I mean, do you not -- do you agree with that?

DR. LISA A. PROSSER: So -- So -- Yes, but, I mean, there -- there are some data from the -- the trial in -- in later-onset SMA patients that shows improvements. And so, we're probably not looking at deaths or, necessarily, ventilator-dependent cases but motor function improvement, so.

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

DR. CAROL GREENE: Coming back to the -- the history that we find, more, with screening -- I think that's also very disease dependent, and it makes sense that we're going to find more of the milder cases that, you know, may be just somebody who thought they were clumsy and weak and never came in.

And we could get a comment from Dr. Swoboda or someone, but I think SMA 1 -- I mean, you can underestimate methylmalonic because the child died and was thought to be sepsis and nobody understands it better, but SMA, the infantile form, is pretty -- it's slow enough, it's dramatic enough, the neurologists always

walk in the room and say, Ah, that's what it is; I don't even need the nerve conduction.

So, I wouldn't be surprised if SMA 1, the infantile form, what's found on the screen really matches and -- but -- for the later. So, I think it's going to be very disease dependent.

That -- that was a "yes" behind me from the neurologist.

DR. JOSEPH A. BOCCHINI, JR.: All right. If there are no questions or comments at this point, we're going to reconvene promptly at 1:00 to continue the presentation on public health impact. So, enjoy your lunch. We'll see you shortly.

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

DR. JOSEPH A. BOCCHINI, JR.: All right, let's go ahead and take your seats. We'll get this session started.

So, we'll start this session with a attendance roll call.

So, Kamila Mistry?

DR. KAMILA B. MISTRY: Here.

DR. JOSEPH A. BOCCHINI, JR.: Mei Baker? I think she is recused for this session. Susan Berry?

DR. SUSAN A. BERRY: Present.

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

DR. JEFFREY P. BROSCO: Here.

DR. JOSEPH A. BOCCHINI, JR.: Carla is also recused. Kellie Kelm?

DR. KELLIE B. KELM: Here.

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

MS. JOAN SCOTT: Here.

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

DR. DIETRICH MATERN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Cindy Powell?

DR. CYNTHIA M. POWELL: Here.

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

DR. MELISSA PARISI: Here.

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

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Scott Shone?

DR. SCOTT M. SHONE: Here.

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

DR. BETH TARINI: Here.

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

MS. CATHERINE A. L. WICKLUND: Here.

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

DR. CATHARINE RILEY: Here.

DR. JOSEPH A. BOCCHINI, JR.: The organizational representatives -- Robert Ostrander?

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH A. BOCCHINI, JR.: Debra Freedenberg?

DR. DEBRA FREEDENBERG: Here.

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

DR. MICHAEL S. WATSON: Here.

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

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

DR. KATE TULLIS: Here.

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

DR. SUSAN M. TANKSLEY: I'm here.

DR. JOSEPH A. BOCCHINI, JR.: Chris Kus?

DR. CHRISTOPHER KUS: Here.

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

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

MS. NATASHA F. BONHOMME: Here.

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

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

MS. CATE WALSH VOCKLEY: Here.

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

DR. CAROL GREENE: Here. Here.

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

So, the next presenter for the evidence review is Jelili Ojodu. Mr. Ojodu is the Director of Newborn Screening and Genetics program at the Association of Public Health Laboratories, Project Director of Newborn Screening Technical Assistance Evaluation Programs, the NewSTEPs program, and he is responsible for providing guidance and direction for newborn screening, genetics, and the public health program at APHL. He is also a member of the Evidence Review Group.

So, Jelili, I'll turn it over to you.

MR. JELILI OJODU: Thank you, Dr. Bocchini. Good afternoon, everyone. Alex, earlier, presented on the evidence for SMA, and Lisa did something similar for the modeling. I'll be presenting on the public system impact for the addition of SMA here. And if you do have any

clarifying questions, feel free to let me know, but I'd like to hold questions until the end as Alex noted earlier.

So, obviously, I'm going to give an overview of the background of how we came to this -- this is not the first time that we are doing a public system -- a public health system impact for a condition -- the role of the association, methods that we took, the results, obviously, of the survey of states' newborn screening programs, and a summary.

So, earlier, I think, this morning, Dr. Bocchini talked a little bit about how we come to either recommending a new condition to the Recommended Uniform Screening Panel. And, obviously, there is the net benefit, which was part of the matrix that was developed by this group, as well as the feasibility and readiness of implementing comprehensive newborn screening systems. So, this is an important aspect of what you all are going to consider as you move forward, and you have, pretty much, all of the

summary of our survey in your packet, but over the next 20-, 25 minutes, I'll be talking about the -- the feasibility and readiness of implementing this particular condition here.

So, we've defined readiness as stated on the slide above here, you know, "ready" being what most state newborn screening can implement within a year, developmental readiness within 1- to 3 years, and then unprepared after -- it would take longer than 3 years to implement.

So, components of feasibility, again, as we defined, are these four bullets here: obviously, making sure that there is an established population screening test that is available, a clear approach to diagnostic confirmation, an acceptable treatment plan, as well as some form of established approach to long-term follow-up.

Why is this important? Well, I think if it wasn't, we -- I wouldn't be standing here in the first place. Certainly, adding the feasibility and readiness of the impact to

newborn screening programs was deemed important by, you know, the Secretary of HHS. Then, that was added to a number of things that we do now, but it's to better understand, at least from the states that do newborn screening programs or do newborn screening for the population, the real-world barriers and to better understand those facilitators, you know, those enablers or enabling factors, to be able to bring on a new condition, and then understand, at different levels, what the opportunity cost is for adding a new condition.

We are talking SMA, so, obviously, we developed a fact sheet -- developed a fact sheet, and I should certainly -- there will be a -- a number of people to thank here. But as you heard from the presentations earlier this morning, there was, for the most part, only one state that has been doing population -- I'm sorry, that has been doing pilot screening for SMA, and we rely heavily on them to be able to better understand how -- how it works, at least in their pilot. And

so, many thanks to the folks at the New York State Department of Health, Wadsworth Center.

We developed the fact sheet in collaboration with all the folks on the Evidence Review panel, but most especially with the experience of the folks in New York. That fact sheet was -- enabled folks, especially, in states in where -- you know, most states are not actually doing population screening for SMA -- to better understand the -- the -- the basics of the screening algorithm, treatment, and just how it would work in a newborn screening system.

And then, we, as we normally would do, do a webinar, a webinar to pretty much anyone but most especially to the states in question to be able to describe the process of the survey.

We surveyed 53 newborn screening programs, so that's 50 states plus District of Columbia, as well as Guam and Puerto Rico, and then we did implement interviews, which are a little bit in-depth, phone, normally 60 minutes to -- 60- to 90-minute interviews with states,

normally states that are either trying to bring on this new condition or states that are already screening, whether it's pilot or population screening for the condition. And in this case, we did 5 state in-depth implement interviews to better understand how they are -- you know, the facilitators and some of those challenges in bringing on a condition.

And then, we also did an additional interview with a state that is not currently screening for severe combined immunodeficiency, and I'll talk a little bit about that in a minute.

So, these are the states that currently have some kind of mandate, whether it's a mandate to screen on a population base, a mandate to do pilot, a mandate to actually do a -- you know, some form of screening for SMA right now. And there have been some changes since we -- we collected or did our survey of the states.

I should highlight that in -- in a minute, but, you know, obviously, there is New

York that's been screening since January of 2016, and as of, if I'm not mistaken, January 27th or 29th, whichever is the Monday, there were 2 states that started population screening for SMA, 1 being the state of Massachusetts, and it's a pilot, but it's for the entire population, as well as the state of Utah. We did not do in-depth interviews, obviously, because it was several days ago, but their information was included as part of the larger survey that I'm going to talk about. And there are a number of states that are, as you can imagine, looking to address and -- and figure out activities that's going to then enable them to bring on population screening for -- or pilot for SMA.

One -- some correction here: So, Wisconsin is noted at the bottom there. Their anticipated target date to start screening on a population basis is July. They are currently using some funds, some grant funds, to be able to move forward with that. They are not using the CDC methodology, and they will not be detecting

any carriers as part of their algorithm to screen, so. That's just a point of clarification that is a little bit of a change on there.

All right. So, survey of states -- We encourage state newborn screening programs to be able to share this with their newborn screening systems, so not just the laboratorians, not just the folks in follow-up or long term, but pretty much anyone in the newborn screening systems. And so, these are from the five plus one states that -- that I pretty much showed on the slide before this that have some kind of activity related to -- excuse me -- screening for SMA.

We wanted to get a sense of what their challenges were, and these are some of the things that they highlighted to us. And some of this is not going to be new to you all, but it's important that we note it, obviously, that -- that it's important to get legislative buy-in and approval for funds, and I'll talk a little bit about this later.

Develop a reporting algorithm -- I think

that, as we collected in our survey, there are states that are trying to determine if they're going to be reporting or actually getting, as part of their newborn screening program, carriers.

Resources in the form of a number of things, but certainly, if you're going to do that, you know, report carriers, the need for resources to bring on genetic counselors are very important.

The establishment of relationships with a new group, obviously, in this case pediatric -- pediatric neurologists, in that you have to foster, one way or another, these kinds of relationships before you actually start newborn screening in your state.

And ensuring the access to evaluation and treatment was key challenges for those states that are either doing pilots or some kind of mandate for SMA right now.

So, enabling factors or facilitators -- You know, I think you've heard a -- a good bit

that, you know, SCID was added in -- add -- SCID was added to the Recommended Uniform Screening Panel in 2010, and over the years, we have been able to -- "we" as a collective, I'm talking about state newborn screening programs -- have been able to expand on molecular capacities and infrastructure and expertise. And so, I -- I think, certainly, this has an enabling factor of building on that particular condition being already on a number of states' newborn screening panel.

Then, obviously, the ability to be able to multiplex with another condition was a key aiding factor in implementation of this particular condition to state newborn screening programs, at least those states.

The cost, also, was -- we -- we tried to -- and I think Alex alluded to this a little bit, that due to a number of factors, we were not able to delve down into the -- the costs, but we -- cost of either adding a condition -- this particular condition, but we were able to gather

initial laboratory costs for some of those states that are thinking about or currently doing pilots here. And at least from what we collected thus far, you know, they ranged between what's noted on the slide here, so a dollar or less, and -- and that's, at least, when you're thinking about multiplexing, you know, with SCID.

So, in the state that, in fact, was noting that there was a higher cost, closer to the dollar, you know, they are thinking about the second-tier testing for -- for SMA using digital PCR, and -- to be able to assess the SMN2 copy number. And we estimated, at least from their perspective, the cost of the start-up instrument to be, you know, between 100- and 150,000, and that cost for the second tier, per baby -- or per specimen, sorry, will be about $50. That's one state.

So, there was additional marginal cost, obviously, for the states as they are thinking about either multiplexing or not. There is at least one of those states that are currently

doing population screening that is not multiplexing, because they are required to actually be able to separate out, as a pilot, the screening for this particular condition.

But as it relates to the marginal costs included in reagents and primers and probes for laboratory staff, it could range between the person that's already doing the test for the molecular activities to a full-time employee that will be needed to add on this particular condition in their state.

And then, follow-up, as well, really does depend on the population and -- well, the number of babies born, but it ranged from zero, at least from the states that we collected, to .3 FTA initially.

As you can imagine, the information that we have is certainly from -- obviously from one -- the only state that's doing pilot screening, and, you know, it's very difficult to be able to estimate the labor cost in moving forward unless, you know, this is being done on a population

basis. And so, I'm sure a number of these answers will be -- questions will be answered in the coming months and years.

Response rate -- I noted 53 newborn screening programs, of which we got a response rate of 87%. Twenty-seven was from state newborn screening programs that have a laboratory that actually does the newborn screening for their state or other states, and then fourteen of those responses came from programs that have outsourced their newborn screening laboratory tests to another state or a commercial entity. And I talked a little bit about the five plus one earlier.

We excluded the five states that we did in-depth interviews for from the survey. We included the state that was not screening for severe combined immunodeficiency as part of the survey responses. So, that's what I'm going to talk about next.

So, a question was -- well, actually, I need to read the question. It's -- Let me make

sure that that's the right thing there. Ah, okay. So, the question here that was asked was, once you've received the authorization to screen -- and that's important. The authorization to screen is necessary before any state actually starts to figure out all of the necessary, additional, kind of, variables that are needed to be able to move forward. Every state has to get that authority, one way or another, first, so. And I can -- I'll go into that in a little bit here, but --

Once you have received the authority or authorization to screen, how long will it take for you to -- how -- sorry, that's the next question. I knew I was going to get that -- Correct question: If SMA was added to the Recommended Uniform Screening Panel tomorrow, how long will it take for you to get authorization to screen for SMA in your state? That's the question that was asked here.

N is 41, and about 20% of them said less than a year. The majority of states said between 1- to 3 years, and then about 10% said a little

bit more than 10 -- 3 years, and then 2 states said never.

And -- and "never" -- you know, this is something that we probably need to go back to, but I think "never," in this sense -- "never," I think it means maybe they don't need the authority or authorization to screen; they can actually just bring on the condition in their state without any kind of legislative mandate. That is important to point that out.

All right. Question: Once you have received the authority to screen, how long will it take for you to -- how long will it take for you to have funds to be allocated for SMA? Authority to screen first, then figure out funds, and as you know, in state newborn screening programs, it's an integrative process of either going back to your state legislators to be able to get the appropriate funds to be able to bring on this test, depending upon what the needs are -- And it's not just the test, obviously; it's, you know, training, education, follow-up,

establishment of relationships with the specialists, all of the good stuff that is part of our newborn screening system.

About a fifth of them said a year, 67%, or two-thirds, of them said 1- to 3 years, more -- 5% said 3 years or more, and then, you know, about 8% of the states -- 3 states -- said that their -- excuse me, that their decision is independent of the inclusion of the condition on RUSP. Excuse me.

All right. So, moving along, a question here that was asked was, Please select the top three challenges related to SMA implementation in your state. A good amount of states, at least a quarter of them, talked a little bit about ensuring that there was a sustainable support for treatment of SMA, ensuring that there is the availability of specialists -- not only are they available, but they're ready to take on the -- you know, the -- the patient load that will be coming in as a result of population screening. And then the availability of a validated test

came in right afterwards. I think the rest is pretty clear, and these numbers don't add up to a hundred because we just rounded up some of those percentages there.

So, let's see here, a question that was asked here is, Which describes the type of screening approach your program would choose once you, obviously, have the authority to screen, have funds to screen, and then bring it up as a mandate to screen? And this, we excluded, you know, states that are doing contract or -- or regional, kind of, testing.

For the most part, as you can imagine, most states haven't actually determined an approach yet on how they're going to screen or what kind of algorithm they're going to screen, and this is, obviously, in relation to if they're going to bring on or screen -- be able to detect carriers.

Five states, or nineteen percent, said that, in fact -- let me make sure I get that right -- they will not detect carriers as part of

their algorithm. And then, 3 states, or 11% of the states, said that, in fact, they're going to -- they're planning to bring -- their approach would detect carriers, and they'd have to plan accordingly for follow-up related to that.

So, then, we go into these more in-depth implementation activities. Again, this is -- is part of your packet. We wanted to get a sense of how -- you know, if -- what are the enablers here, and what are the things that states will not be able to get within a year, or -- or how long it will take to be able to bring on implementation resources. And so, I'm just going to highlight a few here.

Obviously, having the technical expertise is an enabling factor, and states said they have at least -- maybe 60% of the states say they have that.

Another enabling factor is the -- the -- the -- the quality and type of laboratory equipment related to screening for SMA. Obviously, you know, the states have been able to

implement molecular technologies and are very well adapted to making sure that that works on a population basis.

I'll go all the way down and point to some things -- or, obviously, some comments that states noted that they cannot get within a year if this condition is being brought up. And for anyone who is interested, the question was, Please indicate your newborn screening readiness to implement screening for SMA by evaluating the following resources. That's how we posed the question to them.

A good number of states, seems like about 75% of them -- 77 here -- said that, you know, figuring out some kind of second tier for -- approach for SMA to assess SMN2 copy number is very important, and they -- they don't think that they will be able to get it within a year -- you know, LIMS capacity, as well.

So, obviously, when a state is trying to bring on a new condition, they have to either figure how their LIMS is going to be able to

report it out, and that at least in 50% of the states that responded here noted that it will take longer than a year to do that. These are certainly factors and variables that are important to consider, at least from their perspective, in moving forward.

And I'll just note here, treatment centers for expected SMA case load here is close -- just about -- let's see, 44% of the states said that they don't think that they can get that within a year.

So, more colorful question, commentary in reference to implementation factors -- We broke it down into major facilitator, minor, no impact, minor barrier, or major barrier.

So, facilitator, barrier. I'll highlight a major barrier here is -- from the state newborn screening program perspective is the cost of treatment for -- for newborns diagnosed with SMA. This is very important. It looks like about 70% of those states thought that that was a major-to-minor barrier that needs to be considered before

they actually consider bringing on this particular condition as part of their own state panel.

There are a number of priorities, not just in -- at a state public health level but state public health laboratory and then drill down into a state newborn screening program, and those ongoing activities also can be a major barrier in being able to implement new conditions, at least in this case.

Let's see here, I wanted to highlight the extent, so facilitators, obviously. I want to highlight the extent to which newborn screening tests can be multiplexed with another condition. In this case, SMA with SCID was a major facilitator from states. In fact, the majority of states thought that that is something that will help move things forward.

And -- Yeah, well, the other non-newborn screening public health priorities, I think, we can spend a good amount of time on that, so I wouldn't, at this point.

So, we wanted to get a sense, at least from states that outsource their newborn screening, about the -- you know, how this -- how they would be able to either bring on a new condition -- in this case, SMA -- and what are those variables. In fact, there's -- that are either facilitators or barriers and how long it will take, because you're outsourcing; you have to be able to go through all of the processes that I described and then work with the lab that you outsource to, to be able to bring on a new condition.

And so, I just wanted to highlight here, obviously, the -- the state that you're outsourcing to has to have the equipment and be -- be able to screen for SMA in order for them to be able to do it or to bring on SMA in their own state. So, obtaining and procuring an instrument for SMA was something that, at least to those states that outsource, said that it would take a year to 3 years to be able to implement.

Development of follow-up protocols also

was in that range, and consulting with medical staff and specialists in adding this new condition. And I think the -- the same kind of activities, at least on some level, can be -- it -- it would be somewhat similar in states that actually do their newborn screening.

Enabling factors are things that -- that states thought that it -- it would help in moving things along are, let's see, if a -- if the outsourcing state had the existing, you know, testing capabilities to be able to screen for the condition. And the ability to multiplex is also a key factor here.

So, in reference to barriers, for the states that we surveyed -- and as noted here, this was an open-ended, multiple-choice -- we -- we had this in a number of ways -- multiple choice and open ended -- to be able to get different responses back. Question as posed to states was, What is the most significant barrier to implementing screening for SMA in your program?

A good amount of them noted -- let's see, 10 said lack of funding. Treatment cost and equity, also, is a key factor here. Competing disorders and interests, whether it's timeliness, -- you name it all -- were also competing priorities here, at least from the states' perspective, and I talked a little bit about the LIMS. Think I just need to highlight anything else here --

Facilitators -- Again, from previous responses, we -- the ability to multiplex -- A good number of states thought that this was very significant in -- as a facilitator to bring on SMA in their state.

A good number of states -- let me see what the N is here; oh, I don't have that -- did not respond to this question, but as you can see here, a few states -- five -- noted that addition of the -- of SMA to the RUSP is going to be a significant factor as they move forward in the implementation of SCID in their newborn screening panels. And I know that there are a few states

that have the addition of a new condition by this -- by HHS as part of their mandate to move forward, pending funds, pending a number of other things that they need to get in place to move forward.

Existing expertise and infrastructure and the -- the -- the -- the amount of outside partners that can influence, one way or another, the state's ability to be able to bring in the resources that it needed to be able to add on a new condition in advocacy is also very important as significant factors.

So, some of the strengths -- Obviously, we got a good number of states to respond to this. We strive and make sure that they know the importance of why this is key in not only getting a sense of the real world facilitators and barriers but also the -- one way or another -- the information that is provided and put out by this committee affects state newborn screening programs one way or another, you know, in -- in -- in moving forward. And so, we strongly

encouraged them to participate, and we're proud to get that much states to be able to give us information.

Providing a webinar and the fact sheets to states to be able to understand a condition, at least at the basic and a -- a little-bit-more-than-basic level and understanding how the only newborn screening program that does pilot for this particular condition has been able to do it and provide that information, pretty much, to every state was key.

We -- we were able to survey and get a sense of perceptions about implementation based on experience of the only -- this condition, even though most states are not screening for it, but as it relates to other conditions, because we've been at this for a -- a -- a while now, and then get a sense of -- you know, assess real-world experiences from states.

Limitations, which are -- there are limitations. There -- the assumption that a condition has been added, that hypothetical

assumption that a -- a condition has -- or a state has the authority to approve -- has given the authority to approve and allocate funds is key here. And, you know, even in some cases where the funds may be appropriated, there may be a delayed process in actually implementing that condition.

There were a number of hypotheticals here, and, sometimes, the responses could be subjective, and the limited data on SMA in a true newborn screening setting -- You know, we are thankful for the work that is being done in New York, but it's only in three hospitals at this time, and I -- I think we're encouraged by the fact that there will be more data that will be provided by the folks in Massachusetts and Utah in moving forward.

All right, so some, just, overarching conclusions here from the survey, and it is that the majority of states thought that it would take at least between 1 and 3 years to implement screening for SCID after they have the authority

to screen and allocations to screen -- allocations of funds to be able to move forward with this.

I think, in moving forward, we've talked internally, as part of the Evidence Review Group here, to be able to break this down, so that as, you know, we collect information from 1 to 2 -- from less than 1 year, 1- to 2 years, and then 2 to 3, and then, maybe, a little bit after that to get a little bit more specific in this information. But as it relates to this survey, it was 1- to 3 years.

There's quite a bit of variation in state newborn screening programs -- and we talked about that a good bit this morning -- related to just a number of newborn screening system activities. And as you saw from my slides, the question of bringing on a new condition and what it takes in a state does differ from state to state.

And then, the administrative processes in bringing on a new condition -- You know, whether it's increasing the fee, which, in itself,

depends on a number of factors that is outside of the newborn screening program, can delay the process.

Conclusions related to feasibility -- That the -- you know, at least from the -- the preliminary information that we've gotten from the New -- New York program, that the test has shown to be reliable using real-time PCR and that there hasn't been any false positives thus far. The rate of missed cases is some -- anticipated, at least based on frequency, to be 5- to 7% and that we, at this time, will not know the true false negative rate until true population screening does occur in multiple states.

Carla -- or Dr. Cuthbert had talked a little bit about the continuous -- or newborn screening quality assurance program, and we -- in the survey, we know that they are providing quality control materials to states. However, if a large number of states start to implement, you know, that supply of samples may be very limited. And so, you know, it's something to -- that I

know our friends at CDC are aware of and are working to be able to address that.

Conclusions related to feasibility -- We talked a little bit about the diagnostic confirmation, or at least as it relates to -- from the survey, the diagnostic confirmation of SMN1 gene.

The fact that there is an approved FDA treatment is something that, I think, a number of states had noted, but the lack of understanding of long-term outcomes and the cost as it relates to treatment -- You know, we didn't get into any of the costs related to that, but in written comments, we -- a number of states were able to tell us that this is a major concern that they were -- You know, even though some -- Someone has to pay for the screening -- thank you -- of -- someone has to pay for the treatment here, and that was something that they wanted to at least put to our attention.

And then, long-term follow-up is somewhat unclear here.

I have a minute left, and I'm going to be able to cram everything else in the last minute. So, I noted that there are two states that are bringing on population screening for SMA as we move forward. It's -- the -- screening for carriers is something that I -- and what to do with late-onset cases and cost of treatment are going to be -- are -- were common challenges that were reported as part of the survey. And figuring out those screening algorithms and what to do if they screen for carriers is going to be key, as well.

Administrative barriers -- I don't need to add anything more to that, and -- Yeah, I don't think I need to add anything more there.

Strong collaboration -- Obviously, our states work very well together in understanding and addressing common issues, and I think that will be very helpful in moving forward, at least for the states that are screening.

And so, it's very important to note that we won't be able to do or collect any of this

information without the help of state newborn screening programs, and I would especially like to thank them for all of their efforts in providing information to us. Also, as Alex said, you know, K.K. has been very instrumental in making sure that all of this comes together nicely. But from my perspective, you know, my right-hand person is Elizabeth Jones, who does great work in being able to reach out to states and collecting and assessing the information that I've been able to provide to you all, so to states and Elizabeth and -- thank you very much.

DR. JOSEPH A. BOCCHINI, JR.: Thank you, Jelili, very much for that presentation. I think you clearly outlined for us the -- within the limitations that you mentioned, the readiness and feasibility that states feel about this condition.

So, are there any clarifying questions related to this presentation or the prior ones on the evidence review? If not --

Oh, go ahead, Joan.

MS. JOAN SCOTT: I -- I should have asked this of Lisa this morning. It's a question about the modeling. Lisa -- is she here?

MALE SPEAKER: Yeah.

MS. JOAN SCOTT: I want to just make sure I'm understanding the information that's on page 46, when you've got this breakdown. I'm sorry, get -- get to the right page. I just want to make sure I'm understanding the information about what I'm looking at.

MS. JOAN SCOTT: Okay, Table 16 -- Sorry. This one

DR. LISA A. PROSSER: Ah, okay.

MS. JOAN SCOTT: Okay.

DR. LISA A. PROSSER: Yes.

MS. JOAN SCOTT: So, if you could just walk through some of these numbers. So, if an individual who is born through newborn screening, with the deletion, has 2 copies of the SMN2 gene, 91% of those are expected to have type 1?

DR. LISA A. PROSSER: That's right. So, these are all --

MS. JOAN SCOTT: Oh, here you are.

DR. LISA A. PROSSER: -- conditional probabilities. Yeah.

MS. JOAN SCOTT: Okay.

DR. LISA A. PROSSER: Right. So -- so, if you look at the numbers that are not indented -- So, for 2 copies of SMN2, asymptomatic, that's the conditional probability of having 2 copies or 3 copies or 4 copies or 5 copies given that a confirmed case of SMA is asymptomatic. So, .476 or about 48% will have 2 copies, about 47% 3 copies, and then very few would have 4 or 5 copies.

And then, as you had outlined before, that's correct, that the numbers below that are the conditional probability. So, given --

MS. JOAN SCOTT: Okay.

DR. LISA A. PROSSER: -- an asymptomatic case with 2 copies of SMN2, 91% are likely to be type 1 and 9% types 2 through 4, and those change for the other copy --

MS. JOAN SCOTT: Okay.

DR. LISA A. PROSSER: -- numbers.

MS. JOAN SCOTT: So, going all the way down to the bottom, if you have 5 copies --

DR. LISA A. PROSSER: Yeah.

MS. JOAN SCOTT: -- okay, you're not going to have type 1; there's zero probability.

DR. LISA A. PROSSER: So, that's in our base case, and then, in --

MS. JOAN SCOTT: Mm-hmm.

DR. LISA A. PROSSER: -- the next column over, there's a range. So, there is --

MS. JOAN SCOTT: Mm-hmm.

DR. LISA A. PROSSER: -- a range around that in --

MS. JOAN SCOTT: But it'll be --

DR. LISA A. PROSSER: -- the sensitivity analysis.

MS. JOAN SCOTT: -- 2 to 4 -- It could be two to four. Estimated --

DR. LISA A. PROSSER: That's right.

MS. JOAN SCOTT: -- type 2 to 4.

DR. LISA A. PROSSER: Yep, that's right.

MS. JOAN SCOTT: Okay.

DR. LISA A. PROSSER: Mm-hmm.

MS. JOAN SCOTT: Thank you.

DR. LISA A. PROSSER: But as you can see, the ranges for those are very wide. We don't --

MS. JOAN SCOTT: Right.

DR. LISA A. PROSSER: -- have good data on --

MS. JOAN SCOTT: Right.

DR. LISA A. PROSSER: -- what the subtype -- the conditional probability of subtype is likely to be.

MS. JOAN SCOTT: Okay. Thank you. I just wanted to make sure I was reading that --

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

DR. KELLIE B. KELM: Kellie Kelm. The one thing I didn't see noted here -- Do we know of any known harms or potential harms due to the treatment Spinraza?

DR. ALEX R. KEMPER: So, the harms that have been reported around the use of nusinersen

are primarily the harms associated with getting the lumbar puncture to deliver it intrathecally. There are really -- you know, that there -- there are -- there are not notable serious adverse effects associated with the drug outside of, you know, the kinds of things that you can get with getting repeated lumbar punctures, like, you know, headaches and so forth.

DR. KELLIE B. KELM: I noted that in some of their -- that the stuff available on the website for the drug noted increased levels of urine protein, and I didn't know whether or not, with time, that was an issue.

DR. ALEX R. KEMPER: Yeah. I mean, certainly, that wouldn't, you know, fall under what we would typically consider to be a -- you know, a serious adverse event. Now, what happens long term with therapy, you know, we can't comment, and there's -- You know, who knows, there could be, you know, other harms that we don't know that -- that time will tell.

DR. DEBRA FREEDENBERG: Jelili, for those

states that said they would not report carrier screening, was there any correlation with whether they were reporting carrier screening for other conditions, such as sickle trait, cystic fibrosis, and --

DR. ALEX R. KEMPER: Oh, and can --

DR. DEBRA FREEDENBERG: -- was that a philosophical objection, or was it specific to SMA carrier screening?

DR. ALEX R. KEMPER: So, one of the things that -- that I probably was unclear about, the issue of screening for SMA and -- and detection of carriers, is that the -- you know, one of the standard ways, like the -- the CDC method and, like, the method they're using in Massachusetts -- It's not like they're detecting carriers and choosing not to report them. The method simply doesn't identify carriers. All it does is identify individuals who have deletions of that exon 7 on both alleles.

So, it's not -- it's not, like, a purposeful decision not to report carriers; it's

just that the carriers don't come up in the method that they've chosen. So, they're not withholding information that they have.

Now, if your question is, you know, should they be screening for carriers and that kind of thing, I have another clarification that Dr. Caggana pointed out to me, that in the pilot study -- and I -- I didn't appreciate this nuance. In the pilot study in New York, where they're identifying carriers, part of that is because they wanted to do the sequencing to make sure that they weren't missing individuals who had the homozygous deletion of exon 7 in both alleles. It wasn't, necessarily, to find the compound heterozygotes that we spoke about before.

Now, what I can't comment on is what New York's plan is long term, but this was the way that the pilot study was set up, to identify the carriers and just making sure that they weren't missing cases.

DR. DEBRA FREEDENBERG: I was actually

referring to that hypothetical, where the states that were surveyed -- Was at 19% or 11% that said they would not report carriers?

DR. ALEX R. KEMPER: Yeah. Yeah, this -- the -- we haven't checked to see if there's correlation, but this was specifically on SMA, so. Yeah, we don't know.

DR. JOSEPH A. BOCCHINI, JR.: So, I have Scott and then Cathy. Sorry.

DR. SCOTT M. SHONE: So -- So, forgive me. This is my first evidence review on this side, not over there. It's a very different perspective, so I'm not sure if I should ask these questions now or wait 'til next. So, if you want me to wait -- I'm going to ask them --

DR. ALEX R. KEMPER: All right, you can--

DR. SCOTT M. SHONE: -- and then, if --

DR. ALEX R. KEMPER: I would say that if you ask me a really hard question, then I'm going to call on Dr. Lam.

DR. SCOTT M. SHONE: All right. I can start with you, Alex, because I had a question

for Jelili first, but -- No. So, Jelili, you know, I looked at the prior -- This form of public health system impact assessment really started with MPS I, right? So, MPS I, then X-ALD, and now this.

And so, I looked back, and -- and our colleagues in newborn screening -- it always ends up 1- to 3 years. I mean, that's always what it's been. I kind of felt, before -- before we even got the report, that's what the result was going to be, and I think there's a lot of factors around that.

But I think the reality is and I think everybody needs to realize that if you delve deep into your data, I -- I guess the question is, do you agree with -- There's 1- to 3 years for approval, 1- to 3 years for funding, 1- to 3 years to implement. So, it's -- we're really talking, potentially, 9 years, which is what we've seen with SCID, even though you didn't do a public health system impact assessment back then.

So -- so, the -- so, the -- the idea that

it's ready is -- is not --

DR. ALEX R. KEMPER: Okay, just jump in with one thing, too, before you respond?

UNIDENTIFIED SPEAKER: Sure.

DR. ALEX R. KEMPER: Because I just feel compelled to say this. So, remember, too -- Like, we would love to be able to do more granular questions, you know, speaking with, you know -- really, across all the newborn screening programs, but before Jelili answers -- because I -- I just -- I -- I feel very protective of Jelili, as well -- is that --

(Laughter)

DR. ALEX R. KEMPER: -- we have 9 months within which to do the evidence review and the -- and the public health system impact assessment because of the way the -- the authorizing legislation is, and we can't really even ask states that haven't thought about screening for a particular condition until we're able to inform them about what some of the issues are. And then, remember, too, that this survey is held to the

OMB rules, so we can't change up the kinds of questions that we ask each time, and we're limited in terms of the number of people that you would ask.

So, it's -- the -- the point that you're making in terms of, how do you really, really get to, what would it take for all the newborn screening programs to be able to do everything they need to do and get it up to line probably is not feasible within the 9 months. So, I just want to, just, help you understand in terms of what our limitations are in terms of the process, and now -- now I'll let Jelili back.

DR. SCOTT M. SHONE: Well, no -- Jelili -- before you go -- because you started to answer the question that I was going to ask you, Alex, so I'm going to put --

So, the -- the question I have for you is, you've done many of these evidence reviews, so can you compare the quality of data that you used as part of this evidence review? Because, you know, you've talked about, there was -- in --

in the -- in the book, there was weak, there was moderate, there was strong. So, overall, what you were able to accomplish in the time frame -- how does this rank, and, 2) if not for the 9 months, would you feel -- would you feel that this isn't really -- that -- that this 9 months is -- is tying our hands and making us make a decision before -- before, perhaps, the evidence review naturally would have gone if it hadn't been for this -- this legislative requirement?

DR. ALEX R. KEMPER: So, I -- Well, first of all, the 9-months thing is what the 9-month thing is, so we're -- we're -- we're -- we're -- we're held to that, and I don't --

DR. SCOTT M. SHONE: Right.

DR. ALEX R. KEMPER: -- want to, sort of, you know, step into something that's above my pay grade, so to speak, but --

And the other thing is that -- I -- and I think K.K. will agree with me that each time we do a condition, we always think, Well, that was kind of an outlier because -- You know, these --

these are all rare diseases where the evidence base is still emerging.

What I would say that separates this review from some of the other reviews is that the evidence base is really expanding very rapidly as we work on it, and in terms of the outcomes, we're most confident about the outcomes that happen about a year after treatment begins.

So, the data are still emerging. If we had more time -- You know, it would be nice to understand more about the unpublished data, but we tend not to, you know, want to base everything on unpublished data, that there's a lot of stuff that happens through the peer review process, where we learn a lot about the actual work that was done.

So, I would say that this is a case where the evidence base is expanding rapidly, that there's a lot more known, even within the past few months, than -- than -- than we would have guessed. So -- so --

DR. SCOTT M. SHONE: You know, I -- I

have a crystal ball --

DR. ALEX R. KEMPER: -- like -- so, getting back to --

DR. SCOTT M. SHONE: That emerging --

DR. ALEX R. KEMPER: -- like, being protective -- I hate to compare my babies, you know? So, each --

(Laughter)

DR. ALEX R. KEMPER: -- each of these conditions is also different, and so I'm reticent to -- to compare them in terms of the evidence base and that sort of thing, but what I would say is that the -- you know, that this is such a rapidly moving topic that most of the data are unpublished.

DR. SCOTT M. SHONE: And -- and so, it's equally as likely, as this data's emerging and as we're learning more, that -- that it could show even greater benefit than what is seen or perhaps not. We -- So, there's a huge unknown there. Is that -- Could you agree to that?

DR. ALEX R. KEMPER: Well, I mean -- So--

DR. SCOTT M. SHONE: I mean, it's like the graph you showed --

DR. ALEX R. KEMPER: I'm not -- All right -- I'm --

DR. SCOTT M. SHONE: -- the graph you spent time on --

DR. ALEX R. KEMPER: -- not -- All right. So -- I'm -- I'm --

DR. SCOTT M. SHONE: -- where there -- you have this cutoff, right, and --

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

DR. SCOTT M. SHONE: -- the x-axis is unknown. We --

DR. ALEX R. KEMPER: Right.

DR. SCOTT M. SHONE: What happens -- Does it go like this, does it go like this, or does it just plateau, right? I mean, that's where we --

DR. ALEX R. KEMPER: Yeah, so we can't comment on -- on anything beyond --

DR. SCOTT M. SHONE: Or we don't have it.

DR. ALEX R. KEMPER: -- where the evidence is.

(Laughter)

MR. JELILI OJODU: So, Scott, I -- your general thought I agree with, in that we heard, pretty much, after the survey that we sent out to states and knowing what would happen today in understanding, as you described sitting on the other side, the addition or -- of new conditions and -- but then the time that it takes to be able to do that. So, you have the 1- to 3 years, as you noted, the authority to screen, and then you have to find, you know, the other kinds of activities to do that.

And so, yeah. I would just add that if you add that up -- and as you said, 6- to 9 years depending upon what the situation is -- there is the other side, where states actually can do a number of things simultaneously. And so -- at least some states, where that process is a little bit shorter, or they're not actually dependent on -- on this. So -- but your point is well taken, and I completely agree with you.

DR. ALEX R. KEMPER: Only -- and I just I

had to -- I'm going to -- going to say this again. We're -- we're restricted to the information that we have, so it -- You know, what you said in terms of how long states, you know, would take to functionally do it may -- may or may not be true, but we can't comment on that. All we can comment on is what we have.

DR. SCOTT M. SHONE: And the same significant barrier that shows up in every one of these assessments is cost and funding, right? And so, perhaps, the committee should think about that going forward, is, how do we address this? You know, this is clearly an issue that's in every single assessment. States are just saying this.

I don't know what that solution is, but the fact is that -- Yeah, they can do things -- Programs can do things simultaneously, but it's -- We've talked time and time again about timeliness, about cutoffs, about Pompe, MPS I, X-ALD. There's, clearly, more to hear. I mean, I don't want -- This is about SMA, so -- But -- but

I think that there's some valuable lessons -- Even with the limited data, there's some valuable lessons here about the public health system.

DR. ALEX R. KEMPER: Come on up. I knew that it wouldn't take too long.

DR. K.K. LAM: Just, also, on that issue, it --

DR. ALEX R. KEMPER: What's your name?

DR. K.K. LAM: Oh, my name is K.K. Lam. I--

(Laughter)

DR. K.K. LAM: Oh, stop. Gosh, I can tiptoe just fine. What was I saying? Okay, so on our survey, we are looking at some of the response options to try and, you know, take it beyond 1- to 3 years. We're kind of at a point, actually, where we can make some slight revisions to the survey. Right? That was our first time around. We had to stick with it through OMB approvals, right, knowing that, okay, how can we get a little better data, so that's fair.

Those answers on the survey, remember,

are for states that are projecting, right, your -- its intentions. And, you know, nobody -- Really, the best predicter is actually, you know, past behavior, and you just can't really tell.

And on that, right, in this particular case, in addition to the very fast-moving literature and -- and research that's coming out, a number of states have been adding -- states have been adding to the list of those who are beginning or planning to or even starting to screen, right? A couple of states just started within the past couple of weeks.

So, on that note, you know, it's -- Right. So -- so, from the time that they had authority, it's probably been -- what we've seen in an actuality, probably within, like, the year, maybe just over a year, roughly, timeline, right? The same question that states are just quickly checking, oh, 1- to 3 years after we had authorization and funding, what we've seen, at least from the first few who are starting, has been, you know, within a year.

It seems to be a pretty simple -- when multiplexed with SCID, pretty simple to start up. It's a straightforward assay; there's not -- You know, that's been -- that was one of the things that the New York folks and others have emphasized. Very little, if any, extra labor cost or equipment cost. The main costs are, really, just in a -- in the consumables, the specific reagents, right? And so, even funding's not a huge, huge issue. I know, you're smiling -- But, you know, comparatively.

Like, we've seen states that -- The handful of states that are starting up, it's been very fast. It seems to have gone -- gone very fast for SMA compared to other -- you know, faster than other -- others -- other conditions that we've seen.

MS. CATHERINE A. L. WICKLUND: Yeah -- Okay. Cathy Wicklund, and I'm changing directions just a little bit. It's looking at the modeling and the outcomes that we're picking, and you guys might've talked about this in the presentation or

in the report that I did not pick up on. But I think it also getting at, again, like, what outcomes are we looking at? It's survival and ventilation requirements and not taking into account motor development.

DR. LISA A. PROSSER: That's right.

MS. CATHERINE A. L. WICKLUND: Right. And can you talk a little bit about the rationale behind that?

And then, also, I just think there's a bigger picture, again, of thinking about, what outcomes do we define as success.

DR. LISA A. PROSSER: So, the -- the restriction to those endpoints was primarily what were -- were the primary endpoints for the clinical trials, so that's what we were modeling on.

And at the beginning of the modeling, we had looked to see if we could incorporate motor function, but given where the evidence was from the trials and given that different -- different instruments were used in different trials, that

in order to be able to use the trial data, we would have had to create a crosswalk from those instruments to some type of intermediate or milestone of motor function, and it wasn't possible to do that, so.

Yeah, but I agree with you. Like, that's noted as a limitation, that that would have been the third endpoint that we would have included.

MS. CATHERINE A. L. WICKLUND: In the -- in your evidence review, you provided a table that -- and I think you showed it -- that had the distribution of SMN copy numbers in SMN -- SMA cases. Do we know what the distribution is in the general population?

DR. LISA A. PROSSER: There -- they've -- in that same study, they did some estimates of it. I don't know them offhand, because they weren't quite as relevant, but --

DR. ALEX R. KEMPER: Yeah, they looked at -- We actually didn't -- You know, because we were really interested in, just, what the SMN copy number was in cases because of the

predictive value. We didn't really pay attention to the SMN2 copy number in the general public.

That paper from, I think it was, like, 2002, looked at 375, or thereabouts, affected individuals. They looked at a smaller number of first-degree relatives. I think they were, like, siblings or parents or anything like that, and then there were some other, just, you know, controls that they picked, and I can't remember what the numbers were. But to us, as we were going through it, we were just focused on SMN2 as a predictor and so only looked within cases.

DR. K.K. LAM: I will add one note. There was, you know, some -- some thought that it's actually a little bit higher in -- in individuals affected with SMA because -- and we didn't go into all the -- this genetic stuff, but -- But there's a SMN1 to SMN2 conversion thing that goes on, right, because SMN2 -- SMN2 creates about 5- to 10% of this fully functional protein that is no longer available when SMN1 is deleted, when it's gone. Right?

So, there's -- in some cases, there's kind of a natural --

DR. K.K. LAM: -- conversion, and so -- right, where there's more SMN2. I -- I imagine the body's trying to naturally make up for it.

So, they're guessing that it's a little bit higher -- well, overall SMN2 copies are a little bit higher in the SMA population because of that genetic activity that goes on. Does that make sense?

MS. ANNAMARIE SAARINEN: Annamarie Saarinen. Thank you for your really, really good presentations today. That was a lot of material, and I -- I'd read through it ahead of time just so I could be, like, pre-prepared with questions, and then once you all stood up there and explained it, I'm like, Oh, they answered about everything. So, it wasn't until Scott started talking that I wasn't going to say anything, so.

DR. ALEX R. KEMPER: Oh, Scott.

MS. ANNAMARIE SAARINEN: But let's just -- For the record -- So, in terms of -- You know,

I'm -- I'm not sure, like, how much -- I mean, I get what you're saying about where are the endpoints and where -- you know, where do things drop off, because you have limited data sets on things that are emerging and -- and new that you don't have a lot of information on, but that has, I -- I think, been historically what this committee was sort of created for and what -- what we sort of do.

We're on the, sort of, front end of things for a reason, because if we waited another decade, then, you know -- More -- more -- more evidence doesn't necessarily ensure a better program or a better rollout just because you've waited 10 years to do something. And I think -- You know, there's -- there's a -- a little girl in this room that wouldn't be here if not for the evidence that you've presented, the data that's been provided based on the development of -- of drugs that are showing efficacy.

So, that's, I -- I hope, something we're always keeping in mind here. These babies are --

I mean, these children are -- You know, it's the real deal for them and their families, and we had a perfect example here of someone who -- whose son has a completely different outcome than her -- than her daughter is probably going to have, or already has had.

So, desired outcomes, I think, are a little bit -- you know, kind of subjective, right? If you're the parent, your -- what -- what -- what you want, desired outcome, might be, really, a lot different than what a researcher or a clinician might say they want in terms of a desired outcome. Just having your child on -- on the planet and being able to care for them is, maybe, your desired outcome.

I'd also say, you showed a list of states there that are piloting or are what I consider in go-mode for implementing. They've already done some cost analysis; they've looked at what they've got in their labs. So, I'd hate to think that a delay on -- on something like this, or any other condition that we felt had a pretty strong

evidence review, would penalize the -- the states that are ready to go and aren't going to take 9 years to put something into play.

And I know -- I mean, I can tell you, Idaho, last week, maybe 10 days ago, finally put forward their statute on CCHD screening. It's 2018. I mean -- So, we know. I mean, it happens. It can take a long time to implement something in a lot of places, but. I think this goes to the point of, a little -- what can the committee do to -- to try to smooth out some of those things.

And funding -- I -- I -- I wish I could say it was different, but it's -- having spent 20 years of my life in public policy, I -- I -- I can rarely say there's anything pre-funded except the work of committees like this, because they get, you know, large, multi-year packages to make sure that that happens. But when new things are added anywhere, whether it's in health or education, it's almost always that you've got to figure out how to fund it, and -- and I wish that weren't the reality of the world, but it -- it --

it truly is.

So, if there's ways that we can, you know, help states better prepare, help funding entities better prepare, for things we know are coming down the pike, great. But something like this, we don't know until we've looked at the evidence. So, I -- I think that is a little bit of, you know, if you build it, they will come, hopefully.

DR. JOSEPH A. BOCCHINI, JR.: So, Annamarie has really started us on the path of discussing the evidence and how we'll apply it to helping make the decision, so I'm going to -- I guess we've got two additional questions about the evidence itself.

DR. BETH TARINI: The --

DR. JOSEPH A. BOCCHINI, JR.: Scott and then Beth, did you both --

DR. BETH TARINI: Well, I -- to respond, quickly -- this is Beth Tarini, committee member -- that we're -- that you are correct, I think, Annamarie, that it's a subjective outcome, and

you will see this in Dieter and I's slides.

The question is, what's the definition of significant benefit. Are we keeping the children alive? Are we trying to get them to normal? Are we trying to improve them? And if we're trying to improve them, where do we get them to improve that we think that that's sufficient as a committee to justify screening on an -- mandated screening on a national level?

So, it is subjective. And it's not been, to our minds -- at least I think -- explicitly made clear where that bar is, or does it move.

The second is, I -- I would push back that -- We're not saying, I -- I don't think, but I don't want to speak for Scott -- I don't think we're saying 10 years. If this field is so fast-moving, then I would expect, in 6- to 12 months, given that these are already existing trials, we should have additional data points. So, the flip side of fast moving is, it will be fast in -- it -- it should be fast in giving us additional data.

And then the other piece I want to just highlight is that our job is -- is incremental benefit of newborn screening. That is where, I think, our focus is, that -- You know, what is the incremental benefit, and -- and that benefit is defined as to the child; it's defined as significant. That's where the -- that's where the subjective nature is. But the difference we would have is that we would catch the children at birth. And what is the incremental benefit of that compared to catching them clinically?

And that's where, I think, the focus of the discussion needs to be, on where is the evidence and what do we -- what do we see it telling us.

DR. SCOTT M. SHONE: Scott Shone. So, I -- I was ineloquent in the order in which my questions were posed, I suppose. I was trying to ask clarifying questions of the process, not necessarily the evidence, which I'll hold off on until Beth and -- and Dieter can present their data and have a discussion of the actual

evidence, which I have questions and concerns about.

But I will just say that I fundamentally disagree with the idea of adding a disorder to the RUSP so we can create a population of screen-positive children who can then be used to evaluate potential treatments. You know, the -- I think that the data has to precede that.

And I don't discount the benefit that we've seen and we see in families all the time. My first job is a parent, my second job is a husband, and, like, somewhere down the road is newborn screening person. And so, I -- So, I -- I -- I -- you know, I, every day, worry about my kids and my kids' friends and their health.

So, it's not, like -- I don't want to -- I don't want to seem heartless, but I think the process of the evidence is to rely on the data, and that's what I -- what I look forward to hearing now is, sort of, the evaluation of Dr. Matern and Dr. Tarini around, where do we go with the evidence that was presented to us. That's

all.

DR. BETH TARINI: I knew you weren't heartless.

DR. JOSEPH A. BOCCHINI, JR.: So, Carol, I'm going to give you the last comment here.

DR. CAROL GREENE: I'm beginning to realize there's something a little bit unique about this one. I did want to comment that 9 months is 9 months, and it's set as a time, and then it's the committee's job to decide whether what could be done was enough evidence. So, it's -- it's -- it -- it -- it -- there's time in there, and then -- So, you don't want to ask for more time up front. It -- it's just, you can send it back.

But what's new, I'm realizing, is a treatment that -- So, most of the disorders, if you don't treat in a timely fashion, the damage is permanent, and now, we have a treatment that's actually being used in babies who are symptomatic at 2 months and 4 months. And I submit that as interesting as the question is about, you know,

what will we know in 6 months or a year or -- or more, I think it's going to be 10- or 20 years before we know whether -- how much difference it makes if you start it at 2 months, when the baby's symptomatic, or if you start it at 12 days, because we -- there's so much that we don't know. And I would be really surprised if you're going to get an answer to that question in another 6- or 12 months.

So, I'm glad I don't have to be one of those voting, but I think that that's about as much -- I mean, I think you have a lot of data to go on at this point, and I don't think 6- or 12 months is going to answer the question of what's going to be the incremental change with a treatment started at 2 months or at 12 days. I think it's going to take a lot longer to answer that.

DR. BETH TARINI: Can I just respond? Because this -- This is Beth Tarini, committee member. The -- because we've -- I've been -- Dieter and I have been living this for weeks. Not

as long as you, thank God for you.

That the -- the answer to the question is, will additional data change the level of the certainty -- I believe that is how it's worded -- and that is, I think, what the additional data's looking for. We're not looking to see, necessarily, how long they will live, how close they are to normal with walking, necessarily. It's the certainty with which we can say something.

So, there are two, sort of, separate issues here. There's the benefit and how certain we are about the benefit -- And I respectfully disagree that I think additional data, based on the way the curves look, can, to some degree, influence the -- the certainty of the decision. Maybe not the measure of the increment -- that's up for debate, potentially -- but I do think that -- that additional time will give you additional data points, which may change your certainty level.

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

I want to thank everybody involved in the evidence review for providing the information that we needed to then move forward now with committee discussion.

So, as most of you know, for each condition that's nominated, two committee members are selected to serve as representatives on the Condition Review Workgroup. These members are tasked with developing a report for the committee regarding the evidence review of the condition and to help lead the -- the formal committee discussion.

So, Dr. Matern and Dr. Tarini have served as the committee representatives on the Evidence Workgroup, and they will now present their summary. And Beth will start us off.

DR. BETH TARINI: Sure. So, the -- in the interest of time, I'm going to go through those slides which are redundant based on the discussion and try to focus those that were most influential in the conclusions that Dieter and I came to.

So, this is an important slide. The decision matrix has three components. The first is benefit, net benefit, which has two components: What's the magnitude of the benefit, net benefit, and what's the certainty? There's the feasibility of newborn screening for SMA, and then there's the readiness of states, which we just heard a lot about.

And this is the matrix that we are talking about. Benefit is on the left, on the left axis, the y-axis, if you will; readiness is across the top; and feasibility is along the right. So, here we are. Significant benefit on the outermost channel and then certainty on the innermost. There's your feasibility; there's your readiness.

So, we've already discussed this; I'm going to skip it. If you don't know it, I think we're in trouble.

So, this is, as we've discussed, a range of all the SMA types, that the -- that the most severe has the lowest level, SMA type 0, type 1,

and then moving down. And then, as we -- it was noted before, SMA type 1 is the most prevalent of all types.

And this is as we mentioned: Severity decreases, quote, unquote, with -- with type. Copies loosely increase, although there is some overlap, because you can have the same SMN2 copy number and have a different diagnosis, which makes it somewhat difficult, in the studies, to separate these out.

And as I said -- And also, the delay of diagnosis -- Not surprisingly, as was mentioned earlier, given the severity and that there's a delay of diagnosis, but SMA type 1 has not as great a -- a diagnostic delay, if you will, than the other types given its severity and -- and presentation.

The evidence review largely focuses on type 1 and type 2; that is where most of the studies have focused with the participants, and these age of onset for this is less than a year overall. The copy numbers, however, can vary from

one to four.

The treatment, as we've said, is available as palliative or symptomatic, nusinersen or gene therapy, which is in an ongoing trial.

We've talked about nusinersen. The pieces here are: It is the only FDA-approved trial -- FDA-approved treatment for SMA. It is an intrathecal administration, 6 doses in the first year, and then tapers off, 1 dose in every 4 months. Its -- it does have a high cost, reportedly $125,000 per vial, per dose. The data -- limited data available does suggest that treatment effect is greater when initiated before symptoms develop and when more SMN2 copies are pregnant -- are present, sorry, likely because later onset and mild phenotype.

Okay, limitations of these treatment studies -- We've -- we've touched on these. There -- the long-term outcomes are -- are limited -- or the outcomes, I should say, are limited to 2 years or less. The study populations are small.

There are 20 infants in the presymptomatic trial. There is, anecdotally, 1 patient with 2 SMN2 copies that had normal development at 12 months of -- of age. Treatment was started at 13 days following a positive newborn screen in New York.

There are no peer-reviewed publications available on presymptomatic-treated patients. This is the gray literature that Alex was talking about.

The peer-reviewed treatment guideline is not yet published, but the draft has been developed and has -- and we have seen it. It was developed using a modified Delphi technique.

This goes through the summary of the draft guideline, which is, basically, treat unless you are a type -- I believe it was a type -- oh, a 3 or 4? Is that what is was, or was it 4?

DR. BETH TARINI: Wait to treat until you get the symptoms but automatic treatment for 1 and 2. And so, it's probable, because you cannot differentiate types reliably on SMN2 copy numbers

you saw in the previous slide. And you -- so, the problem is, you -- you can't strictly correlate SMN2 copy number with disease category, because disease category takes into account disease assessment, but you don't have disease assessment because you're asymptomatic, because, by definition, you've been screened to determine your disease status or your diagnosis.

So -- let's see -- and this is the curve that has been much discussed. And I will tell you that the conversations that we had had on the phone focused largely on the differences between the green curve, which is the presymptomatic group, 2 or 3 SMN2 copies, and the red curve, which is the infants -- infantile-onset group with symptoms.

And the concerns brought up about this curve -- the one noticeable piece is the gap that is in -- on -- of the total milestone score. One -- some concerns that were brought up were, the curves seem like they could be converging, especially when -- and they are closer when you

look at the -- at the confidence intervals.

In addition, you have smaller numbers. You have five in that last dot, on the NURTURE trial, in the green, because these children are processing through the trial, so they don't -- haven't all reached to the endpoint.

And you also have an unclear case mix comparison between the two groups, so that it's hard to say -- at least, this is my understanding -- that -- what is the case mix severity, in the green, compared to the red. What that does is say, how much of the difference is due to severity of disease, and how much is due to effective treatment?

So, when -- in our discussions, we came -- wrestled with, what is the definition of significant benefit, and we focused entirely on neuromuscular development and survival. We did not -- correct, we did not discuss -- we had discussed but did not put here our feelings about death and survival.

So, if improved neuromuscular development

and survival is defined as a significant benefit, we had felt that moderate -- there was moderate certainty of significant long-term benefit. If normal neuromuscular development and survival, then we felt there was low certainty of significant long-term benefit given the limited available data.

We could not correlate -- It's my understanding, we could not correlate those neuromuscular scores in an individual basis with the actual development of the child. We could not pull it out. Is that correct? Dieter, am I -- Yeah. So, we couldn't say how much each child was from normal. That was not there in the available data. And so, the significant benefit we placed at B.

DR. DIETRICH MATERN: So, let's move on to the feasibility. A newborn screening test is available. I think we can all agree on that. The real-time PCR assay detects, specifically, the exon 7 deletion, SMN1. This is expected to identify about 95% of all SMA cases. It might

miss about 5% of SMA cases that are not homozygous for the deletion but are compound heterozygote.

So, if you want to overcome that and identify the last 5%, then you would have to do additional testing on all of the carriers, of which we know, from New York, it's about 1 in 72. In the literature, it kind of is between 1 in 40 and 1 in 60. So, you would either have to follow them up clinically, or you would have to perform a second-tier test in the laboratory.

So, with the net benefit being moderate, we would think that the feasibility is high given that there is a test that can -- can be multiplexed, et cetera, and let's look at the readiness.

So, we were also struggling a little bit about the definition of what, actually, readiness is, but looking back at the paper that was published in 2014, about the matrix, it states there that "ready" means when most newborn screening programs could implement screening

within 1 year after the state makes a decision to include the condition and funding is made available.

Now, if you look at the developmental, it actually does not specifically say that the time is the same where it starts, meaning after the state makes a decision. It just says, “Most newborn screening programs face barriers that would require 1- to 3 years to address.” So, you could read that either, again, when a state makes a decision to screen or once it gets on the RUSP.

And finally, "unprepared" means, most newborn screening programs would take longer than 3 years to implement, even with a decision to add the condition and the availability of funding to begin comprehensive screening.

So, what is it? So, in newborn screening, the test is available, can be multiplexed with SCID. The CDC Newborn Screening Quality Assurance program can provide training, quality control, and reference materials. The incremental cost, as we heard, is small, especially when you multiplex

the test with SCID screening, but the incremental cost would be higher if you want to have 100% sensitivity, which means you have to test 1 in 60 newborns that are carriers, again, or have to follow them up clinically.

So, also what is of importance, I think, is that the test is already used, with the New York pilot study ongoing, however, very small: in three hospitals with consent. And, again, they identified 1 in 72 carriers and are currently reporting that.

But, again, the families are consented, so they know this is a potential outcome versus when you have a mandated screen. The families usually don't know much about what's going on and might be rather surprised to hear that their child may have SMA when they are carriers -- when they are identified as carriers.

Massachusetts actually began, last week, screening. They do a pilot study with consent. They will not identify carriers, so they also will not be able to report them, and currently,

it's not multiplexed because of the consent process. So, they need to separate the ones that are consented from -- from the other babies.

Utah began, also, last week, screening on the same day. They don't do consent. They do not identify carriers, and it's multiplexed with SCID.

Minnesota will begin in March, without consent. Carriers will not be identified, and it's multiplexed with SCID.

Wisconsin will begin sometime this year, probably this summer. They're going through some rulemaking decisions.

Missouri will begin this next year, probably no later than the first of -- January of 2019. North Carolina will begin a pilot study in April.

And as you heard, the PHSI assessment found that the majority of states can implement within 1- to 3 years, and, at least for some states, addition of the condition to the RUSP would actually help to get it on the states'

panels.

If you look at the programs that are screening now or are about to screen -- and this is a table that you saw before, with just some modifications, where we added when SMA was actually added to the newborn screening panel.

So, in communication with Anne Comeau in Massachusetts, I found out that the advisory committee there decided, in 2015, December 2015, to add SMA but didn't start, apparently, until last week. So, it took them quite a while. However, the delay is primarily because they had some significant changes in their program, one of which was a physical move of the whole program to a different location. So, that kind of made things a little bit more difficult.

Minnesota added, officially, SMA to the Minnesota panel at the end of the year, 2018. The advisory committee had recommended to the commissioner to add SMA at their meeting in October of 2018. The whole state will be screened. Carriers will not be identified, just

as they will not be identified in Massachusetts.

Missouri -- On July 11th of last year, the governor signed Senate Bill 50, which requires the state to start January 1st of next year. There is going to be a decision whether carriers will be identified or not in April, when their advisory committee will discuss that issue.

New York -- again, it's an ongoing study.

Utah began last week. They added it to the panel, basically, in August, following Rule R438-15, and so they started last week. They are not identifying carriers, and the fee is to be determined but will be not much more than the other states.

Wisconsin, again, expects to start sometime this year, after it's been added to the panel, and they will also not identify carriers.

So, if we consider the issue of readiness in terms of, how long does it take to implement, you can see that Massachusetts took a long time, but, again, based on discussions with Anne Comeau, they -- she believes that they probably

could have done it much faster if they didn't have the other issues ongoing. But you can suggest -- think that, probably, most states have some kind of issue that may cause a delay.

Minnesota, very fast, at least on paper; however, there was a discussion ongoing in Minnesota for a while, and the state lab had worked around with -- or played around with the CDC assay for quite some time until it was actually added. So, you could also suggest, well, it's probably more than a year that it took.

Missouri -- again, they have the law, but it -- the implementation -- they have time, and it's probably going to be less than 1-1/2 years until they start. North Carolina, New York -- no decision has been made. Utah -- again, very quickly, but I don't know how -- when they actually started looking at the assay. And Wisconsin, again, this year.

So, it looks like most states should be able to do it within a year, but, again, reality is usually a little different than what it looks

like when you do a retrospective review.

So, net benefit is moderate, feasibility is high, and we decided, in the end, to go with developmental, and then this puts this into the B2 category when it comes to the recommendation.

Do we need to wait for peer-reviewed guidelines for the management of specific SMA types? So, we've seen the draft. The draft has been, apparently, submitted, as we saw in a slide earlier today. So, that should be in the literature soon. I don't think we have to, necessarily, wait for that.

What role does nondisclosure of carriers and cost of treatment play in the decision whether SMA should be added? I don't think, especially cost -- And I think we all agree that cost should not be an issue. Carriers might be a different issue, but it seems to me that most states will not identify carriers.

So, newborn screening for SMA is possible at low cost and with high positive predictive value when not disclosing carriers and accepting

that circa 5% of SMA cases will go undetected. So, I think that is very important. Any state who makes that decision should make it very clear on their websites and otherwise, in their newborn screening education materials, that they're not looking for all of SMA types.

To achieve 100% -- 100% sensitivity or otherwise, you need to have a second-tier test or a very expensive follow-up program. Remember that if you have a carrier frequency of 1 in 60, and you had a state with a birthrate of 100,000, that would mean 32 carriers every week. So, I think that would change, maybe, our minds if -- if that was really required.

So, the other thing is, the RUSP has core conditions and secondary targets, so we could wonder about or should wonder about whether the core condition is SMA just due to the homozygous deletion, or is it all forms of SMA due to SMN1 mutations, or other can be assumed that there are either no secondary targets, if we only look for the homozygous cases. Otherwise, we would have,

potentially, other secondary targets as all the cases that are not homozygous.

Newborn screening would likely show, as we thought about it earlier, that it is -- type 1 is not actually the most frequent condition. If you remember the table earlier, about the frequencies of the different SMA types, it was 40- to 60% for SMN type 1. So, it doesn't take a lot of identification of SMN 0 and the later forms to pivot that frequency to non-SMN1 types being more frequent. And, again, we experienced, in newborn screening before that the late-onset, non-classic forms of disease are actually more frequent than the classic ones.

So, overall, given that type 2 and type 3 are very likely to benefit from treatment, most patients that would be identified would benefit from treatment.

And follow-up protocols are still needed, but, again, for -- to determine when to start treatment, that is forthcoming very soon, I expect.

And the other issue that I understood from -- in talking to some pediatric neurologists who see patients, apparently, some insurances require regular updates on how the treatment is going to determine whether the treatment should be covered as an ongoing treatment form. So, I think they would probably appreciate it if there were some guidelines on what, exactly, needs to be done, because not every center might be able to do all of the relevant HINE, CHOP, whatever, studies. So, there should be some agreement as to what is necessary to justify treatment or make this very difficult decision whether that should be continued or not.

So, in summary, then, Beth and my recommendation to the other committee members is that newborn screening for SMA due to homozygous deletion of exon 7 in SMN1 should be added to the RUSP as a core condition on the matrix category B2, to the benefit of most patients with SMA. Thank you.

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

Dieter, thank you, Beth. So, let's proceed with additional discussion, questions, comments, discussion from committee members.

Cindy.

DR. CYNTHIA M. POWELL: Cynthia Powell. Could you just clarify what you mean by, the most benefit will be for types 2 and 3?

DR. DIETRICH MATERN: So, type 2, type 3, are the later-onset cases, and I think if we consider that conditions that are milder, they're usually more easily treatable than the classic CVA cases. We -- we -- again, we don't know much beyond 12 months in the presymptomatic-treated type -- assumingly type 1 cases, basically, those with 2 copies.

If that green curve that you saw continues to go up, that probably suggests, well, they are going to benefit very much, as well. If the curve actually went the -- the wrong way, then, I guess, a -- a patient with 2 SMN2 copies may not benefit as much as the later ones. It's an assumption.

DR. JEFFREY P. BROSCO: So, following up on that, Dieter, did -- did we see any evidence that there -- that types 3 and 4 do benefit from presymptomatic treatment? I don't remember seeing that.

DR. BETH TARINI: There are -- This is Beth. There are no presymptomatic studies on types 3 and 4; is that correct? That is correct. There -- there are no presymptomatic studies that we saw. Go ahead.

DR. KATHRYN SWOBODA: Yeah, the NURTURE study includes babies with 2 or -- or 3 copies. And so, the ones in the study -- They're mixed together in that curve, but the ones that have 3 copies are being completely rescued so far, many of them. So --

DR. BETH TARINI: So --

DR. KATHRYN SWOBODA: -- in other words, they're completely following normal development now, but the two copies are -- are not as uniformly responding. And that is not published, unfortunately, because it's still a trial, but

that's absolutely the case.

DR. BETH TARINI: So, does that mean -- that's helpful, Dr. Swoboda. So, does that mean that green curve has types -- well, it could have type 3 in it, because it has people with 2 -- individuals with 2 copies in it.

DR. KATHRYN SWOBODA: It -- it's -- Yeah. I'm -- I shouldn't be talking.

DR. BETH TARINI: No, you --

DR. ALEX R. KEMPER: I -- I just -- I -- I just want to be clear, and it's very easy to do this, too, to not conflate copy number with type. So, it is true that in the green curve, there -- it's mostly -- I'm looking at K.K., because she has a steel-trap mind.

DR. BETH TARINI: Can you put the green curve up?

DR. ALEX R. KEMPER: It's mostly type -- it's mostly two copies, with -- Well, the minority has three. But it's mostly type --

DR. BETH TARINI: Say it again.

DR. ALEX R. KEMPER: So, of the green

curve, which shows the presymptomatic -- Oh, thank you, Catharine -- which shows outcomes of the presymptomatically-treated newborns with, you know, what's expected to be type 1 SMA, most of them have 2 copies of SMN2, and there's a minority with 3 copies of SMN2. But I can't remember what the split is, so I'm looking at --

DR. ALEX R. KEMPER: Oh, you had to get it --

DR. BETH TARINI: I guess my, then, question is, how do we know that the ones with three are type --

FEMALE SPEAKER: We don't.

DR. BETH TARINI: We don't.

DR. DIETRICH MATERN: So -- This is Dieter. I think the -- the concept we have to get our head around is that the whole typing is gone, because you have an asymptomatic child -- unless it's type 0. I guess, then, we know. But everything else, we will not know any more when it is copy number one -- two or three because of the overlap.

DR. BETH TARINI: But the --

DR. ALEX R. KEMPER: Right. And -- and --

DR. BETH TARINI: But when we were on the conversation call, when we had this conversation and we said, Oh, so copy number correlates with severity, we were told no --

DR. ALEX R. KEMPER: Well --

DR. BETH TARINI: -- that that's not -- that there's no -- that that's not -- we can't say that, remember?

DR. ALEX R. KEMPER: I'm missing my -- Hey, can I steal my thing? Yeah. I got it.

DR. DIETRICH MATERN: I -- I think --

DR. ALEX R. KEMPER: It's like I got to -- I got to hold the remote. Same thing happens to it at home. I -- I'm just -- I'm just going to go back. Oh, can you bring the other presentation up?

FEMALE SPEAKER: No, it's all one continuous, so it's going to be a while.

DR. ALEX R. KEMPER: Oh, all right. So, maybe I -- I won't do that for the purpose -- So,

I want to make two points. One is to underscore what Dieter said.

So, this whole notion of typing SMA really goes back many decades and before therapy, certainly, was -- targeted therapy was available. And the -- the thing that really defines type is the -- the highest motor development.

So, if you begin therapy, you would have had -- You know, presumably, there have been some kids who would, you know, develop, you know, the problems -- you know, the -- the -- you know, not -- not -- would -- would not develop much in the way of motor development. They would have been called SMN type 1, but now they don't really fall under that category because they're treated.

So, once you begin -- Oh, okay, I'm just telling you. Once you begin treatment, this -- You know, I mean, you could think of it as an archaic typing system, kind of falls apart, you know? So, that's one issue.

The other issue is, it -- it seems clear, from the evidence, that if you have 2 copies of

SMN2, with the homozygous deletion of, you know, exon 7 and SMN1, that most of those -- you know, nearly all those children are going to go on and develop type 1 SMA. The same thing is true for 2 copies, that there certainly, you know, seem to be in there, and once you -- you're going to pull up the numbers, because I can't remember the, you know -- but as you get up to, let's say, 4, there's a lot of overlap.

So, when we asked the experts, as part of our technical expert panel -- and I think this is borne out in the expert guidelines, that if you have 3 or fewer copies, then most people, at that point, would presume that it's going to be SMN type 1 or, perhaps, SMN type 2 but would benefit from therapy and would go -- go on to treat. If there's four, I think that that's where there's more, you know, uncertainty about which way the child is eventually going to progress.

So, the -- when you think about copy numbers, it's not 100% predictive of what's going to happen. I wouldn't think of it as a screening

test, but it's more of a risk stratification.

DR. BETH TARINI: So, then, Dr. Swoboda can verify the comment, then, of the rescue. Was it type 3s that are rescued or 3 copies?

DR. KATHRYN SWOBODA: Well, I'll just say that -- Sorry. So, again, type is irrelevant if you're following them prospectively, so -- as Dieter pointed out. So -- but the copy -- the difference between having two copies versus three copies is very different in terms of predicting prognosis.

So, the majority of babies who have 2 copies at birth should be predicted to go on to have type 1, and the majority of babies that have 3 copies at birth should be predicted to go on to type 2. Of course, there is overlap across that demographic distribution, but that's what the epidemiologic data shows very clearly, and -- so.

DR. ALEX R. KEMPER: Correct. And -- and -- and just, you know, to restrict it to the evidence that we have, I can't really comment on, you know, of -- you know, if you're treated pre-

symptomatically, if you have two copies versus three copies or whatever, what's -- what's your likelihood of benefit.

DR. BETH TARINI: The data she just said about -- Dr. Swoboda just said about rescuing them, you don't have the --

DR. ALEX R. KEMPER: Well, I mean, that's -- those are unpublished data that we don't --

DR. ALEX R. KEMPER: -- have access to.

DR. BETH TARINI: Right --

DR. ALEX R. KEMPER: So, I want to be clear that there's -- you know, we were able to go back to gray literature publications and pull some of this stuff forward. There's some stuff that lives in databases that, certainly, we're not able to analyze --

DR. BETH TARINI: That lives --

DR. ALEX R. KEMPER: -- for the purpose of that.

DR. BETH TARINI: That does not live -- That lives in a database and not in your evidence review? That's what I want to clarify.

DR. ALEX R. KEMPER: Correct.

DR. BETH TARINI: Okay.

DR. KELLIE B. KELM: Well, this is your best 1 year with 3 -- with 3 copies and 6 with 2 copies, and you can see the difference. Potentially, enough that --

DR. BETH TARINI: It's commenting on the full rescue. I had not heard that from Alex, so now I was -- wanted to make sure in which part of the gray literature we were.

DR. ALEX R. KEMPER: Right. So, this is -- is -- as Dr. Kelm pointed out, and now that's behind me, this is -- You know, we can comment on the nine children that were treated presymptomatically, you know, who are -- who are a year old. And this, again, was from one poster that was recently published -- or presented in France. We did not get to go there.

But -- but I do think that -- Again, it's hard -- You -- You know, you can't apply statistics, right, when you're dealing with numbers this small, and, again, we don't have

access to a full publication. So, this is the best that we have, splitting two copies versus three copies in terms of outcomes.

DR. DIETRICH MATERN: Nothing new, really. I think, again, we -- we have to -- going -- If you screen every baby for SMA based on SMN1 deletion, and you identify homozygous babies, and then you do the SMN2 copy number, if you have 2 versus 3 versus 4, those with 3 and 4 are likely to have a better outcome than those with 2.

But we do not know anymore, because you don't have a comparison. You treat them. So, you don't know anymore, whether they would develop symptoms at 4 months or at 8 months or at 14 months.

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

DR. SCOTT M. SHONE: Oh, but -- Dieter, would you agree that we also -- Scott Shone -- we -- we also don't know what the potential risks of treating those? You know, sort of -- Just like we don't know the benefit, we don't know the potential harms, of -- of including those babies

in that group?

DR. DIETRICH MATERN: So, this is Dieter.

So, the -- the harms are as Alex mentioned earlier, is the -- the approach to treatment; it is not the drug itself as far as we understand. And the harm, otherwise, if you treat too early, is that you spend a lot of money that you didn't have to spend.

DR. SCOTT M. SHONE: We're basing that, again, on just 1 -- less than 2 years of data, though, right? I mean, that's my understanding of what we're -- Do you -- Okay.

I mean, because I -- You know, I reflect back on something that you said in -- after Pompe, where Dr. Rogers from Missouri presented on the outcomes of adding Pompe, and you said something to the effect of, you know, it's -- it's sobering to think about the outcomes of the decisions we make on the committee in terms of approving conditions and not, at the time, deciding what potential harms could be. And so, I just wanted to make sure that we are cognizant of

that lesson, because I -- I -- I -- I remember sitting in the audience when you said that, so.

DR. DIETRICH MATERN: Yeah, so that brings up a very important point, I think -- thanks for reminding me of it -- is that when you identify these babies that are homozygous and may have just -- just 2 SMN2 copies, I think there has to be a very honest discussion about the benefits of treatment, that we don't know, for those cases in particular, what the long-term outcome is, and allow the parents a choice whether they want to move forward with treatment or not.

DR. SCOTT M. SHONE: So, just to clarify, you don't think we should know that as a committee before recommending the addition to the RUSP.

DR. DIETRICH MATERN: Do we live in a perfect world?

DR. MELISSA PARISI: I'm -- I'm willing to cede if what you want to say is directly relevant to what he just said. Okay.

DR. BETH TARINI: Thank you. This is Beth Tarini, committee member. I -- I think, to be fully transparent here -- and this is also a hypothesis, as well -- is that there was some discussion about whether or not we should separate mortality from benefit that is non-mortality benefit.

And I wonder if, to some degree, that there is -- at least, in my mind -- I'll be transparent; it's influential in mine -- that the mortality data is compelling. And -- and having the improvement data and the background of mortality data like that makes a difference that we have not -- to me, that I have not seen in other data, because the children tend, I think, to not die so quickly. And so, they tend to, you know, become impaired and live.

And in this case, there's a difference, and I think, to some degree, that does have a -- I -- to -- in my mind, has an qualitative effect, that it brings up the issue is that what we're deciding. Are we deciding on -- is mortality a

significant benefit in the absence of -- or in -- in an uncertainty about a type of quality, and what is our judgement?

I don't know that we've actually had to talk about that before. But I -- not to put words in Dieter's mouth, but that's, from my perspective, where the -- the trouble emerges.

DR. MELISSA PARISI: This is Melissa Parisi. So, that, actually, was going to be my comment and/or question for Beth and Dieter. If you were just considering mortality alone with regard to the consideration of net benefit and the certainty of that determination, would your rating have been different?

DR. DIETRICH MATERN: I think our rating was primarily driven by the fact that we only have such short-term data.

DR. JEFFREY P. BROSCO: So, to follow up, then: If you had outcomes at -- at 2 years or 3 years that were fairly similar, then you'd say this is an A1? Is that what -- Is that what you're saying?

DR. DIETRICH MATERN: That's what I would say.

DR. BETH TARINI: Say -- I didn't -- Can you repeat it?

FEMALE SPEAKER: So -- Okay.

DR. BETH TARINI: Or ask the question? Or is --

DR. DIETRICH MATERN: So, if that --

DR. BETH TARINI: -- Dieter's response sufficient?

DR. DIETRICH MATERN: If that famous green line --

DR. BETH TARINI: Yes.

DR. DIETRICH MATERN: -- continued that trend up to 24 months, would we consider it a higher --

DR. BETH TARINI: If you just literally -- - In that --

DR. DIETRICH MATERN: -- net benefit.

DR. BETH TARINI: If you literally -- Are you asking, if you change the x-axis to 24 or if you continue to split them? What are you asking

me? Do you see what I'm saying? If the trend -- if the slope continued without the bump down, or are you asking me if that was 24 months? Or 36 months.

MALE SPEAKER: Yeah.

DR. BETH TARINI: Yeah, yeah, he's asking the green curve.

FEMALE SPEAKER: He's asking survival.

DR. JEFFREY P. BROSCO: Yeah, I'm --

DR. BETH TARINI: That's not --

DR. JEFFREY P. BROSCO: -- trying to follow-up on -- on Melissa's question, saying --

DR. BETH TARINI: That's not survival.

DR. MELISSA PARISI: No, but the prior one was, with the bar graphs.

DR. DIETRICH MATERN: If your development improves, you probably survived.

DR. BETH TARINI: Right.

DR. JEFFREY P. BROSCO: Yeah, so saying that it -- it -- you're either 24- or 36 months, not the dip toward the end but staying at a plateau.

DR. BETH TARINI: Oh, maintained. Yes, if it didn't cross -- or didn't become nearly crossed.

MS. CATHERINE A. L. WICKLUND: I guess I just want to underscore, again, the importance of this discussion when it comes to the value that we're putting on what these outcomes are and how the -- the designation that we're going to give this changes depending on the outcome that we choose, whether or not it's survival or survival with certain motor milestones met. I don't know. I -- I just find that we -- we are going to continue to have this discussion as we move forward through other conditions, and this is such a societal, philosophical, value-laden discussion. I just -- it is so difficult to make these decisions for a population.

And I think what Dieter's bringing up -- Like, when I'm sitting with my patients, I can do the one-on-one consent and information and talking about the pros and cons and the value of -- for them, but when I'm making a decision on a

public-health level, it's just really difficult. I -- This is not adding anything to the conversation.

(Laughter)

MS. CATHERINE A. L. WICKLUND: However, other than just the complexity of this -- and I -- I just think it requires us to -- And -- and, again, if you look at the B -- the level we're giving it right now, that, from our -- the rules that we put in place for ourselves was, no, it should not be added. So, I just want to be really transparent about what we're doing here, again, as we continue to have this conversation over and over.

DR. JOSEPH A. BOCCHINI, JR.: So, before we go, let me just address the -- the B. You know, when we initially created this, the -- it wasn't that it was going to be absolute; it was a guide. And, initially -- you're absolutely right; the decision was, a B would not go forward.

But if you were on the committee at the time, there was tremendous amount of discussion

and whether that was an appropriate decision, because we would come across B's, it was thought, that there was a moderate degree of certainty, and yet, the -- the difference in outcome was enough that might -- you might consider that the chance that it would change with additional data would be small, but you wouldn't -- didn't have all that data. And in fact, the committee, with MPS I, did make that same decision to move ahead with a B.

So, I -- I think it means we need to kind of go back and relook at our matrix and decide whether it's serving us correctly. But I -- I think we've already looked at that and made the decision that we could move forward if we felt that it was appropriate with the individual condition. So, I think we -- we've already made that decision. But I think you're absolutely right that it's -- it was different when we started, but.

Kellie?

DR. KELLIE B. KELM: I think that's a lot

of -- Yeah, MPS III -- I looked it up -- was a B3, I believe. MPS I. Sorry, MPS I was a B3. A lot of my struggle, obviously, with this unpublished data is also that a lot of this, we -- we can't tease out the data for these children, and depending on, for example, the copies, which would really inform us a lot more about the outcomes and whether or not the 2 copies or just 3 copies is significantly different and -- Because that really is going to play into --

When I -- when I look at what people are doing, whether it's companies covering this treatment, et cetera, a lot of it is based on copy number or type, which it's not going to be type anymore -- and -- and following them and deciding, you know, what makes sense for the -- for the kids. But it's very hard, when you have data on 5 kids at 1 year or, you know, 9 kids at 1 year, to really, you know, decide that it's a public health mandate, you know, for states to screen for.

And I did want to -- just to be

transparent, because the drug review by FDA is online, is that they did note that in the later-onset SMA, subjects that were on for a longer duration or period, 69% of them had proteinuria, and nusinersen is known to accumulate in the kidneys. So, they acknowledge in their review that they don't have long-term data on the renal toxicity, but it is a known issue for oligos. And I just think that it is something that we don't have, and it would be interesting to have it because, you know, the longer that you're on it, what happens, and, you know, will you be forced to go off it if it winds up being, you know, something that impacts you.

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

DR. BETH TARINI: The -- the one thing that I want to comment on is, we're sitting here deciding, at the precipice, do we have enough data, do we not, and it seems like we make our decision and never look back. And I'm not saying we don't have to make a decision.

The data we have was done in 9 months.

We're dealing with the reality we live in. That doesn't mean we can't alter the reality moving forward or what we collect.

And in the past, the conversation has come up of, are we going to review conditions to see whether or not we're going to take them off. And I -- I actually think, and I've discussed this with others -- I think that that's the wrong frame. It's not -- the intention -- it should not be -- Collecting additional data should not be with the intent of taking them off but understanding we're -- how -- how were -- the hedges that we made, how did they come out, you know, in the lotto, so to speak. Like, were we right or were we wrong?

And I think the other issue that this condition brings to bear is, should we place -- put a mechanism in place to formally assess whether or not what we thought was going to happen would happen, because, otherwise, we're always dealing with uncertainty. And we can never come back -- we're not coming back to the issue.

It's just, well, we've -- we're right or we're wrong. We'll make a guess and we move forward. And I -- I think that's unsettling when you're making these decisions, and I think it might help with the decision to start screening if we -- we're able to have a reflection on additional data at a later time.

DR. JOSEPH A. BOCCHINI, JR.: I -- I think that's certainly appropriate for us to -- to do that. I agree.

Annamarie?

MS. ANNAMARIE SAARINEN: Annamarie Saarinen. I just -- I'm really glad you raised that, because I've -- I've been sitting here, like, noodling ideas and looking back at how other conditions that were, like, on the borderline or -- or didn't have what we'd, maybe, consider broad consensus went through. And is there -- is there a way to do what Beth just --

DR. BETH TARINI: I mean, that's what B is. Can a B go from a moderate to an A is the additional -- That's --

MS. ANNAMARIE SAARINEN: Yeah, that's --

DR. BETH TARINI: -- why I think that putting a B on --

MS. ANNAMARIE SAARINEN: But --

DR. BETH TARINI: -- is reasonable, because you're looking for the additional data to give it to an A.

MS. ANNAMARIE SAARINEN: Right. So, everything about what you said was -- was just, like -- That sounds like it would work. Like, that really feels like it would alleviate a lot of the stress and anxiety that some of the -- Listen, I'm -- I'm the person who voted for adding it to the panel in Minnesota, so I'm sort of, like, a foregone conclusion, but for -- for the rest of the, you know, committee and the things that we've been talking about here, they're all important, and I -- and I think that's -- sounds like a really viable solution.

I just don't, procedurally -- and I would defer to the -- the -- the chair and DFO to -- Like, is that, procedurally, something we could

do, sort of, on the fly, or is it, like, Oh, well, if we want to do that, we'll have to wait, because we have to type something up that has to be -- You know? What do you think?

DR. JOSEPH A. BOCCHINI, JR.: Well, you know, I -- I think we can do that more formally. I mean, we certainly have taken some of the decisions that we have made more recently and asked for what has happened with implementation and outcome. So, we have looked at that. Certainly, we did it for critical congenital heart disease recently. We've done it for SCID. And, certainly, the more recent ones may need a little more time because of the delay in getting them implemented into -- in states.

But I think it's a very valid approach to go back and see what happened. And if there was anything that we could learn from prior decisions to help inform the next ones, I think that'd be most appropriate.

So, I think, maybe, we should be having one of our workgroups, in the future, be looking

at, what would constitute an appropriate approach, on a standard basis, for reevaluating our decisions once they've been made and -- and implemented. So, I -- I -- I think that's something we need to add to the future agendas.

Sue?

DR. ALEX R. KEMPER: Can I -- I -- I just want to -- I -- I apologize. This isn't directly relevant to the conversation you're having, but I do want to correct the record, because I -- I got an email as I was sitting back there. And then, we had our resident health economists take a look at the cost per data of adding -- or the -- the cost for adding SMA to newborn screening, and it's probably closer in the $1- to $5 range per screen. So, it's -- it's more expensive than -- than had originally been put in there, but it's in the $1- to $5 range. So, I just wanted to correct the record that way.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. It shows that there's continuing update of the rapidly evolving information --

(Laughter)

DR. JOSEPH A. BOCCHINI, JR.: -- which is right. Thank you.

Sue?

DR. SUSAN A. BERRY: So, obviously, people are -- are feeling, in their hearts, the angst and difficulty of making this decision, and the matrix, as we've watched it be applied and used through the years, has obviously been a -- a moving target, a little bit, as well. We -- we created it -- It was created as a mechanism to make our deliberations as uniform as possible.

But it's possible that one of the things that we've learned from our most recent adventures has been that we may need some different paradigms with regard to how to implement, because we have, kind of, an all or nothing here. Either you do it or you don't, which -- which we even didn't do when we did, for example, SCID. That's not how SCID got implemented when we said we were adopting it. But we're going to add it, but --

And I -- I guess I want to make a pitch for some work that's taking place, sort of, as a think tank operation in the NBS terrain, where we're kind of noodling around the idea of having what I might call a conditional approval, a -- a situation where you bring something on and see how it goes for a while, and then get a report and then make a more final decision based on interim investigation. It allows states to have the opportunity to add things, to implement, to undertake the utility of --

And this is -- you -- this not a decision, I think, we'll make on the fly either, but I just want to speak to the idea that we want to be thinking, I think, as we go forward, about ways that we can, essentially, have our cake and eat it too, that we can learn what's needed for families, for states, for the babies that we're speaking for, without locking ourselves into something that feels so final. And it gives us the flexibility to learn.

So, I'm just passing that out as a -- as

a consideration for future activity. Thanks.

DR. JOSEPH A. BOCCHINI, JR.: So, a couple of comments. One is that Florida -- and, probably, many other states -- has law in place that says once something's approved by the RUSP, the clock starts in our state, and we then have to decide in a certain time and implement within a certain time. So, the decision we make does have implications for the states.

Secondly, I have to feel really uncomfortable about voting right now. I mean, we -- it seems to be based on unpublished data for a very small number of children, with data, sort of, coming in as we speak. And it makes it really difficult to make this, sort of, wide-ranging decision as things are, sort of, shifting under our feet. I guess that's what we have to do, but it's really tricky.

DR. DIETRICH MATERN: Dieter Matern. I appreciate that it's tricky, but I think we have to face the music. I mean, we can actually do what we want. As we know, two states started last

week. Other states will start this year. Do we really need to know it for 12 months, for 24 months? How many months do we need to know?

I think -- While I understand we shouldn't bring something up and assume that we'll take it down again, I think we -- for -- for SMA, there seems to be benefit to the patients if we identify them.

What I like about the test is that if you limit the screen to the babies with SMA, you -- that are homozygous for SMN1 -- the SMN1 deletion, you have no false positives, which is rather unique for newborn screening. So, you will only identify patients that will require treatment at some point, or you make a diagnosis very quick, and then you can determine, A) this is the diagnosis and B) we have no treatment for you when it's SMA type 0. So, from -- from that perspective, I think it's doable.

But I do also believe, as I said earlier, we need, on our website and -- a process, to remove conditions from the panel. And I -- I

agree, the easiest thing is to revisit these conditions on a regular basis through our workgroups, but I think we need to allow outsiders to come to us and suggest that a condition should be removed. And then, it should go through the evidence review, and then we would vote it up or down at that point again.

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

DR. SCOTT M. SHONE: So -- Scott Shone. So, I just want to thank Jeff, I think, at least, for reading my mind, because I -- I agree. It -- it -- it -- you know, it's -- the -- I -- it just feels rushed, really, in -- in terms of trying to get -- And Alex is used to, you know, rushing through the 9 months almost. So, I just want to say that.

But I -- I -- I think -- You know, I'm -- I'm still just struggling with that -- that certainty and magnitude of -- of net benefit that we've talked about that -- that -- that's been demonstrated. I -- I just don't -- You know, I don't dispute what you said, Dieter, but I'm

struggling with, you know, it's -- you -- you just said, It seems that there is a benefit. And I don't know that -- that -- that a condition gets recommended for the RUSP based on what seems to be a benefit but what actually is a demonstrated benefit.

So, I -- I -- that's -- I -- and I don't -- You asked, what's longer, 12 months, 18 months? I don't -- who know -- I mean, we don't know, right? I mean, with SCID, it was, wait until you find that baby, and -- and it -- it seems condition by condition. You know, what's the difference between B1, B2, B3, B4?

You know, we -- we haven't delved that deep, and -- and I think, when it comes up every time with a new condition is, we need to review the process because the new condition comes up. And so, I -- I don't -- I mean, we can't just change the process every time a condition comes up to make it so that that condition would have fit or that the next condition would fit.

So, I also don't agree with the idea of

adding a condition with the thought that it could always come off, because as -- what's been discussed routinely is, the amount of effort that it takes for the system to implement a condition to just say, Well, they could just take it off. I mean, the idea is, you would have to actually demonstrate harm to really -- to have the impetus to take it off. I mean, there are many states who -- there's either not demonstrated benefit or just mild benefit to screening, and they just continue because it's just easier to continue than to take it off.

So -- so, what if -- what if the next 12 months, 24 months of data show that -- that -- that the -- the lines converge but don't ever cross again, but state -- 12, 15 states have implemented it? I -- I can't imagine they're going to take this off. It's just not how the -- it's not how the system works, so.

DR. JOSEPH A. BOCCHINI, JR.: Did you -- Yes.

DR. KATHRYN SWOBODA: I just want to say,

I think the -- that, you know, Alex and team did this incredible review, but I want to reassure that the data is not as limited -- You know, in other words, you saw a lot of data, and I just want to, sort of, you know, think back to this little girl and think of what a tremendous -- So, this was a fatal, progressive disease, these 2 copies, and no -- I mean, I honestly, having done this for 20 years with SMA, never thought I would see that Phase 3 infantile trial show a benefit, and I certainly didn't think it would stop early. And so, just because that's what's published -- there is, you know, 6 years of data, cumulative data, of safety on this drug, thousands of exposures.

And so, I just want to say, from a point of the evidence review, I think the evidence review was thorough, it was complete, and I think it is far more compelling than lots of disorders that the committee has reviewed over time that I've seen. And, again, I'm speaking as a neurologist, of course, who knows this disease,

so -- It's not a bias, though. I see every nerve degenerative there is, and they're all bad, and this is transformational, this therapy.

So, I just want to keep in mind that A) the process isn't broken, B) there was a tremendous thoughtfulness that went into evaluating this data over a very short period of time, yes, but pulling together, you know, publications and gray data. And what you see is a big stretch, and I don't, for a moment, think that that's not going to continue. And there's 27 patients in that trial now, and we have 2-1/2 years of data; it's just that you don't see it. That's the problem.

FEMALE SPEAKER: That's the problem.

DR. KATHRYN SWOBODA: But that shouldn't preclude -- that's what the point of having these reviews are, right, is -- is to gather as much data -- And that's going to keep happening with every disease. That's the problem.

So, it -- it really may require a change in mechanism, but I don't want anyone to think

that there's not compelling data that went into this recommendation, because I think it is quite compelling.

FEMALE SPEAKER: But --

MS. JOAN SCOTT: Yeah, I -- I -- I want to thank you for that comment, because that's very helpful to hear, but I will say that this committee is bound by the evidence that we see. And there is -- It concerns me about not having published, peer-review literature to look at and be -- Like, with the case of the nine kids, it's a poster presentation. And I think it's -- it's really, really exciting, and I look forward to seeing that, but it concerns me about making a decision of this magnitude based on a poster presentation.

DR. JOSEPH A. BOCCHINI, JR.: But in terms of indirect evidence --

MS. JOAN SCOTT: Yeah, I -- it's --

DR. JOSEPH A. BOCCHINI, JR.: -- that you'd -- I mean, it does provide indirect evidence --

MS. JOAN SCOTT: Yes, it absolutely does.

DR. JOSEPH A. BOCCHINI, JR.: -- but the other studies provide indirect evidence to that.

MS. JOAN SCOTT: Yeah.

DR. JOSEPH A. BOCCHINI, JR.: So, I think -- So, that -- I think it's important.

DR. BETH TARINI: Beth Tarini, committee member. So, I -- I want to separate out, again, the issue of clinical treatment and newborn screening. The tremendous, Lazarus-like transformation that occurs with this treatment is separate from newborn screening. The question -- the -- our vote does not, in any way, I don't think, nullify that this drug has done something that some of us would never see in our lifetime. Two children who have been diagnosed clinically, and that it is -- it is, in some ways, unbelievable.

But the question the committee, I think, must wrestle with is, what is the incremental benefit of having done it at birth versus waiting, and is that incremental benefit worth a

mandatory screen for all states. I'm not saying either way. I'm just saying, that's the issue.

And -- and stopping the trial early was not based on -- is based on clinical treatment; it's not -- Right? It's based on clinical outcomes. It's not -- it still doesn't speak directly to what happens when you -- What is the incremental benefit then assumed, therefore, if you put it at birth.

So -- so, I'm -- I'm not -- and, you know, this whole 12 -- this post hoc analysis at 12 weeks, my understanding is that the FDA does not approve anything based on a subgroup or a post hoc analysis. Is that true?

DR. KELLIE B. KELM: Well, I'm not involved in --

DR. BETH TARINI: Oh. Oh.

DR. KELLIE B. KELM: -- reviewing on the drug side, so I can't speak to --

DR. BETH TARINI: Mm-hmm.

DR. KELLIE B. KELM: -- this one --

DR. BETH TARINI: Okay.

DR. KELLIE B. KELM: -- for example, but, obviously, the review is available, and you can -- you --

DR. BETH TARINI: Yeah.

DR. KELLIE B. KELM: -- can review what their determination was based on.

DR. BETH TARINI: So, I -- I guess my -- my larger point is, I -- I'm not saying that we shouldn't be adding it; I just don't want to conflate the issues of the -- the tremendous impact you have when you -- when you treat clinical -- after clinical diagnosis and the incremental gain of adding it to a newborn screen.

And then, the -- the whole -- the -- the issue could, sort of, be flipped, and I -- and I'm not trying to be flippant, but -- but our waiting -- You know, the committee is sitting here struggling that if we could have had 20 more patients, we could have this. The SMA community could also have waited to give us a little more data to bring us to a further-along point.

So, it sort of goes in two -- in two ways. I -- I'm -- I'm saying, if -- if -- the judgement was made to go forward at this point. It -- it could have been delayed, and that could have provided us a bit of a more robust data sample if you -- if you will.

DR. CATHARINE RILEY: Hi, just logistics. Can those folks on the phone -- can you please mute your phones? Thank you.

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

DR. DIETRICH MATERN: Yeah, just about having the proponents, just, come later -- I mean, that's, of course, would have been perfect, but it's not just the proponents. We actually voted to bring this to evidence review. So, we were convinced that there would be enough data to look at, or -- at least by today there would be enough.

DR. BETH TARINI: And there's an example where our hedge may or may not have been accurate. That was a hedge, exactly.

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

DR. CAROL GREENE: Actually, I think Dr. Tarini -- Carol Greene, SIMD -- said similar to what I was thinking but better, that the issue is newborn screen. I think I said earlier, this is something, I think, unprecedented, where the treatment that brings us to discuss, should newborn screening be instituted, actually may work very well on the people who present symptomatically. And that -- that's a fundamental question.

But I did also want to say that I, personally, didn't review all the data, and I can't really say, but I'm maybe a little troubled with the -- the assignment of B2, because I think there is an extraordinarily high level of certainty that the treatment works, that newborn screening would be benefit. The problem, then, is -- comes right back to what Dr. Tarini said. Is there an incremental benefit? Do you need to have newborn screening --

DR. CAROL GREENE: Yeah. So, is the newborn screening really that different than

starting the treatment at 2 months or -- or 4 months or -- And -- and I think that's hard.

So, the question is, is this B2 really about the certainty that newborn screening would add the benefit, which makes sense. It's not about the certainty that treatment would add a benefit, because there, there's a high degree of certainty.

And if you stick to the newborn screening, which Dr. Tarini is talking about, then there's a little bit less certainty. And if you stretch too far, then you go back and say, “Well, we did it for that one, and we did it for that one, and we did it for that one”, you keep bending the rules. So, I -- I think the fundamental question is, does the -- does newborn screening make the difference in the context of this new treatment.

DR. BETH TARINI: This is Beth Tarini. To answer that point, if we believe that we can make a -- a philosophical leap with indirect evidence from clinical -- I'm not saying we can or can't

or should or shouldn't. If we believe that we can do that from clinical trial, symptomatic treatments to pre-symptomatic, then I call into question why we need pilot studies at all in states. We don't need them.

FEMALE SPEAKER: Well, it depends on what you're piloting.

DR. BETH TARINI: Right. If -- if -- there's no need for a pilot study, because we can make the -- if we can make the judgement with a -- with an -- an assumption based on the clinical data.

DR. ALEX R. KEMPER: I'm going to give my disclosure again that we, as the Evidence Review Workgroup or Condition Review Workgroup, do not try to drive any decision but just want to make sure that we -- we're all working from an understanding of the evidence.

So, in the past, there are examples where we haven't had presymptomatic, you know, directly -- Like, newborn screens identified presymptomatically have gotten treatments and

been able to find a benefit. So, for example, like MPS I and that kind of thing that we've needed the pilot studies to be able to make sure that we can find -- It's an indirect pathway. So, finding the case and then using whatever evidence is available to suggest whether or not presymptomatic intervention makes a bigger difference compared to a later intervention or ALD, you know, those kinds of things, have been the case. Because, oftentimes, pilot studies identify so few subjects you'd never be able to really evaluate that directly.

And I just want to go back and make sure -- because I -- I want to make sure that I didn't confuse people, too, that they're -- and -- and Beth, Dr. Tarini, my good friend, you brought this up before, and I just want to make sure everyone's clear about this. So, there's the mortality difference, and then there's the developmental difference. And the mortality difference seems more clear, at least for the first year or so of life, but it's the way that

the developmental outcomes have been reported that are less clear and where you have those, like, you know, lines that maybe are coming back together and -- and that kind of thing.

But I -- I'm just worried about the way that I presented it. I might have conflated those things too much.

DR. BETH TARINI: That's helpful, about MPS I. Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Next is Carol and then Dr. Swoboda.

DR. KATHRYN SWOBODA: One more comment, and then Carol. So, I just want to make -- Dr. Swoboda, MGH Boston. I just want to make one more comment about incremental benefit.

So, Jill Jarecki, when she gave her presentation, for Cure SMA, talked about work that I and others did. The problem -- the fundamental problem we have with the more than 50% of the babies that are born with type 1 and wait to present clinically symptomatic is, they are fully denervated by then. So, it doesn't --

the -- the -- the transformational thing was that you could even prove they showed benefit with anything in a trial that was a sham control.

So, the idea that there's not an incremental benefit based on even that small number of children -- You don't need more than nine. To me, I look at that, that is equivalent to newborn screening. They were -- that's a presymptomatic trial. Yes, you only have 9, yes, you don't have the full 27, but those 9 kids went like this. And there's no chance those curves are coming back together. I -- I can't prove that today --

DR. BETH TARINI: Would you bet your house on it?

DR. KATHRYN SWOBODA: Yes, I would bet my house on it. I'd bet my life on it. I mean, it's just not going to happen. So, anyway.

DR. BETH TARINI: I have a question -- I have a question while she's --

DR. KATHRYN SWOBODA: Sure.

DR. BETH TARINI: -- there. So, can you

tell me what the severity ratios are between those two curves, the green and the red? Can you tell me that those curves are equivalent on a case mix, so -- the -- the populations in those two different curves have an equivalent distribution of case severity?

DR. KATHRYN SWOBODA: Yes, and the reason I can say that is because I've reviewed even more detail of the data than published, but the reason I can say that is, by the time they reach the -- So, you -- you talked about the shift between the ages, because they had up to 6 months to enroll. That 6-month delay in enrollment would even make them more denervated, and they're even going to be worse.

There's no chance those curves are coming together. So, yes, from an objective standpoint, we have the predictive ability, based on algorithms, just knowing the natural history data of progressive denervation, that those are -- are very different curves.

DR. BETH TARINI: But -- but two

children, one with a 2 copy --

DR. KATHRYN SWOBODA: There's six --

DR. BETH TARINI: -- if you had 6 months, and you had different copy numbers --

DR. KATHRYN SWOBODA: Yep.

DR. BETH TARINI: -- are the proportions of severity based on copy numbers different between the 2 curves? If copy number is -- is a--

DR. KATHRYN SWOBODA: Yes, because the -- the trial, the controlled trial, had only two copy patients in it. But you could get the same effect by taking just the six that have the two copies. It's so different. It doesn't matter, is -- is the point. There's still this incremental -- this major, incremental difference you're going to see, you know, from taking that data and comparing --

What -- what would even be a better data set would be if you take the babies in the NURTURE trial -- and not that -- You shouldn't even be comparing them to the -- to the treated babies in a way, or you could match individual

babies. But we don't have that here.

So, you have to look at what you have, and what you have is a disease that, normally, wouldn't have gained any of those milestones -- any of those milestones, right? And then, you've changed it to gaining a number of milestones and not getting a G-tube and feeding and still being able to lift up toys and rolling over and sitting. You know, that may be more modest -- and, you know, that -- to me, that's more important than the survival/mortality issue.

DR. BETH TARINI: The -- the thing is, we thought this with CF, right? We thought that CF -- I mean, not to the extent of the mortality, but we were certain and -- that all we were going to -- that what we were going to capture were the delta F508s, and -- and there has been a -- there has been a -- a range of risk -- has there not? -- in -- or severity, rather, in what we captured from birth. There's always a range of severity when you don't have the clinical -- the clinical data to -- on.

So, that's what I struggle with. Like, if we're taking them from birth, how do we know all of their -- the severity's -- always is the same in that mix? Just because the two and three copies.

DR. KATHRYN SWOBODA: One phrase: sib pairs, which I did give the unpublished data to the group, but they can't use it because it's not published. We have 30 sibling pairs --

DR. BETH TARINI: Mm-hmm.

DR. KATHRYN SWOBODA: -- that -- that show you the difference, and that's what a lot of rare diseases have used is the -- Well, I can only do so much when I got to compete with Spinraza.

(Laughter)

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

DR. DIETRICH MATERN: Yeah, Dieter Matern. So, about the sib pairs, just as -- about that for once. I think there are data to suggest that the consistency between -- within families with patients is about 80%. And, actually, at

Mayo, there's a family where they have a 2- and a 5-year-old. Both have the same copy number and have very different phenotypes.

So, that's one thing. But --

DR. KATHRYN SWOBODA: Two copy versus three or more. So, the two -- the --

DR. DIETRICH MATERN: Okay, so not within families.

DR. KATHRYN SWOBODA: Yes. So, if you look at families that have 1 type 1 child, the chance that they will -- It -- it has to do with the size of the deletion and -- and the molecular, underlying cause. If you have a bigger deletion, you're more likely to not have a -- a gene conversion event. And so, if you have type 2 or 3 in a family -- or 2 or 3 -- 3 copies or 4 copies, you're much more likely to have a change in the phenotype than if you have 2 -- a family with 2 copies, 1 for each parent.

So, that wasn't totally clear, but the chance is higher than 90% that you're going to have concordance with type 1 for 2 copy, and

there's less concordance with 3 or 4 copy. And it has to do with the recombination events.

DR. DIETRICH MATERN: Okay, so the other -- If I may -- Dieter Matern again. The other question that I wanted to first ask to make sure that you don't go homeless -- When you say that--

(Laughter)

DR. DIETRICH MATERN: -- that -- that they will -- the presymptomatically treated patients will never get to where the sham treated patients are, is that because the sham-treated ones are going to die before the others lose the milestones? Because you can lose milestones, and that is what we are concerned about when we see the green curve have that one data point for five or so cases, that it's suddenly a bit lower. Where is this going to go?

DR. KATHRYN SWOBODA: I think -- Is that the right question? I mean -- So, the -- if the question is, will we completely rescue every baby with two copies so that they're never going to start declining at all, I don't think that's the

right question.

The right question is, is there an incremental benefit -- because we don't know, yet, enough about -- We -- we haven't had these kids live long. What we know is, when we trach a baby and we follow them over years, and they live to 20, they're getting worse and worse and worse over time, and, pretty much, they're completely quadriplegic, paralyzed, and then they lose their ability to smile, and they die. You know, that's all we know.

So, in terms of -- You -- the -- But if you look at the incremental benefit, when you're mixing, when that curve goes down, you could drop in your motor function because you got sick the week before, and you haven't completely recovered. And what we're seeing in the NURTURE study is that, like little Mary that you met, they -- they are slower to gain milestones, but out 2- and 2-1/2 years, they're continuing to gain milestones, and they're not doing that. However, if they get sick, because they aren't

perfectly normal, they could still have a decline. And that's the problem with small numbers.

DR. SCOTT M. SHONE: I -- I -- I just -- So, I wanted to say, you know, thank you, Dr. Swoboda. Your -- your -- your opinion, your expert opinion, is appreciated.

The problem is that this -- You know, we had a 9-month evidence review and, like, we have this huge packet, which I took more notes on than I did in graduate school. But, I mean, it's not part of what we've -- Like, this isn't part of that. Like, you -- I appreciate you -- you being here and standing up and -- and testifying during the evidence review process, but I don't know -- but if that -- if all this robust data exists, why was it not presented --

DR. SCOTT M. SHONE: No, no, no, I -- I -- I mean -- That's not actually a question for the evidence review, not for --

DR. KATHRYN SWOBODA: No, but I -- but I think it is there, and I think that the way

you're focusing the points -- I think the data is there.

DR. KATHRYN SWOBODA: It's whether it meets your criteria or not, end of story. It seems like we're arguing about differences in things that are very subjective instead of the objective data, and I encourage you to just look at the objective data, because it's there.

DR. ALEX R. KEMPER: So, I -- I just want to comment, and I -- I -- I appreciate all the -- the work that Dr. Swoboda's done, and also participating on innumerable calls and stuff like that. I'd just remind the advisory committee that our charge is to look at published data and data that appear and have been presented within the gray literature, but we can't, especially within the window that we have, go back and look at primary data.

So, I don't discount that these primary data are very important, but within our charge, in terms of being able to understand, especially within this 9-month period, the validity of the

data that we present to you, we really have to stick at, first, peer-reviewed publications and, second of all, things that have been presented at -- at meetings and those kinds of things. As I said before, this is a very quickly moving field, and the clinicians and researchers that are involved in this understand the -- the challenges of getting things to publication.

So, I certainly don't want to discount anything that Dr. Swoboda said. But I would just -- if you really want to know about the benefits of presymptomatic care in terms of things that we've been able to find -- and this is in the, you know, non-published and peer-reviewed literature but within the gray literature -- come from two general streams.

There's the stratification of disease duration in the -- now I can never remember which, the -- I'm going to -- or ENDEAR and NURTURE, whichever one is the -- the Phase 3 trial that was halted early. So, there is a -- a -- you know, presentations talking about, if you

stratify at 12 weeks that the -- the outcomes are better.

And then, the second thing is the unpublished data from those children who are treated presymptomatically, of which there're, you know, 20-some -- although I think there were just 20 that we've been able to find -- discussed in presentations, and 9 of them who made it -- you know, 9 of whom were reported on at a year. All nine of those subjects are -- are still alive, and, you know, we should -- we talked before about their developmental outcome and how it related to SMN2 copy numbers.

So, I don't doubt that there's a lot of very important unpublished data that would inform the committee, but I just want to bring everyone back to what our charge is as the Evidence Review Group in terms of looking at published data and gray literature.

The one point -- place where we were able to use the database that Dr. Swoboda very kindly made available was through the modeling, to be

able to get the ranges on expected outcomes. And that was tremendously useful, but because of the limitations in the published literature and the gray literature, we were only able to do that model out to a year of life. But had we not had access to the kind of data that Dr. Swoboda gave us, there would have been just too much uncertainty around the role of copy number and -- excuse me -- copy number and that kind of thing.

So, that's -- in terms of our charge, that's where we're limited. Now, if the advisory committee wants us to go and begin to use unpublished data, you know, we -- we'd be happy to do that, but that would just change, you know, the evidence that we'd be able to put together.

DR. JOSEPH A. BOCCHINI, JR.: Thank you, Alex. I -- I think I'm going to have to bring this back to the committee now, and I -- I'm sorry, Carol, but -- I -- I think we've had a thorough review of the evidence, and -- and I think we've had a significant discussion, which has highlighted a number of the issues. But I --

I think it's time for the committee to -- to move ahead with a motion.

And so, I'll entertain a motion. This is on the board as a recommendation, and I'll entertain a motion whether to accept or to not accept this, with a second, and then bring this to a vote.

MS. JOAN SCOTT: Are we -- are we voting on whether or not is it A or B level of evidence first, and then followed by a recommendation, or are we doing it all in one vote?

DR. JOSEPH A. BOCCHINI, JR.: We're doing it in a vote. We're doing whether we're going to accept this as a specific recommendation of, screening for homozygous deletion should be added to the RUSP as a core condition, Matrix Category B2, to benefit patients.

Dieter?

DR. DIETRICH MATERN: Dieter Matern. I motion in favor.

DR. JOSEPH A. BOCCHINI, JR.: Is there a second?

MS. ANNAMARIE SAARINEN: Annamarie Saarinen, I second.

DR. JOSEPH A. BOCCHINI, JR.: Annamarie second, all right.

Any additional comments before we vote?

DR. JOSEPH A. BOCCHINI, JR.: If not, let's go --

DR. JOSEPH A. BOCCHINI, JR.: -- ahead then with -- I'm sorry?

DR. JOSEPH A. BOCCHINI, JR.: Yes, you can. Yeah.

DR. BETH TARINI: This is Beth. I see the anguished looks on the -- help my fellow brethren. I -- I -- I don't -- Dr. Bocchini may disagree with me, but I think that after, you know, the vigorous debate in pushing all of this, that those of us tied to evidence can take some solace in the fact that those curves, on survival, even in a post hoc analysis, are quite compelling. So -- That's it.

(Laughter)

DR. JOSEPH A. BOCCHINI, JR.: And -- and,

certainly, the committee needs to be looking at the evidence and its evaluation of the presentations and the analysis of -- of that evidence review.

So, let's go ahead and start. We'll go alphabetically.

Mei Baker is recused.

Susan Berry?

DR. SUSAN A. BERRY: I vote in favor of the motion.

DR. JOSEPH A. BOCCHINI, JR.: I vote in favor of the motion.

Jeff Brosco?

DR. JEFFREY P. BROSCO: I vote in favor of the motion.

DR. JOSEPH A. BOCCHINI, JR.: Carla Cuthbert is recused.

Kellie Kelm?

DR. KELLIE B. KELM: I vote against the motion.

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

DR. DIETRICH MATERN: In favor of the motion.

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

DR. KAMILA B. MISTRY: Against the motion.

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

DR. MELISSA PARISI: Approve.

DR. JOSEPH A. BOCCHINI, JR.: Cynthia Powell?

DR. CYNTHIA M. POWELL: In favor.

DR. JOSEPH A. BOCCHINI, JR.: I'm sorry?

DR. CYNTHIA M. POWELL: In favor of the motion.

DR. JOSEPH A. BOCCHINI, JR.: In favor? Okay, thank you.

Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: In favor of the motion.

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

MS. JOAN SCOTT: Not in favor of the

motion.

DR. JOSEPH A. BOCCHINI, JR.: Scott Shone?

DR. SCOTT M. SHONE: Not in favor.

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

DR. BETH TARINI: Approve.

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

MS. CATHERINE A. L. WICKLUND: Not in favor.

DR. JOSEPH A. BOCCHINI, JR.: All right. So, the motion passes, with eight positive votes versus five negative votes and two recused. So, the outcome is that the motion is approved to put SMA on the RUSP, and we will go ahead and prepare a letter to go to the Secretary with that recommendation from the advisory committee.

So, I want to thank everybody involved. I -- I think this has been a -- a really important discussion, and -- and I want to thank the Evidence Review people. This is the first time

we've done a 9-month review, and I think it was successful. And -- and so, I want to thank everybody for going through this in a -- in a timely fashion to reach this decision.

I know a number of people will need to leave to get to their airplane. Do we have --

DR. CATHARINE RILEY: Well, we do have one more quick agenda item.

DR. JOSEPH A. BOCCHINI, JR.: I know, so do we have time to do that one more agenda item before we end up?

DR. CATHARINE RILEY: We have a hard stop at 4:00 p.m.

DR. JOSEPH A. BOCCHINI, JR.: Okay, so, Jeff, do you want to come up real quick for the last item on the agenda?

DR. JEFFREY P. BROSCO: All right, Jeff Brosco. Talk about anticlimactic. Okay, this should only take a couple of minutes.

I wanted to bring the committee up to date on what we reported on in November and back in August. There are no major changes to this

report. It's in your briefing book. Hopefully, you had a chance to take a look at it.

And we just wanted to do a couple of things: first of all, thank the many people who worked on this report. Alan Zuckerman, of course, led us through it over the last 18 months. A number of people with stars next to their names also were part of a quality sub-workgroup co-chair, and everyone here participated. It -- it was really a group effort.

Remember, this report was drafted in response to a charge from 2016, and our aim was to focus on quality measures to assess and drive long-term follow-up, and in the report, which is 65 pages, we describe quality measures. We provide case studies. We identify gaps and some possible next steps.

You've heard the content of this before, including the possible next steps, so, really, what we're asking for is an informal consensus from you about our dissemination plan, and the plan is, if you agree, that we would like to post

the committee -- the -- the workgroup's report on the committee website, and we would certainly encourage our -- our -- our friends and other organizations to highlight the report that's there, each with their own constituents.

We would like to pursue publication of just the executive summary. It's a 3-page executive summary, and we know of at least 1 peer-review publication that's willing to, sort of, take, just as it stands, our executive summary.

And lastly, there is some enthusiasm among workgroup members and others to publish, in their specialty journals -- for example, in Child Neurology -- about some -- that are -- publications that are based on the report but would not be outcomes of the workgroup or the committee. And so, it would allow them to make recommendations and to, sort of, use the -- all the work that we've done but would not be coming directly out of our workgroup or the committee.

And just to remind you, here were the

possible next steps. I won't spend much time on them, because you've heard these at least a couple of times before, but the first and foremost was to a -- to encourage a broad range of stakeholders to participate in long-term follow-up of newborn screening and use research networks that are already out there that are particularly family focused, parent based, to try and -- and move forward long-term follow-up.

Secondly, to identify a core set of quality measures and associated data resources for newborn screening, encourage this in large data sets, whether it's through HEDIS, through the National Survey of Child's Health, and others to make sure that newborn screening is identified population, and lastly, work with the health information technology community to make sure that this is included in electronic medical records and other data sets.

That's basically what we wanted to say. If there's questions, committee discussions, I'll leave these up in case anyone's interested. We

just want informal input from the group to say that it's okay to put our report on the committee's website and disseminate according to the plan there. And no one has any energy for any comments now.

(Laughter)

DR. JOSEPH A. BOCCHINI, JR.: So --

DR. JEFFREY P. BROSCO: It's perfect.

DR. JOSEPH A. BOCCHINI, JR.: -- I imagine people are a little worn out, but I -- I think that --

DR. JEFFREY P. BROSCO: It's also possible it was a perfect presentation. That's the other possibility here.

(Laughter)

DR. JOSEPH A. BOCCHINI, JR.: I -- I -- clearly, we've all seen this report. The committee has made recommendations that have been now included in the report, and -- and I think Dr. Brosco and -- and the workgroup have come up with a plan that, I -- I think, is appropriate.

And all we need is consensus from the

committee to allow this report to -- the final version to be placed on our website and then distribute it by the members of the workgroup to their relevant organizations to try and get better dissemination of the report and -- and -- and -- and see if we can get some traction with some of the recommendations on the potential benefit for using the quality approaches to -- applying them to long-term follow-up.

So, do I hear any concerns about that, or is there, sort of, broad consensus that that's a good approach?

DR. JOSEPH A. BOCCHINI, JR.: Yep, I see a few heads shaking "yes."

(Laughter)

DR. JOSEPH A. BOCCHINI, JR.: More heads shaking "yes."

DR. JEFFREY P. BROSCO: Just nodding off.

DR. SUSAN A. BERRY: May I make a comment?

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

DR. SUSAN A. BERRY: I'd just like to

thank Alan Zuckerman for the energy that he put into this. It was a tremendous amount of effort, and --

DR. JEFFREY P. BROSCO: Yeah.

DR. SUSAN A. BERRY: -- this was, like, his baby. And I -- I want to congratulate him on the hard work that he put in and the product that came out.

DR. JEFFREY P. BROSCO: Alan would be here to accept some of our congratulations, but he has a bad case of the flu, and he decided not to infect the rest of us. So, we doubly appreciate Alan's efforts.

DR. JOSEPH A. BOCCHINI, JR.: Dr. Zuckerman gets the gold star for this, for sure, yeah.

All right, other comments?

DR. JOSEPH A. BOCCHINI, JR.: If not, we accept the report and enable it to go on the website. Yes?

DR. JOSEPH A. BOCCHINI, JR.: All right, thank you. Okay. Jeff's already off the -- Okay,

good.

(Laughter)

DR. CATHARINE RILEY: Jeff has to get to the airport.

DR. JOSEPH A. BOCCHINI, JR.: He -- Okay. All right. So, again, I want to thank everybody. I think -- I appreciate the effort that everybody made in a shortened meeting that certainly was shortened for -- with issues beyond our control, and -- and yet, I really appreciate everybody's involvement. It's very clear that everybody today was very engaged in each of the presentations and -- and involved in -- in leading and participating in some very significant deliberations to make the decisions that we did today. So, I want to thank everybody. Safe travels home, and we'll see you again in May. Thank you.

(Whereupon, the above-entitled matter was concluded at 3:52 p.m.)