U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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DISCRETIONARY ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

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MEETING

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THURSDAY
FEBRUARY 12, 2015

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The Advisory Committee met in the Terrace Level Conference Room, 5635 Fishers Lane, Rockville, Maryland, at 8:30 a.m., Joseph A. Bocchini, M.D., Chair.

MEMBERS PRESENT

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

Bismarck

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

EX OFFICIO MEMBERS

COLEEN A. BOYLE, Ph.D., M.S., Director, National Center on Birth Defects and Developmental Disabilities, CDC
DENISE DOUGHERTY, Ph.D., Senior Advisor, Child Health and Quality Improvement, AHRQ
KELLIE B. KELM, Ph.D., Chief, Cardio-Renal Diagnostic Devices Branch, Division of Chemistry and Toxicology Devices Office of In Vitro Diagnostic Devices Evaluation & Safety, FDA
MICHAEL LU, M.D., M.P.H., Associate Administrator, Maternal and Child Health Bureau, HRSA
MELISSA PARISI, M.D., Ph.D., Chief of the Intellectual and Developmental Disabilities Branch at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health, NIH

DESIGNATED FEDERAL OFFICIAL

DEBI SARKAR, M.P.H., Health Resources and Services Administration, Genetic Services Branch, Maternal and Child Health Bureau

A G E N D A

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

8:36 a.m.

Welcome/Roll Call

CHAIR BOCCHINI: Thank you. Good morning. Welcome everyone to the February 2015 meeting of the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children. I'd also welcome you to this new location. It's not that we're hiding out and we have to go to different places each time.

(Laughter.)

CHAIR BOCCHINI: First, I'd like to take roll, and so let's go through the list. If you'd respond as here. Don Bailey.

MEMBER BAILEY: Here.

CHAIR BOCCHINI: I'm here. Jeff Botkin.

MEMBER BOTKIN: Here.

CHAIR BOCCHINI: Coleen Boyle.

MEMBER BOYLE: I'm here.

CHAIR BOCCHINI: Denise Dougherty.

MEMBER DOUGHERTY: Here.

CHAIR BOCCHINI: Charlie Homer.

MEMBER HOMER: Here.

CHAIR BOCCHINI: Kellie Kelm.

MEMBER KELM: Here.

CHAIR BOCCHINI: Fred Lorey is on his way. Michael Lu.

MEMBER LU: Here.

CHAIR BOCCHINI: Steve McDonough.

MEMBER McDONOUGH: Here.

CHAIR BOCCHINI: Dieter Matern.

MEMBER MATERN: Here.

CHAIR BOCCHINI: Melissa Parisi.

MEMBER PARISI: Here.

CHAIR BOCCHINI: Alexis Thompson.

MEMBER THOMPSON: Here.

CHAIR BOCCHINI: Cathy Wicklund.

MEMBER WICKLUND: Here.

CHAIR BOCCHINI: Andrea Williams.

MEMBER WILLIAMS: Here.

CHAIR BOCCHINI: And Debi Sarkar.

MS. SARKAR: Here.

CHAIR BOCCHINI: And then our

organizational representatives in attendance. From the American Academy of Family Physicians, Freddie Chen.

DR. CHEN: Here.

CHAIR BOCCHINI: American Academy of Pediatrics, Beth Tarini.

DR. TARINI: Here.

CHAIR BOCCHINI: American College of Medical Genetics, Michael Watson.

DR. WATSON: Here.

CHAIR BOCCHINI: American College of Obstetrics and Gynecologists, Nancy Rose.

DR. NANCY -ROSE: Here.

CHAIR BOCCHINI: Association of Maternal and Child Health Programs, Debbie Badawi.

DR. BADAWI: Here.

CHAIR BOCCHINI: Association of Public Health Laboratories, Susan Tanksley.

DR. TANKSLEY: Here.

CHAIR BOCCHINI: Association of State and Territorial Health Officials, Chris

Kus.

DR. KUS: Here.

CHAIR BOCCHINI: Department of Defense, Adam Kanis.

DR. KANIS: Here.

CHAIR BOCCHINI: Genetic Alliance, Natasha Bonhomme.

MS. BONHOMME: Here.

CHAIR BOCCHINI: March of Dimes, Siobhan Dolan.

DR. DOLAN: Here.

CHAIR BOCCHINI: National Society of Genetic Counselors, Cate Walsh Vockley.

DR. VOCKLEY: Here.

CHAIR BOCCHINI: And the Society of Inherited Metabolic Disorders, Carol Greene.

DR. GREENE: Here.

Opening Remarks

CHAIR BOCCHINI: Thank you. Do we have -- and then Fred, I just called your name, but we now have you here. Okay, great.

Let's see. For my opening remarks,

I did put some slides together, because we do have some changes and I'll get you up to date with those, and a ton of this committee-related work, because as you know, the bill to reauthorize this Committee has passed, and has been signed and now it is in law.

So there are some changes in the bill that are very important to the work of this Committee, so next slide. Okay. So before we get into that, we did send a letter of support for the National Committee on Vital and Health Statistics' efforts to advance health informatics within public health, supporting the efforts of that committee, and we did receive a response from the Secretary, which is included in your briefing book.

Next slide. So as I indicated, the Newborn Screening Saves Lives Act reauthorization did pass, became law on December 18th, 2014. So the Committee's charter will be amended to address the issues, the new duties and responsibilities that were

added to the work of the Committee.

But the bill, now law, allows the Committee's work to continue uninterrupted. So we should have a seamless change from the discretionary committee to the Secretary's committee. And so on our meeting in May, May 11th and 12th, we will resume as the Secretary's advisory committee. So this would be the last meeting of the discretionary committee.

Next slide. So based on that, as you know, we kind of put everybody in sort of a steady state while we waited for this to happen. So we will now have to go back and resume rolling term limits for both the Committee members and the organizational representatives, and Debi and I will be working on that over the next couple of months.

We certainly recognize the extra work and the longer terms that you've all served and appreciate that, and we will do our best to try and make sure that we have an

appropriate transition.

We can't transition everybody off at the same time. So we will work with you to see if you have significant difficulties continuing or otherwise, we'll try and find a reasonable way to move people off and replace people on the Committee following your terms of service.

Next slide. So some of the new duties that we need to address, one is that we are asked to provide technical assistance as appropriate to individuals and organizations regarding the submission of nominations to the Uniform Screening Panel, including prior to submission of such nominations.

I think that the Education Committee has already been working in this area, and I think this just highlights the fact that we need to continue to develop ways for individuals and organizations to come forward and to help them be able to put together the packet that's needed to move a nomination forward.

Next slide. In addition, we're asked to take appropriate steps at our discretion to prepare for the review of nominations prior to their submission, including for conditions for which a screening method has been validated, but other nomination criteria are not yet met.

Again, I think this strengthens the ability of the Committee to provide recommendations and to provide information about what might be needed to develop a nomination packet that might make a condition successful, in terms of getting through the process of nomination acceptance by the Committee and then sent to the work group for evaluating the evidence related that's present.

Next slide. The next slide, please. So the Advisory Committee shall review and vote on the nominated condition within nine months of the date on which the Advisory Committee referred the nominated condition to the Condition Review Work Group. So this creates a

very different time line for us, once a condition has been accepted by the Committee and moved to the Condition Review Work Group.

Next slide. So I think this obviously will have a significant impact on the workings of the Committee, and I think this will be something that we will need to evaluate carefully. So these are some of the things I think we will need to address, to attempt to meet this nine month requirement.

We need to first determine what are the ways to assist the Condition Review Work Group, so that they can get their work done within this time frame, and come back to the Committee with the evidence that's needed for the Committee to vote.

Thus, we may need to review the entire nomination process, the nomination form and the data required for submission of a condition for review by the Nomination Prioritization Work Group. I think a number of things would probably need to move towards that

evaluation, so that the Nomination Prioritization Work Group would have what information is needed to bring it forward to the Committee, so we can make a more timely review of the evidence and then make a decision.

Then this also highlights our need to work towards the finding and standardizing pilot study requirements, and it's very clear we're already doing that, and we'll hear a report from Jeff Botkin later on the process and where that work group stands. So I think we're already moving in the direction to try and standardize that.

Next slide. The other duties that we've been asked to address, one is the timeliness of collection, delivery, receipt and screening of specimens to be tested for heritable disorders in newborns, in order to ensure rapid diagnosis and follow-up. We will hear the final report from that work group and we will be voting on recommendations for these

aspects.

But this will give us a different responsibility in terms of following this, and we're going to need to evaluate that and determine how we will go forward with that. In addition in multiple areas, the cost of newborn screening expansion was added to what we needed to do for the evaluation of a new condition, which for acceptance into the RUSP.

We'll begin that discussion today, because of the importance of that aspect. The Committee's been authorized to go from three to four, up to four meetings a year, to attempt to enable us to move forward in a more rapid fashion with the outcomes of what we're doing.

Next slide. So I think the next steps, we need to obviously reprioritize the Committee's work, and determine the best ways to accomplish this work. I certainly need significant input from the Committee members in assessing our priorities on how to meet them, and so some possible strategies, I think, are

to either form work groups with representatives from all of the subcommittees that we have, or to change the charge of one or more of the subcommittees to meet some of the standards that have now been added to our work list.

I think one of the things that I've asked, I've asked the leadership of each of the subcommittees to focus today on the products that they're working on now, so that we can get a time line for where those each are and what the likelihood is for completion of those projects, so we can see whether we're going to wrap up those and then move in a different direction, or whether those are part of what we really need to flesh out, to address some of the issues that have been raised.

Next slide. So I've already mentioned this, to address the current activities. So I did ask that each subcommittee determine the status of the current projects and establish a time line for closing out the current projects, so that we

can move forward. I think that's the last slide. Are there any questions? Okay, Steve.

When you answer, just so that we have the proper information, if you'll identify yourself and then you can make your comment or ask your questions.

MEMBER McDONOUGH: This is Steve McDonough. How often does Congress get involved with tasking a committee with such detail on what they should be doing? Does it occur very often or is it a rare event?

CHAIR BOCCHINI: I'm not the one who can answer that. I don't know. Can anyone answer that? I don't know.

MEMBER DOUGHERTY: Shouldn't there be an expiration date for the legislation?

CHAIR BOCCHINI: Denise, I think it's 2019.

MEMBER DOUGHERTY: I think that's -- so they'll start considering issues maybe in 2018? That's my guess, but you never know with Congress.

CHAIR BOCCHINI: One other thing that was in the law was that if reauthorization is not completed in time, this Committee can continue to do its work, until such time that that happens. So that was another thing that was included.

MEMBER DOUGHERTY: Joe?

CHAIR BOCCHINI: Yes.

MEMBER DOUGHERTY: This is Denise Dougherty from AHRQ, and was any more money allocated to do this work more quickly, have more meetings, provide TA, that kind of thing?

CHAIR BOCCHINI: If you can answer that.

MS. SARKAR: Unfortunately no.

CHAIR BOCCHINI: Charlie.

MEMBER HOMER: Charlie Homer. I was wondering what the implications were of both the annual audit, I think a review from the inspector -- controller's office or Inspector General's office and the Secretary's report, and the reports on required timeliness, on

their actions and things like that? Are there any implications for us? Do we need to be providing great support to that? Do we need to be conscious of those audits, etcetera?

CHAIR BOCCHINI: Yeah. Debi, I don't know if you can answer that. But I think we're part of that, so I think we'll have input into that. But I think that's going to be beyond us as well. So Debi.

MS. SARKAR: Yeah. I believe what you're referring to covers the entire Act, so all the grant programs that are funded through that Act. We don't have details right now about it, but I would imagine that the Committee would be providing information.

CHAIR BOCCHINI: Okay. Hearing no further questions, we'll now go to the next item of business, which is we need to approve the minutes of the -- oh, okay, all right.

MEMBER HOMER: Sorry, I do have one additional question.

CHAIR BOCCHINI: Yes sir.

MEMBER HOMER: If I may. Charlie Homer again. My perception was that issues around long-term follow-up were not -- I mean they were included. It looked like that they -- I'm just curious if we could get either a sense of -- your sense of the sense of Congress about the importance of or relative weight of long-term follow-up.

It seemed to me the greatest emphasis was on timeliness, particularly around the early assessments.

CHAIR BOCCHINI: Although follow-up was included in a number of the areas added as well. So I think that there is -- there was some focus on being, of providing information about follow-up. So I think that clearly was an important part, and I did not mention that.

But follow-up was added in a number of the areas of the bill. So I think you're right. We need to -- that is another focus. Yes.

MS. SARKAR: I just want to add

something. So yes, Congress added a few things to the scope of work for the Committee. But that doesn't mean that the other things that the Committee was doing is not important. So I think what Dr. Bocchini needs to do is, and the Committee as a whole, we need to prioritize everything that we're working on, including the new tasks that have been given.

CHAIR BOCCHINI: Okay. So just to summarize some highlights of today's meeting, we want to welcome Dr. Mabry-Hernandez, the medical officer from the U.S. Preventive Services Task Force program. This morning, we're going to hear from Dr. Botkin as I mentioned earlier, and get an update on the pilot study from the Pilot Study Work Group.

We also have a vote scheduled to finalize the newborn screening timeliness recommendations, and an update from the Condition Review Work Group on ALD. We also have a cost analysis discussion, as I mentioned earlier, and tomorrow we'll devote a

significant amount of time to the discussion of MPS I nomination, and have a final vote on that nomination.

I'd now like to turn this over to Debi for some housekeeping items.

MS. SARKAR: Good morning, everyone. So just to kind of reiterate what Dr. Bocchini said, that we at HRSA are working on amending the charter, so that there is no break in the Committee's work. And then I just wanted to let everyone know, for people who are listening in on the webinar, you have two options of listening to the Committee proceedings.

You can dial in. There's a phone number on the side there, or you can hear the proceedings through your speakers. Upstairs is a cafeteria with coffee, snacks, and lunch items. Today, we only have 30 minutes to get lunch, so that we can have a working lunch. So please get your lunch, Committee members especially, as quickly as possible. We will begin promptly at 12:45. So as soon as I have

eight Committee members here, that's quorum, we're going to get started.

Lastly, I think you guys have noticed we have some owls around the tables. They're there to remind you to please state your name first before you speak. This is going to help everyone listening in via the webinar, and it's going to also assist our transcriptionist who is here on site, and he's going to be recording the Committee proceedings. That's it for me.

Approval of September 2014 Meeting Minutes

CHAIR BOCCHINI: Thank you, Debi. Now in your briefing book, you have the minutes of the September meeting of Discretionary Committee, and are there any additions or corrections to be made to the minutes of the meeting?

MEMBER BAILEY: This is Don Bailey. It's a minor detail, but it says that I was here afternoon only, and I was here the whole time.

CHAIR BOCCHINI: Maybe you were too quiet in the morning.

MEMBER BAILEY: I think I stayed awake the whole time.

CHAIR BOCCHINI: Okay. So that's good, okay.

(Laughter.)

CHAIR BOCCHINI: All right. We can make that correction. Any additional?

(No response.)

CHAIR BOCCHINI: All right. So based on no other comments, we will have to take a roll call for approval of the minutes, and so it's either by yes or no or is there anyone who needs to abstain?

(No response.)

CHAIR BOCCHINI: All right, then. We're going to go alphabetically. Don Bailey?

MEMBER BAILEY: Yes.

CHAIR BOCCHINI: Yes for me. Jeff Botkin.

MEMBER BOTKIN: Yes.

CHAIR BOCCHINI: Colleen Boyle?

MEMBER BOYLE: Yes.

CHAIR BOCCHINI: Denise Dougherty?

MEMBER DOUGHERTY: Yes.

CHAIR BOCCHINI: Kellie Kelm.

MEMBER KELM: Yes.

CHAIR BOCCHINI: Charlie Homer.

MEMBER HOMER: Yes.

CHAIR BOCCHINI: Fred Lorey.

MEMBER LOREY: Yes.

CHAIR BOCCHINI: Michael Lu.

MEMBER LU: Yes.

CHAIR BOCCHINI: Steve McDonough.

MEMBER McDONOUGH: Yes.

CHAIR BOCCHINI: Dieter Matern.

MEMBER MATERN: Yes.

CHAIR BOCCHINI: Melissa Parisi.

MEMBER PARISI: Yes.

CHAIR BOCCHINI: Alexis Thompson.

MEMBER THOMPSON: Yes.

CHAIR BOCCHINI: Cathy Wicklund.

MEMBER WICKLUND: Yes.

CHAIR BOCCHINI: And Andrea Williams.

MEMBER WILLIAMS: Yes.

CHAIR BOCCHINI: All right. The minutes are approved, with the one correction. So the next item is entitled "U.S. Preventive U.S. Preventive Services Task Force

CHAIR BOCCHINI: So the next item is entitled "U.S. Preventive Services Task Force Overview and the Transfer of Newborn Screening Topics to the Discretionary Advisory Committee," and here to present that is Iris Mabry-Hernandez, who is medical officer, U.S. Preventive Services Task Force program, from the Center of Evidence and Practice Improvement from the Agency of Healthcare Research and Quality.

Dr. Mabry-Hernandez received her Bachelor's degree in Chemistry from Xavier University in Louisiana. She graduated from medical school at the University of Tennessee Health Sciences Center College of Medicine,

completed a pediatric residency at the University of Arkansas for Medical Sciences.

She's a board-certified pediatrician, and she completed a fellowship in general pediatrics at Johns Hopkins University, and a fellowship in Pediatric Health Services Research at the University of Michigan. Dr. Mabry-Hernandez currently sits on the Child and Adolescent Health Advisory Group at AHRQ, and is a member of the American Academy of Pediatrics, Academy Health and Ambulatory Pediatric Association, which I think is now the Academic Pediatric Association.

Her research interests include childhood overweight, child health and primary care, and prevention. So let's bring Dr. Mabry-Hernandez -- oh, she's already here. All right, great. The podium is yours.

DR. MABRY-HERNANDEZ: Okay, thank you. Good morning. Thanks for the introduction. I am Iris Mabry-Hernandez and I serve as a medical officer for the Task Force.

Thanks for inviting me to speak to you today.

All right. So my overall goal for this talk is to improve the understanding of the knowledge about the U.S. Preventive Services Task Force or Task Force I'll refer to it from now on, to explain the connection between the Task Force and AHRQ, to describe how the Task Force develops recommendations, and then to discuss the process for topic referral to other organizations.

And so the Task Force makes recommendations on clinical preventive services to primary care clinicians. The Task Force scope for clinical preventive services includes screening tests, counseling and preventive medications.

The recommendations address only services offered in the primary care setting or services that can be referred by a primary care clinician. Recommendations apply to adults and children with no signs or symptoms, in other words, asymptomatic.

The Task Force uses a rigorous review of existing peer-reviewed evidence to make their recommendations. The Task Force does not conduct research studies, but it reviews and assesses the research. It evaluates the benefits and harms of each service based on factors such as age and sex, and importantly, it is an independent panel of non-federal experts in prevention and evidence-based medicine.

So the Task Force is made up of 16 volunteer members, who represent disciplines of primary care, including family medicine, internal medicine, nursing, OB/GYN, pediatrics and behavioral medicine. It's led by a chair and two vice chairs, and individuals serve four year terms.

Task Force members are appointed by the AHRQ director with guidance from the chair and vice chairs. Current members include deans, medical directors, practicing clinicians and professors. For example, we have our own

Dr. Alex Kemper who's a member of the Task Force.

Now to kind of step back and look at AHRQ. So AHRQ's mission is to produce evidence to make health care safer, higher quality, more accessible, equitable and affordable, and to work with the U.S. Department of Health and Human Services and with other partners, to make sure that the evidence is understood and used.

AHRQ also provides administrative, scientific, technical and dissemination support to the Task Force. AHRQ's director, with guidance from the Task Force chair, as I mentioned before, appoints Task Force members. While AHRQ provides support to the Task Force, it's important to note that again, it's an independent entity.

The Task Force was created actually in 1984 by the Public Health Service. In the mid- to late 90's, AHRQ was tasked with providing support to the Task Force, and is Congressionally mandated to, as I say, produce

evidence-based recommendations.

So topics can be nominated, and anyone can nominate a topic for the Task Force to consider. Its website is noted here. The public can suggest a new topic, recommendations -- recommend consideration of an existing topic due to new evidence, changes in the public health burden of the condition, or availability of new screening tests supported by new evidence.

Topic nominations are accepted year-round and are considered by the Task Force at its three annual meetings. Before we go into making a recommendation, I do want to add that as far as with the topic nomination process, that usually is taken care of by a topic group, Topic Prioritization Work Group, which is a subgroup of the Task Force.

They look at the nominations, rank them in priority based on stakeholders and so forth, and then present that to the larger task force and they will rank it according to

importance, and that process can take anywhere from 12 to 18 months.

Once the topic has been nominated and decided this is high priority, we're going to update this topic, there's a research plan that's created. So Task Force members work with AHRQ staff and the evidence-based center or EPCs, who actually conduct the literature reviews, to create a research plan that guides the recommendation process.

This process usually takes anywhere from 9 to 15 months from the date that the research plan is approved, to the date that the peer-reviewed evidence synthesis performed by the EPC and the draft recommendation statement, are presented to the Task Force for a vote at one of their three meetings.

After the draft research plan, there is an opportunity for public comment. So the draft research plan is posted on the Task Force website for public comment, and it stays on for four weeks. After four weeks, the Task Force

and the EPC review all the comments, address them as appropriately, and they create a final research plan.

So the next step is looking and creating the evidence review and recommendation statement. So after the Task Force has their final research plan, the research team at the EPC independently gathers and reviews available published evidence and creates a draft evidence review.

The Task Force discusses the draft evidence review and the effectiveness of the service, and based on this discussion they create a draft recommendation statement. Both the draft recommendation statement and the draft evidence review are posted simultaneously on the website for public comment as well.

The EPC reviews all the comments on the draft evidence review, addresses them as appropriate, and creates a final evidence review. The Task Force discusses this final evidence review and any new evidence. The Task

Force also reviews all comments on the draft recommendation statement, addresses them as appropriate, and creates a final recommendation statement.

The desired time line from the Task Force vote to recommendation release is about nine months.

So next we come to disseminating the final recommendation statement. So the final recommendation statement and the supporting final evidence review are posted on the Task Force website, and the final recommendation statement is also made available -- thank you -- of course, I cough on the day of talking. Sorry.

And so the final recommendation statement is also made available through other tools such as electronic tools, EPSS, peer-reviewed journals. AHRQ assists in creating consumer guides as well. The evidence summary, the final evidence summary is published in a peer-review journal, which outlines the

evidence that the Task Force reviews. So usually it's either in *Annals* or *Pediatrics* if it's a PEDs topic.

I'd like to step back and show, as part of creating the research plan and backdrop to what the evidence review is, this is an example of the analytical framework that you would see posted as part of a research plan, and basically the purpose of this framework is to just have a graphical presentation of the specific key questions that need to be answered in the literature review, for the Task Force to be able to evaluate the effectiveness and safety of the proposed service that they're -- preventive services that they're looking at.

So as you can see there, well I don't know how well, but there are key questions. Starting from the left of the picture, that's whatever the population that's being looked at. Then at the right, those are the health outcomes that are being examined, and the arrows represent the linkages.

So for example for Key Question 1, that looks at direct evidence. Now the RCTs, they're looking at screened versus unscreened. The other linkages with the arrows will represent mostly your indirect evidence, and those curved arrows represent harms of screening and harms of treatment.

There's also a box with a rounded edge that represents intermediate outcomes, which is slightly different from the box on the extreme left, where you see the rectangular box with the non-rounded edges, which are the health outcomes. The intermediate health outcomes being -- intermediate outcomes being like blood pressure or weight or glucose, lab values, health outcomes being the outcomes you would feel.

So that serves kind of as an evidence map. So the EPC uses -- does their work to get the evidence, reflecting the questions asked in an analytical framework. Once they bring back the evidence, the Task

Force does the following steps to arrive at a recommendation.

So they assess the adequacy of evidence at the key question level, as well as assessing the evidence, the adequacy of the evidence at the linkages levels, where those arrows are connecting. After assessing the adequacy, they estimate the magnitude of benefits and harms of the preventive service.

They also evaluate the certainty of the evidence for net benefit of the preventive service, and then estimate the magnitude of the net benefit of the preventive service. Through these steps, they develop a recommendation grade for the preventive service based on these parameters.

So when looking at -- or synthesizing and making a judgment about the overall strength of evidence, evidence can be considered in three groupings. One is being convincing, where you have well-designed, well conducted studies in your represented

populations, which directly assess the effects on health outcomes.

Evidence can be judged as adequate. That's where you have sufficient evidence to determine the effects on health outcomes, but the evidence might be limited by the number or quality or consistency of the studies, looking at whether it's externalizable to routine practice, or is it an indirect link, the indirect nature of the evidence.

Then the evidence can be inadequate. So is it -- it's insufficient, because there are a limited number or power of studies. There are important flaws in the design, gaps in the chain of evidence that can't be overcome, or there's just lack of information on important health outcomes.

So again, when the Task Force looks at net benefit, they assign a certain level based on the nature of the overall evidence to assess the net benefit of preventive services. So you could think of or define the net benefit

as the benefit minus harm of the preventive service, as implemented in a primary care population.

In looking at the certainty, there are three groupings. So there's high certainty, which is you have evidence that provides consistent results from well-designed, well conducted studies in primary care populations using the health outcomes, and the conclusion is unlikely to be strongly affected by results of future studies.

Moderate uncertainty is where the evidence is sufficient to determine the effects on health outcomes, but the confidence and the estimate could be constrained by limitations in the research, and as more information becomes available, the magnitude or direction of the observed effect could change, large enough to change the conclusion.

Then there's low certainty, where the level of evidence is just insufficient to assess effects on health outcomes that they're

looking at. So this is I think a picture to represent what I just talked about, and this is the Task Force recommendation grid. This is what they use when creating their grading -- providing a grade for a recommendation.

And so, you know, in looking at the evidence, deciding what the magnitude of the benefits are and the harms, and then deciding what is that net benefit, doing that equation of, you know, how much of a benefit or how much of a harm do you have, and then looking at the certainty of the net benefit.

So for example, you can have it be recommendation if there was moderate -- if you had moderate -- if you had a moderate magnitude of net benefit, and you had a moderate level of certainty about that, versus if there is a lack of evidence. I mean you have low certainty of net benefit, it's just insufficient, because you don't have any evidence to make a recommendation.

And so with A and B recommendations,

you basically provide it to the eligible patients. C recommendations you either offer or discuss with eligible patients, and use this shared decision-making. For the D recommendation, where you have zero or negative benefit, you don't provide and you don't offer that particular preventive service.

If there's -- with insufficient evidence at low certainty, you have a I statement, and there's no recommendation. It's a statement just saying, you know, due to low certainty of evidence for net benefit, we can't -- the task force can't say anything about the benefits or the harms.

So in those particular instances with I statements, in the recommendation statements you'll find their recommendations are from research, to address research gaps. So actually in all the recommendations, but especially in the I statements it's really important to take note. Here's just another, the recommendation grades as I mentioned, A, B,

C, D and the I statement.

So kind of what led to this particular presentation today is that the Task Force deals with -- in topics of clinical preventive services, and so for certain topics, that might seem to be out of their scope, they will consider referring that topic to other organizations.

So you know, why nominate topics? Part of it is to avoid redundancy of research used by the Task Force. An example would be the Advisory Committee on Immunization Practices. The Task Force actually has referred the recommendations on immunizations to the ACIP. So they do not make recommendations on immunizations.

And the Task Force, you know, likes, does this if they can identify an organization that's in a better position to make an accurate and timely evidence-based recommendation.

So how are topics nominated for referral? So the Topic Prioritization Work

Group, which I mentioned earlier, will identify as potential organizations that, you know, makes evidence-based recommendations, and decides to consider topics for possible referral.

AHRQ staff reviews the previous Task Force recommendation statement in the evidence report, and then also reviews the recommendations and review methods of the other federal agencies and professional organizations that they might be considering to refer.

Okay. So AHRQ staff prepares a brief summary of why the topic's been chosen for referral. As I said, the Topic Prioritization Work Group will decide whether to proceed to discuss this with the full Task Force body, and if the Topic Prioritization Work Group decides to proceed, an AHRQ summary is presented at the Task Force meeting for general discussion, and then the Task Force votes on the decision to refer the topic to a specific organization.

AHRQ will add a brief summary statement to the Task Force website that will include a link to the organization's recommendations, if it's -- if in fact the referral is agreed upon.

So the criteria for referring to another organization's recommendations are that the organization has to be identified as an appropriate source; the organization has a process for updating the recommendation in a timely manner; the organization has a written and available evidence-based methodology, including the use of systematic reviews that assess benefits and harms, and that the Task Force judges to be adequate for the topic.

And so last year, the Topic Prioritization Work Group worked with the Child Maternal Health Work Group, which is another subgroup within the Task Force, and looked at the newborn topics that the Task Force had. So these were the newborn topics that we looked at, hyperbilirubinemia, newborn hearing,

gonococcal ophthalmia neonatorum, hyperthyroidisms, screen for sickle cell disease and PKU.

And so the recommendation from the Child and Maternal Work Group leading to the Topic Prioritization Work Group was to refer newborn screening topics to this body, and in particular sickle cell disease, congenital hyperthyroidism and PKU.

The criteria for referral is whether or not a newborn screening test is obtained via dried blood spots. The Topic Prioritization Work Group agreed with this recommendation and decided to proceed with a full Task Force discussion.

The recommendation was presented at a 2014 Task Force meeting for a general discussion, and the Task Force accepted the recommendation and voted to refer newborn screening topics in the acceptance. Did I say -- is that the correct way, to this group, to this body.

So as a result of that, a letter from our chair, Dr. Michael LeFevre was sent, requesting participation from you all as a partner organization. Thank you.

CHAIR BOCCHINI: All right. Thank you for a very nice presentation, and gives us a really good understanding of how the Preventive Services Task Force operates and how you came to this conclusion. This is now open for discussion, first from the members of the Committee, if you have any questions or comments, and then we'll go to the liaisons. Don.

MEMBER BAILEY: Hi. This is Don Bailey. Thanks for that great, great overview. Two questions. One, our Committee also considers feasibility of implementing a recommendation, and I didn't see any reference to that, and I just was curious whether the Preventive Services Task Force takes that into consideration.

Also, you know, I was interested in

your criterion in referring to us, where the newborn screening test is obtained through dried blood spots, because I know in the past, you know, the Preventive Services Task Force is the hearing screening, for example, which is not done through dried blood spots.

So are you saying that anything like that you would still retain in your authority and we wouldn't? I don't understand what all that means.

DR. MABRY-HERNANDEZ: Sure, sure. I'll start with the second question first. So that was just -- that was the criteria that they decided, that I guess in some ways I won't say make it simpler. But when you think about newborn screening, usually you're thinking about what's done and using the dried blood spots.

As you could see, there was newborn hearing that was listed and it was discussed, and at the time, the Task Force decided to keep that topic in its -- under its topic list, in

the event that they want to have it, or to update it, although --

So it was considered. But that was just how they decided to define, you know, newborn screening in some way. So did that answer your question?

MEMBER BAILEY: Well, not completely. I'm not understanding -- but maybe we can open it up for some other comments about this. I just was curious what that functionally means, about you keeping hearing screening, for example, under your purview.

DR. MABRY-HERNANDEZ: Right. They would have the ability to update it again, basically, if they chose to, depending on how it ranked in priority. Although we've recently, they've been considering to actually retire the topic and maybe not address it at all. But at the time, that wasn't the thinking.

Oh sorry. You had a first question. Can I hear what that was? Sorry.

MEMBER BAILEY: Does the Preventive Services Task Force consider feasibility, or do you just focus on net benefit?

DR. MABRY-HERNANDEZ: Oh, right. So when the Task Force is looking at the recommendation, they're looking at right, the net benefit, the benefit -- that balance between benefit and harm.

So you don't take a look at cost effectiveness. Certainly in discussions, and it has to be able to either happen in a primary care clinician's office or referred to. So in that sense perhaps.

So for example, with the screening for recommendation, screening recommendation that looked at obesity, the evidence showed that you needed intensive interventions, which would not be feasible in a primary care physician's office. However, the recommendation included about referring out.

So yes, in the sense of either primary care practice it can happen there, or

it can be referred. Something you need to do in an intensive outpatient -- I mean an inpatient type of setting. Oh sorry.

CHAIR BOCCHINI: Charlie Homer.

MEMBER HOMER: Thank you very much, Iris. A great presentation, and I was a member of the Task Force a decade or so ago, a U.S. Preventive Service Task Force.

DR. MABRY-HERNANDEZ: Yes, uh-huh.

MEMBER HOMER: Just following up on, I think, both of those questions, one the issue of feasibility has come up, at least did a long time ago. For example, a long time ago the U.S. Preventive Service Task Force did recommend depression screening, and there was substantial discussion that there isn't yet capacity, for example, or the competency in either primary care or the behavioral health to manage that.

The explicit conversation at that time was that the evidence supported it, and therefore the Task Force should recommend it

and the field should follow and create the systems in order to meet the need that the evidence supports. So I do not know if there have been subsequent ones, but that was certainly the feeling on the Task Force at that time for those issues.

I did want to go back to that first question about why hearing screening? I was on the Task Force when we first discussed hearing screening, and Alex Kemper was also an expert on the evidence reviews related to some of those topics.

I do think that's an unusual one, given the charge of the U.S. Preventive Service Task Force, in that it is focused on activities that really take place or primarily involve primary care, as opposed to public health system interventions.

So I think it's worth maybe our -- assuming we accept the ones that are being referred to us, we also raised with the U.S. Preventive Service Task Force. Not that we're

choosing to necessarily expand our purview, given the added responsibilities that the new law has.

But I do think we could ask that any topic related to systematic newborn screening which involves, for example, the interface between clinical practice and public health systems, that they encourage the U.S. Preventive Service Task Force to consider this Committee as an appropriate place.

So you know, the cyanotic congenital heart disease would be another type issue that we obviously feel is within our purview, and would encourage should such topics come to the U.S. Preventive Task Force in the future come to us.

CHAIR BOCCHINI: Thank you. Melissa.

MEMBER PARISI: Melissa Parisi. I just wanted to ask a question for clarification about the time frame for the Preventive Task Force efforts. You mentioned nine months, but

I think that was just in that second band.

I'm just curious about from the time that a condition actually gets accepted, the creation of the research plan and then the development of the evidence review by the EPC Committee to a final recommendation, how long on average does that happen or does that take, if you know?

DR. MABRY-HERNANDEZ: Right, yes. So when a topic is nominated and if it moves forward to be presented, moves forward to be updated, that can take anywhere from 15 to 18 months. That's just saying okay, we're going to do this topic and it's going to be reviewed.

So from yes, we've decided that we're going to contract with the EPC and do this topic, and then it becomes published, I'd state safely a year and a half to two years for that is kind of Part B or that part of the process. So --

MEMBER PARISI: Thank you. I just wanted to compare with the requirements that

are now being put upon us.

DR. MABRY-HERNANDEZ: Yes, yes, and overall topics, the Task Force tries to update topics every five years. So say you have Topic A by year. By Year 3, they start that process of, you know, looking at -- this is in the case of an older topic, the topic nomination process.

Of course, there are other topics that are nominated and, you know, there's a process of prioritization. So depending on public health, the public burden, whether there's new evidence and so forth, that kind of affects how topics will fall out in the prioritization. But they try to do it every five years.

CHAIR BOCCHINI: Okay. We have Cathy, Steve and then Alexis.

MEMBER WICKLUND: Thank you for that presentation. Do you -- from the point of the person nominating the condition.

So from that perspective do you find

that there's a lot of overlap between the conditions like newborn screening conditions that are getting nominated in both groups, and do you feel like the -- from that perspective, people are -- how they're thinking about what they nominate for this group to add to the RUSP, and what they nominate to your group for an evidence review?

Like how -- what do you see happening right now with that, and how are they might be thinking about that do you think?

DR. MABRY-HERNANDEZ: So to my knowledge, as far as with the topics that have been nominated, I don't -- I haven't seen a big overlap between the topics that have been nominated for the Task Force to look at and necessarily newborn screening topics.

But let me say it with the caveat that as a medical officer, that's not the particular work group I worked with. So I don't see all the particular, you know, nominations.

DR. KEMPER: Alex Kemper, and now

I'm wearing my Task Force member hat. The Task Force hasn't addressed that many conditions that can be identified through dried blood spots, since congenital hyperthyroidism, PKU and I can't even remember the other one off the top of my head. Oh, sickle cell disease, right.

So those topics were coming up again for reevaluation, and it was recognized that it didn't really make sense for the Task Force to weigh in on that, since this group was doing that. But it's a big deal for the Task Force to defer to another group to make recommendations about it.

So the plan we had was just to start with the dried blood spot disorders, because as Dr. Homer mentioned, these are really things that are outside of the typical program of the Task Force, being that they're not really directed by primary care physicians.

But I think that after that happens, then the issue of these other newborn screening

tests will naturally come up. So I really see this as the first step in a larger thing. But it just didn't make any sense for the Task Force to be looking at tests that were done by dried blood spots.

But this is again a big deal for the Task Force, to defer to another organization. So the plan was just to start here and then hopefully have bigger conversations as these other topics came up.

But the Task Force only addresses a handful of topics at a time, and I don't think that the Task Force really has the desire to move too far into the newborn screening world, beyond what it's already done in any case.

CHAIR BOCCHINI: I'll certainly echo what Alex said. But I think this first came up when we were working on developing the matrix for evidence review, and we did have Virginia Moyer, who was I think at that point chair of the U.S. Preventive Services Task Force, who indicated that the only way the Task Force

would move a topic to another organization is if they felt that the evidence review met their standards. So I think that is a very big portion of this.

MEMBER McDONOUGH: I have a question about resources, and what the Committee can do.

MS. SARKAR: Dr. McDonough, can you tell us who are?

MEMBER McDONOUGH: Steve McDonough, yes sorry, and it's very nice that the Task Force is asking us to take this on for newborn screening. But say the Task Force wants to update or relook at sickle cell or hypothyroidism, and they send a request or task to us to, you know, to revise or take -- go back and take a look at it again.

When I think we're going to be, I think, struggling under a nine month time frame. You know, the way I look at it, my observation of the Committee, we're lucky if we can do one evidence review a year. If we're not going to get any additional resources to

help this Committee, I'm concerned that we may get backlogged or people are going to get frustrated on our timeliness response.

So one of the questions I have, does the U.S. Preventive Health Task Force have any resources they can assist this Committee with, in relooking at these issues?

DR. KEMPER: The Task Force is not going to send a specific request to look at any particular condition. The idea being that this Committee has already made recommendations about screening for congenital hyperthyroidism, PKU and sickle cell disease.

So they're just not going to go back and look at it again. They're going to assume that if something changes, then this Committee will be on top of it and change the recommendation. But the Task Force isn't going to be nominating anything to this Committee. They're just going do it for any decisions to this group.

And I doubt they're going to bring

any money this way, but that would be a better question for Iris, Iris “Moneybags” Mabry.

(Laughter.)

MEMBER THOMPSON: Alexis Thompson. I was wondering if you could describe -- you mentioned publication of your recommendations. But could you describe, give us a little more detail on dissemination and implementation of the recommendations, what that path looks like for the Task Force?

DR. MABRY-HERNANDEZ: Sure. Yes, thank you. So the Task Force uses several different tools to disseminate its information, and also -- I guess put in a plug for them, they're also working to help make things very transparent.

So first, as far as talking about dissemination, with the final recommendation statement and the final evidence review, those two documents would usually appear simultaneously in a peer review journal. Usually it's *Annals* or PEDs, and this is based

on a relationship that the Task Force has with these particular journals.

Also, simultaneously when these -- when there's going to be a release, there will be consumer guide that is -- and all these things are on the website -- that's made available, and there's an EPSS, which is an electronic tool that clinicians can use to, you know, search the Task Force recommendations and figure out what they can do with their patients. So that tool is updated.

As part of the efforts, I mean oftentimes that's what members have to end up doing, you know, interviews in the media and all of that. But you know, you have the consumer guides which are on the website, as well as the clinical summary, which appears on the website. It's like a one-pager. It's kind of a snapshot of what the recommendation is about.

And the Task Force also tries to make sure that people are aware of what's going

on, being transparent. So as I mentioned before, you know, there's two public comment periods, and that's when the draft research plan is posted.

People can, you know, give their comments by our framework of the draft and the draft research -- excuse me, recommendation statement and the evidence report. When that's posted, people can, you know, give their comments and the Task Force will read the comments and make changes as appropriate.

MEMBER THOMPSON: Just a follow-up question. Does the Task Force interface with stakeholders like the medical societies that are appropriate or insurance companies or other payers?

DR. MABRY-HERNANDEZ: Right. So the Task Force does have or has stakeholders. They're partner organizations actually, and these partner organization, these particular partner organizations, they represent the various professional societies. AHIP is, you

know, a partner, for example, AARP.

And so they attend Task Force meetings and certainly also provide comments when, you know. Public comments are available they too provide comments. But yes, there's dialogue and interaction with stakeholders in the partner organizations.

MEMBER THOMPSON: Payers?

DR. MABRY-HERNANDEZ: Well AARP. Yes, I mean, as an example anyway.

MEMBER BOYLE: So just to follow-up on the discussion around what gets referred and what doesn't get referred, I don't know if it's worth us, you know, going back to the U.S. Preventive Services Task Force and saying that, you know, we would like to consider all conditions that would be incorporated with the newborn screening panel.

I mean there are two, hyperbilirubinemia and hearing that are remaining within their charge. I just think that in terms of clarity of committees, and not

duplicating efforts. I mean obviously the 2009 hyperbilirubinemia review was very helpful for our evidence base, but now I think that anything that's considered, I personally think anything that should be considered part of that newborn screening panel should be something that we would consider.

CHAIR BOCCHINI: Freddie.

DR. CHEN: I got it, yes. Freddie Chen with the AAFP. First of all, I think it's terrific that we've come as far as we have as a committee, in terms of our evidence review process. Much thanks to the work of Ned Calonge and others of course, so that they are comparable.

I like the idea of the referral because I think for our members, the worst thing that would happen would be differing opinions on the evidence, which certainly could happen and you could imagine a situation where you get a contradictory rating from the USPSTF versus sort of what our Committee would decide,

and that would be not ideal, not disastrous.

So the other sort of interesting nuance, of course, is that with the ACA, all the A and B recommendations from the Task Force are in fact covered and required to be covered by insurance. So that sort of puts A and B recommendations in a different place than, for example, state labs.

CHAIR BOCCHINI: Denise.

MEMBER DOUGHERTY: So I actually would like to go back to the feasibility question that was asked early, and to Charlie's recollection of what happened with adolescent depression screening. What the latest recommendation says, and Iris can tell us if that's -- if it was controversial to do this or not, is that it kind of gives primary care providers an out.

So it says you should screen for depression for 12 to 17 year olds, but only if there's capacity either in your office or in the community to do a follow-up. I think I

have that right. Is that right Iris? So it's a recommendation, but it's not -- well, none of this is a requirement. But it is -- it does address the feasibility issue in a different way.

DR. MABRY-HERNANDEZ: I mean it's just kind of an evolving process in the discussion about, you know, feasibility.

CHAIR BOCCHINI: Okay. Don, I'm going to give you the last comment. We need to move on.

MEMBER BAILEY: Well I guess I don't think this is being presented as an action item for us to do anything or vote on anything. But I would recommend that as a Committee we thank the Preventive Services Task Force for acknowledging that our Committee exists and that we actually do do a good job of evidence review, and that --

And we -- and I agree with what Freddie's saying, that some clear boundaries about which committee's doing what is really

important, and I agree with Coleen, that we should be -- that we ask the Preventive Services Task Force to, you know, refer all newborn screening questions to this Committee.

CHAIR BOCCHINI: All right. That was a good summary Don, and I think -- Iris, again I want to thank you for this presentation, and the work of the U.S. Preventive Services Task Force, and unless there's an opposition, we're running out of time. So we're going to have to move on.

So if there's no opposition from the Committee, I will accept for the Committee these three conditions to come under our purview from the Task Force, and then look forward to further discussions with you and a close relationship on developing a plan for other newborn screening conditions that have public service impact, because I think that's probably the key thing for our Committee and the work. So thank you again.

(Applause.)

Pilot Study Work Group Update

CHAIR BOCCHINI: Next we have Pilot Study Work Group update. We have a panel of speakers, led by Jeff Botkin, who is a Committee member and chair of the Pilot Study Work Group. In addition, Carla Cuthbert, Chief, Newborn Screening, Molecular Biology Branch, Division of Laboratory Sciences, National Center for Environmental Health from the CDC; Tiina Urv, Program Director, Intellectual and Developmental Disabilities Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the NIH; and Michael Watson, organizational representative representing the American College of Medical Genetics; and Anne Comeau, Deputy Director, New England Newborn Screening Program, Professor, Department of Pediatrics, University of Massachusetts Med School. So he will lead this panel. Jeff.

MEMBER BOTKIN: Thanks Dr. Bocchini. I appreciate time on the agenda today. I'm

going to try to be quick with some introductory comments about the pilot group and then turn it over for a panel discussion.

So here's our work group members. We've had the opportunity to have three teleconferences about this. We won't have in-person meetings at the Discretionary Advisory Committee meeting as yet. So we'll continue to do our work over the phone. But it's been an excellent group to continue thinking about this work.

Now in terms of pilot studies, what we're talking about, from my perspective at least, are studies that mimic the newborn screening system. So that we're looking at the implementation on a pilot basis of screening for new modalities, with identifiable babies, with follow-up for those infants to look at the impact of early intervention on the outcome morbidity/mortality for those conditions.

I think the general consensus certainly in the field at this point is we've

got an excellent evidence review process. What we need now is more evidence. So I think developing a system by which we can acquire higher quality and more volume of evidence to make better quality decisions by the Committee is important.

So here's the charge to the work group. Recognize and support current efforts regarding pilot studies and evaluation. That will be primarily what the panel is doing today. Identify other resources that could support pilot studies and evaluation, and then an interesting and creative third bullet here, identify the information required by the Committee to move a nomination condition into the evidence review process.

Meaning define the minimum pilot study data required for a condition to be accepted for evidence review. So we've not as yet launched into that particular set of discussions.

So this is a little bit of an aside,

and has been dropped on the newborn screening community with the reauthorization of the Newborn Screening Saves Lives Act. Everybody, of course, has been waiting for that reauthorization for a while. This provision, Section 12, was included in the bill.

I just want to highlight this for the group's awareness at this point. To my knowledge, there was not any great deal of background discussion during the legislative process of this particular provision. So this came as a surprise, at least to a lot of us. A lot of language here, but basically what I want to point out is that what this provision does is says that research with dried blood spots is human subject research.

As folks may know, that the regulations only traditionally have required human subjects research to be individuals who are identifiable to the investigator. So this means this is human subject research, regardless of whether the dried blood spots

have been de-identified or not.

As folks know, the vast majority of research on dried blood spots is with de-identified blood spots. So that brings it under IRB oversight, brings it under the rest of the regulations. Also, this first section says that Sections 46.1168 and 116(d) of Title 45 shall not apply.

Those are two provisions that allow alteration or waiver of informed consent in certain circumstances. So this means that informed consent of parents' -- the intent here is the informed consent of parents will be obtained for research using dried blood spots.

And so that adds -- this is consistent with a lot of the research on what we know parents want, consistent with what the plaintiffs in the lawsuits the past couple of years in Texas and Minnesota have been pushing for. So this is presumably in response to that sort of initiative.

So two caveats here just to point

out now. We can spend a lot of time on this that we don't have. But this only applies to federally funded or HHS funded research. So that's a specific important restriction, and it only applies to blood spots acquired 90 days after the implementation of the loss. So all of the -- so the legacy spots that have been collected over the years, this would not pertain to those.

So federal government needs to implement draft guidance within I believe 60 days or so, and then implement regulations within two years or so. I believe I'm hoping we have Dr. Jerry Menikoff, Director of the Office of Human Research Protections on the phone here this morning.

DR. MENIKOFF: Yes. Can you hear me Jeff?

MEMBER BOTKIN: Yes. Good morning, Dr. Menikoff. How are you?

DR. MENIKOFF: Dr. Botkin, I'm pleased to be here.

MEMBER BOTKIN: So I wonder if I might turn it over for you, just some comments about OHRP would be the agency that would be responsible for drafting guidance on this. So just an opportunity for you to comment just briefly on how that process might work.

DR. MENIKOFF: Sure. So as you know, this is sort of news to us when this came along. We didn't have a lot of, you know, notice ahead of time in terms of this law being passed. We've been trying to reach out various players in terms of getting information on what's going on.

I could sort of mention, in terms of your own involvement obviously, we have the Secretary's Advisory Committee on Human Research Protections, of which you are the chair, and we have asked that committee to take a look at this issue and to provide some advice to us.

Again, our goal is to come out with some guidance. This is early in the process,

so we don't really know what it will say at this point and what topics will be covered. But bottom line, we're collecting information and we hope to kind of at some point or another come out with some guidance that it helpful to people.

A key point as you highlighted is this only applies to such research that is conducted and supported. But from our viewpoint, conducted and supported by the Department of Health and Human Services, and we're not aware that there is or is not a huge amount of that. So that's going to be a key issue, and it could be people on your end have more information about that.

So why don't I leave it at that, and if people have questions or whatever.

MEMBER BOTKIN: Do we have time for a question or two for Dr. Menikoff? Anybody have any questions?

(No response.)

MEMBER BOTKIN: Okay, not at the

moment, but stay on the line.

DR. MENIKOFF: Okay. I will be. Thanks.

MEMBER BOTKIN: Thank you. So our -- we have subcommittee meetings of the Secretary's Advisory Committee on Human Research Protections earlier this week, spent a lot of time on this issue and I think it's premature to say what we're going to do. But I think everybody recognizes the value of this research and want to meet the letter of the law, but also try to develop recommendations that would allow this important research to go forward without excessive administrative burdens at least.

Interesting how these bullets changed from the draft. I had an experience in the past where they changed to dollar signs, and folks thought I was making some editorial comment. But so this is just a quick comment, a little bit premature.

Also Kathy Swoboda, formerly at Utah

now at Harvard, has an NIH-funded study looking at -- pilot study of SMA screening. Marci Sontag, also a part of this research group and the only specific gain there was to engage general public about decision-making processes around pilot studies. I think it's become clear that parents alone or the general public is not the only stakeholder group.

So we've had some very preliminary discussions at the investigator level about whether this grant might be reoriented to some extent in its later years, portions of this grant might be reoriented to try to garner opinions from other stakeholders like state programs, clinicians, other professionals who are involved in the pilot screening process, try to get a better sense of what are the opportunities and barriers for conducting pilot screening.

So all of that quite premature at this point, but we're hoping we might be able to support the work of the pilot group through

some of the resources that are available through this grant. All right. So I'm going to now turn to our panel, and we have four individuals who I'm privileged to have comment about their activities, to bring us up to speed on really a variety of important activities that are already being conducted around pilot studies.

So Carla Cuthbert from CDC will be our first speaker.

DR. CUTHBERT: Thank you Jeff. Okay. So my name is Carla Cuthbert. I'm the Chief of the Newborn Screening and Molecular Biology Branch, and I'm just going to be talking to you about some of the things that we have been doing with regards to implementation of new conditions and the support activities that we have, when states are deciding to implement new conditions for pilot programs.

Just by way of introduction to our branch, our branch comprises about 40-45 scientists who are actively engaged in doing

laboratory work and having oversight of their production of quality assurance materials. So the branch itself has what's called a Newborn Screening Quality Assurance program, and that's headed by -- these are -- all our programs are headed by specific subject matter experts.

We have a team also called the Newborn Screening Translation Research Initiative, and they do a number of activities with respect to pilots. So they have been very actively involved with the SCID and the LSD and now SME initiatives. In 2011, I broke out and I created two additional teams that are specifically focused by laboratory platform on different activities, biochemical mass spectrometry laboratory and the Molecular Quality Improvement Program.

This we did because we saw that there was a distinct need to make sure that state programs had a focused area that was present in our branch, that dealt with these particular applications. So there are a lot of

people doing a lot of work, and again our goal, the goal of the branch is to assure early and accurate laboratory detection of heritable disorders in newborns through dried blood spot testing.

One of the main things that we have been doing -- not main things, but in terms of funding opportunities, we have had funding opportunities for SCID since 2008, thank you, and since 2008. We funded the first public health pilots, and these were -- the recipients of these were Massachusetts and Wisconsin.

We're going to be hearing from Massachusetts shortly, and the initial pilots were for three years, because they were the first ones, and the earliest adopters, especially for things like Pompe, they now know that it takes a longer -- it takes a little bit more of a challenge when you're the first one.

We also funded SCID pilots in the Native American populations, and after the first two states were funded, we've continued

to fund two-year implementation activities. In 2011 and '12, we supported Michigan and Minnesota. In 2013 and '14, Oklahoma, Virginia and Georgia were the recipients of our activities. In the fall of 2015, we don't know yet. We are looking forward to being able to support another group of states.

The early research objectives are listed here, and this is just for your information only. But again, there was not really anything -- there was not really anything done in the context of a public health environment, and that's very important to understand, that these laboratories -- these programs were charged to develop and evaluate blood spot testing in a high throughput environment, developing second tier tests, looking at novel ways for data analysis and developing statistical algorithms, and disseminating that knowledge and skill to other laboratory scientists within the newborn screening community, and of course training

other public health community members.

So they did a great job at that, but that's not -- that's not the only thing that we have been involved in doing. There are a number of things within the branch that we are involved in, in support of the sustainability of these pilot programs. That includes production of quality assurance materials.

Again, you may hear us talk about this a lot, but these are not trivial activities. The creation of quality assurance materials is quite involved, and all of our scientists are very, very much involved in the scheduling of every single activity.

We provide -- we're the only comprehensive quality assurance program that uses dried blood spots in the world, and we produce quality assurance materials. We orchestrate proficiency testing, and do some filter paper evaluation and do transmission research to develop new materials as new conditions become presented.

So quality control materials are necessary to provide a high degree of confidence that your testing is accurate for that batch of samples that are being tested. They in fact monitor performance of your method over time, and it documents trends in performance, so you can identify and take corrective actions as quickly as you can, so that all of your samples would always been in control.

CDC quality control materials are supplemental materials, not generally for every day use but most of our programs tell us that they do use them on a daily basis. We provide QC data twice a year.

Proficiency testing involves laboratory evaluation, and we look at the laboratory ability to get the same results on a set of examples as its peer laboratories. Again, it's assessing your ability to do testing at one point in time, similar to patient testing, and we provide materials three

times a year for both U.S. and international participants, with a one month turnaround of results.

This slide is just to give you an idea of how long we have been doing this. This has been happening for about 35 years, since 1978, when the first program rolled out for our congenital hyperthyroidism. This is also to give you an indication, but things don't happen at the flick of a switch. We need to be very much prepared, and we need to know what is being considered, so that we can start developing the level of expertise that we need within the branch, to provide quality assurance materials.

This is an indication of our quality assurance programs, both for quality control and for proficiency testing, and we have some new ones that are going to be developed, going to be initiated in this upcoming year.

These are just pictures that just show some of the process that's actually

involved in creating the samples. We are approaching about a million dried blood spots are being produced every year now.

The key point I want to make sure that you understand that it's critical for CDC to be very much involved in the early stages of any newborn screening condition that is being considered for nationwide implementation. It takes a while for us to do this, and if we want to develop robust quality assurance materials, we need to evaluate it, and this is often a very iterative process.

We need to develop and we need to find what we need. When you're just adding a simple compound to pooled blood, that's one thing. But if you're actually starting to look at enzyme activity and you're looking at molecular markers, that requires a lot more evaluation. So it's very important for us to be involved in at the very early stages.

In addition to making quality assurance materials, we also have to have

methods in house, so that we can evaluate those quality assurance methods. But not just that; we need to be able to have in-house expertise to troubleshoot with state laboratories. We are sometimes called on to help states move things forward, and we are also a venue for training state programs, especially as they're rolling out these new conditions.

So we're -- everyone, all teams within the laboratory, within the branch, are actually very much actively involved in some form of method development, depending on their level of expertise, and I didn't list them here, but every group is involved in some activity. This is just to show here on the left-hand side just the process involved in our in-house method for the TREC assay.

At the bottom here, we've just described an innovative technology that allows us to do some absolutely TREC copy number evaluation, using digital PCR. So these are activities that our scientists have been able

to develop in-house, to help support state laboratories as they do their work.

We provide technical program support by means of training, and providing different forms of technical expertise. We have held national meetings and we continue to do so this year. In collaboration with APHL, we are holding a number of different national discussions.

On laboratory-based training and courses, we have one on one consultation laboratory data review site visits, website resources. The national conversations are -- and national meetings are particularly important, because they allow states to have an opportunity to share best practices with each other, certainly from those who are more experienced to those who are later adopters of pilot programs.

On the bottom here is just descriptive bullet points on one of the national meetings that we had in 2010, when

SCID was finally added to the newborn screening panel. We do a lot of workshops, and this is just a depiction of when any particular state attended one of our workshops and when they actually began screening, and you can see that as this was charted, there are a number of different programs that have attended our SCID workshops.

These are small workshops, so the states have a chance to have a lot of interaction with the subject matter experts. Again, this is just another indication of some of our workshops and technical meetings. We have a number of courses that again offer an opportunity for staff when they have -- if they have high staff turnover, to become educated again with different laboratory platforms.

We also have a program called the Molecular Assessment Program. That's a site visit activity that allows various experts within CDC and state public health programs to go visit new laboratories, and give an

assessment of their work flow. Again, this can help very much with helping these particular states to secure more equipment, adequate space and personnel, especially when these issues have become really difficult issues when you're considering expansion of newborn screening.

Partnerships is something that we could not -- we couldn't do any of these activities without. APHL has been one of our closest partners, and through APHL we've been able to support the Newborn Screening and Genetics and Public Health Committee, a QA/QC Subcommittee and the Newborn Screening Molecular Subcommittees.

These committees each have public health representatives in them, and that allows us to be very sensitive to all of the issues that are -- that they are actually facing. So we have a very close, very great opportunity to hear from them very directly, issues that they would be facing, and we have an opportunity to have a very easy way to respond.

We also have relationships with the Clinical and Laboratories Centers Institute, the CLSI group, and we have been -- CDC has had subject matter experts on many of their committees and subcommittees, to help provide documents that have national guidance and especially national guidance for SCID. I think there's one coming out on LSDs shortly as well. So these are also things that we've been doing, and that, I think, is my last slide.

MEMBER BOTKIN: Thank you, Dr. Cuthbert. Maybe if it's okay, we'll just have one question now, and then I think for the most part, folks should jot down questions and we'll try to come back if we have time at the end, with questions for the whole panel.

MEMBER McDONOUGH: Thank you. Steve McDonough. What's the potential impact of the Informed Consent Reauthorization Act on your ability to do your work within the newborn blood spots?

DR. CUTHBERT: Well, it will impact

us. The materials that we actually produce we have permission to actually do. So we collect full blood, and we have relationships and consent to collect the blood that we actually need to create our materials. But when it comes to evaluation of our methods, we will need residual specimens to actually verify that we're doing what we need to do.

So it will impact us to some extent, and we're looking at ways to try to address that ourselves internally.

MEMBER BOTKIN: Thank you Dr. Cuthbert, and we'll try to get back for other questions later. Dr. Urv.

DR. URV: Hi, good morning. I'm here to talk about newborn screening pilots at NICHD. But I'm going to give a quick overview, because some in the audience might not be aware of the Hunter Kelly research program that resides at NICHD and NIH, which focuses on research using dried blood spots and focused specifically on newborn screening disorders.

When the NIH and NICHD defined research in newborn screening, we think of it as a newborn screening system. Not just the development of a test but, you know, we kind of -- I think of it as us going from soup to nuts. Our investigators develop some of the initial tests or the initial studies that lead to the development of tests that can identify disorders, so we count that as falling under newborn screening.

So what would touch us is getting those specimens to do natural history studies or to identify -- do population studies to identify the prevalence incidence of disorders in the whole population. Our investigators are also studying treatments for diseases of these kids as they are being followed through natural history studies as when is the best time to treat and how. So the dried blood spots are being used in those situations.

We also look at -- we do have pilot studies in implementing newborn screening into

tests, and seeing how well they work in the public health system. We work very closely with the CDC. Carla Cuthbert is one of our great partners, and Joan Scott at HRSA is one of our strong partners. We try to work very closely together in newborn screening.

I have very few slides. I was told to keep it quick, keep it short, but I couldn't help but put that commercial in, sorry. So what I'm going to talk about is pilot studies that we've had and we're going to implement. Mike Watson, who is part of the NBSTRN who leads it, is going to talk about it. They are our resource, funded by the NICHD through a contract, to support our investigators working in newborn screening.

So he's going to give you a little bit more of the nuts and bolts, and I'm going to talk about just an overview of how we view pilot studies in newborn screening for the implementation of new disorders.

Sorry. So we have a model of

newborn screening. I'm just going to click through this. So our model for pilot studies is we have a contract right now. I can talk about this a little bit because we have a sources slot out on the street.

So we had -- we funded a pilot contract for Pompe disease, is this is very similar to that, where we identified states that would be able to screen or a small business or what we're looking for, that are able to screen a lot of babies in a very short period of time.

They go into a pool that kids that are identified are then followed, tracked with these. They have their little names on them. They're identified. So the first round spots are de-identified. We do the screening. The kids who are found, we follow through short term or long term studies, and they're able to use the NBSTRN resource, and Mike will talk a little bit more about that.

As I said, we have a sources slot

out on the street right now, or it was. What that means to you who are unfamiliar with the contract system in the federal government and its contract, a request for proposals will be coming out soon. We're looking for states that can screen for -- that are capable of piloting and on-boarding something very quickly.

That's one of the challenges that exists, is bringing a state on quickly. We work closely with Jelili and APHL, talking to them about what's going on. We talk to the states. We try to be supportive. So this will be out on the street. We're looking for states that can perform. We're trying to have a pool of states, so when the pilots come up that we need to do, we can implement them in quick time.

One of the challenges we've had in the past is that, you know, something might come up to the committee and we won't be able to do anything for two years, because that's basically when we request money. It takes two

years, you know. We have to do a contract. That might take another year. So that really holds things up.

So by having this pool of contractors ready to go, that we can request to be on call, we hopefully will facilitate pilots moving through a little bit quicker. So Mike, you're up next, and he'll describe the NIH-funded programs that his group is supporting in a great way.

DR. WATSON: Thank you, Tiina. Are my slides attached to those?

All right. So I'm going to give you some information about the Newborn Screening Translational Research Network, primarily focusing on its role in the pilot studies, although aspects of the reauthorization of the bill have implications for other parts of NBSTRN as well.

All right. Which one moves this thing? Is it on the remote?

All right, yes, okay. So this is

the entry to the NBSTRN. There's a lot more slides in that packet that I'm going to speak to. Most of them go into more depth about some of the issues. So they're available for your information, not that I won't speak in great detail because there isn't really time. There won't be time if I can't hit the arrow.

All right. So as Tiina already alluded to, Section 6 of the reauthorization of the Newborn Screening Saves Lives Act is specific to the Newborn Screening Translational Research Network that operates through the Hunter Kelly Newborn Screening Research program.

It's directed to provide research and data for newborn conditions under review by the Advisory Committee, that are to be added to the RUSP, and to conduct pilot studies on conditions recommended by the Advisory Committee, to ensure that screenings are ready for nationwide implementation.

What I'm going to try to cover

briefly is some of the infrastructure we have built to support pilot studies, give you some information on some of the pilots in which we've been involved, some of the issues that have come from those pilots that leave us pondering our capacity to keep up with what's really on the launch pad potentially for newborn screening integration.

That will be our experience with the severe combined immunodeficiency disorders. The newborn screening sequencing pilots, which aren't really newborn screening pilots, they're at the very earliest stage of a pilot when you begin to assess whether it's even feasible or not. It's not even out to the broad application range yet.

We'll talk a little bit about the Pompe disease pilot that's ongoing, and then talk more broadly about the lysosomal storage disorders that fall under one of the grantees in the NBSTRN program, Melissa Wasserstein, who is looking more broadly at LSDs than just

what's in the Pompe contracts that have been recently funded.

Then I'll try to give you a sense of what's on the launch pad that we keep an eye on, because it's something that's going to make us crash and burn if we haven't figured out how to resource this kind of an activity.

I'm going to skip that one. The three major tools we have in NBSTRN are the virtual repository for dried blood spots. We're looking at how we're going to reconfigure this as this requirement for consent comes in, because after March 18th, anything taken into the repository has to be consented. Whether that's opt in, opt out or all those other forms of consent, we'll await the OHRPs, look at this problem and recommendations about how we're going to approach it.

But it's going to a while between a guidance, what two months out. So some time in mid-May to a rather two yearlong window to getting something final. We also have the

longitudinal pediatric data resource, where we actually capture the data from the patients who are screened positive and diagnosed, to get a sense of their longer-term outcomes.

Then we use the R4S resource that Dr. Piero Rinaldo developed, to support really quality improvement in newborn screening programs and improvement of cutoffs and things of that kind, that we have adapted to prospective use in pilot studies, because it had all the bells and whistles required for that kind of an exercise at a multi-state kind of level.

I'm going to gloss over this. This just says we have actually already generated the data sets, working directly with the National Library of Medicine and groups there who are trying to standardize data dictionaries that can be used in an electronic medical record environment.

That's the way we approach virtually all the common data elements for developing for

the conditions, is to build something that's much more long-lasting, by paying close attention to how it integrates into these EMR environments, where manufacturers are ultimately obligated to use those data dictionaries to support their platforms that are being used for EMRs.

So R4S is really what we use at the initial stage of the pilot, when the states are beginning to initiate their pilot screens. As Jeff said, this world of definitional stuff that we have to sort out, that distinguishes analytical pilots that states always have to do after something's proven in the clinical pilot. So we're going to be addressing some of those things in the work group.

R4S is a web-based database, collects and displays data. It allows quality improvement in newborn screening, discovery of new markers, when you have really a vast number of analytes that are being captured by the various laboratories, and then prospective

collection of data in pilots.

It's international. This is what the web site looked like at least until this week, when it went through a revision, and I didn't have time to change out slides. But you can see that it's used by a number of different groups who are resourced differently. We're the greenish in the middle right now, where we did the SCID pilots and we're working in the LSD area now.

Nice data display. This is one of the most attractive features of it really. Nicely integrated, statistical programs and data display. This SCID pilot was -- I think the only message I want to deliver here is actually I think relates to the pace at which this happened, when we had an organized set of pilots going on.

You can see as Carla mentioned when she spoke, CDC funded Wisconsin, or Wisconsin initiated some work themselves. Then CDC funded Massachusetts and Wisconsin, and I think

you can see in each of the bars more states being added. The first four are really states that were funded initially by CDC, then NIH funding, which really increased the number of infants supported by the pilot tremendously.

Then you can see expansion in the states as the data came in, and the Advisory Committee recommended inclusion of SCID. I think that's a relatively more rapid pace than we've seen, certainly for those early phases, where we had multi-state involvement and much larger numbers of babies participating in the pilot.

That's where we are today. That's just for your information in the file on SCID screening across the country. A message I wanted to draw out of this slide is this is basically two million babies having been screened now in the SCID pilot, and continuing on a bit after that.

It's not so much the incidence rate, but this vast number of conditions that are

diagnosed out of a SCID screen. It's a functional assay of human ability to do recombination of your immunoglobulin genes, and there's lots and lots of disorders. You can see how getting robust data on everything that might come out of a screen of a functional type is really quite substantial, and you won't get comparable levels of data about all of the potential outputs of a SCID screen.

But that's something that we're having to think about. How do we have more of a post-marker surveillance kind of data acquisition, that allows us to act on good data initially, and then make sure it's holding up over time, which can happen through the systems that are being built.

I'm going to skip that. That's just more detail about the various types of conditions that have been identified in SCID screening. Quickly turn to the Pompe pilot. NICHD funded several states to initiate that. Some states had already mandated some of the

LSDs in newborn screening. All have agreed to participate in this pilot that we're now developing.

The NICHD funded programs, where Emory University, working with the state of Georgia; New York State, which began screening on October 1st; and Wisconsin, which is in the process of bringing the screening online. We have Illinois that has mandated LSD screening and Missouri which began in November. All of their data is being brought into our databases to support the pilot, and then more broadly Melissa Wasserstein at Mount Sinai received a grant from NICHD to support pilots in LSD done in a group of hospitals, I think four or five hospitals in the New York City area.

But even at that, it's 80-90 thousand babies have the incidence of some of these conditions. Not a whole lot are going to be coming out of that particular pilot.

I'll skip that. So we have some unknowns, and Jeff's already alluded to some of

these. The consent issues in the Newborn Screening Saves Lives Act, we'll be watching to the extent that they utilize dried blood spot material and they will if we're doing them actively within programs.

We'll have to wait for OHRP to rule on how it's going to apply the common rule to specifically newborn screening, which was an interesting way of having asked them to address this, was to be specific to newborn screening.

Then there's the area that the FDA has recently become more involved in around laboratory-developed tests, which most of the tests done in newborn screening are, and because FDA has decided that LDTs all under its authority for oversight, they now oversee newborn screening-based laboratories that are using LDTs, as opposed to products that have been approved and cleared out of FDA.

So both of those are things that are in development right now, that we'll be keeping an eye on. The specific rules that relate to

our pilots are that HHS has -- is addressing the common rule, and it's going to require that federally funded research that I'm not going to go into. Jeff's talked about the fact that it is federally funded research that is really captured under this particular set of rules. OHRP theoretically could broaden that, I guess.

So just to give you a sense of this pipeline that I've become more concerned about, because we are there to support people who are receiving grants in this area, and people who -- I mean our contract does support some of what we do, but we're now beginning to be asked to do more and more, and are having to figure out how to work with grantees to build some limited funding into their own grants, that allow us to adapt our tools to their work, as opposed to expecting us to just take on everything, because we clearly won't be able to do that.

So if you look right now, we have about 31 primary conditions in newborn screening, 20 by tandom mass spec, three

hemoglobinopathies, nine other conditions. You see the two most recently added functional assays of SCID and CCHD. 26 secondary targets that could be diagnosed from having screened for those primary conditions.

I think if you look -- I'm going to page through this. So that gives us a total of 57 conditions potentially being identified out of newborn screening. As we go to begin to look at really where this seems to be going, here's a quick, another 16 that are pretty well on the launch pad. Some have issues of the paradigm that justifies newborn screening for a particular condition like Fragile X, where a lot of data still needs to be generated.

Others are really right on the cusp of going into pilots. That gets you up to about 74 conditions. If you take just that group that's called the LSDs, there's -- what is that, 10, 13, 14 or something individual conditions that are ready for consideration for newborn screening. That puts us up to 87

potentially.

As we look at adrenoleukodystrophy that's already mandated in some states, and is obviously up for pilot studies, that's a number of different potential conditions being diagnosed by the screen. Creatine defects, another one where multiple analytes downstream of a creatine assay.

You take all these together and there's well over the potential for 100 conditions, somewhere probably in the neighborhood of 110 or so that could potentially be in newborn screening, as they move their way through the pilots, because these are the ones closest to needing those pilots done.

So obviously capacity-building is going to be important. I wanted to include those slides, so you begin to think about what's really on that pipeline coming through this committee potentially, because I don't know that we have the capacity right now to

deal with everything that's coming up.

You know, there's some things that aren't clear yet as to where the boundaries between newborn screening quality improvement versus research. When I listened to Carla's talk, I thought much of what she was doing was quality improvement as opposed to research. But those are lines that I think are going to have to be drawn somewhere on OHRP's activities.

There's a lot of new opportunities. Developing the Precision Medicine Initiative that the President announced a week or two is a data collection activity, and newborn screening, despite the fact that it is the most vulnerable population one could imagine, has the potential for a very unbiased ascertainment population.

No issues about diversity in the population. If you screen positive or diagnose with a condition, you become part of these kinds of assessments. Then how do we integrate

this ultimately into a learning health care system, because that's really what post-market surveillance is about, is how do we continue to build up data that allows us to do a better job with the next patient we see coming out of these kinds of programs. On that, I think I am done.

MEMBER BOTKIN: Thanks, Mike. I think we'll forego any questions right now -- oh Tiina?

DR. URV: (off mic) -- me to remember to remind the group that one of the things that NICHD is doing right now is Alan Guttmacher, our director, has called a meeting for March 9th, that brings together federal representatives, representatives within the community, the newborn screening community, to directly address the concerns related to this.

So there will be a meeting on March 9th. There will be information forthcoming afterwards, where we're really going to discuss a lot of these issues as they relate to the

federal government and our implementation of programs, as well as how they will impact the states and other individuals that are involved as well.

So that will be on March 9th, and look perhaps there can be a report at the next Secretary's committee meeting coming out of that.

MEMBER BOTKIN: Good, thank you. I think what we'll do is turn to Anne Comeau now, and my understanding is Anne was detained through some weather anomalies in the Northeast. They got more than a couple of inches, I guess, so Debi, are you going to run the slides or should I do that?

MS. SARKAR: I can.

MEMBER BOTKIN: Anne, are you with us? Maybe the phone lines are down too. Anne?

DR. COMEAU: Hello.

MEMBER BOTKIN: Hey, how are you? This is Jeff Botkin.

DR. COMEAU: Good. I'm glad I got

on.

MEMBER BOTKIN: Yeah, good to hear you're with us. You're on deck.

DR. COMEAU: Yeah. Wish I was there. Next slide, please. I want to thank the Committee and the Pilot Studies Work Group for inviting this presentation. Many of us who run newborn screening programs, and all of us who run ahead, generating and validating quality improvements, welcome the opportunity to be the presenters of what we do, and to talk to you about what we'd like to do and how we'd like to work together to do it. It's good to have representation.

Can I have the next slide please? I want to emphasize that the data that you'll see in this presentation is by far not comprehensive. I'm giving you just a sampling of what goes on, and furthermore, to bring forward that I might have some opinions that other people do not have, do not share. So what is on the slides is approved by other

people, and what I say I own.

Next slide, please. When asked to present to the Committee, I started with a small group of colleagues which grew, and these colleagues have different interests, different resources and different state rules.

Next slide, please. Before I go any further, I'd like to remind the Committee of this 2006 publication, in which we anticipated one of the more problematic issues in moving forward.

Next slide, please. Language, and for the purposes of this presentation and in response to the Secretary's inquiry about states' readiness and willingness to run pilot studies, I'm using the following definition of pilot studies: A pilot program or a pilot study is an evaluation of the clinical merits of a particular newborn screen.

Two questions that need to be answered are that of clinical validity and clinical utility. When run at a population

level, is the test valid, and is the effort worthwhile. Next slide, please.

In contrast -- that this is in contrast to what I would call a pilot phase, which is an essential part of any laboratory development or quality improvement. But here, the focus of the evaluation is the marker. Can we measure the marker? Can we see the marker? Can I still see and measure the marker when I'm running the test in a high-throughput situation?

Next slide, please. Let's go back to the focus on clinical merit. Here's a sampling of two early sets of pilot studies that yielded expansion of newborn screening panels. These pilot programs were identified research. These studies were largely initiated by states, working in concert with their clinical consultants.

For CF, the pioneering work in Colorado and Wisconsin set the stage. The Wisconsin clinical trial paved the way for more

study, and the Massachusetts pilot, using a multi-mutation panel, showed that this could be done, and that it could be done responsibly.

We did this in Massachusetts. We did this with consent, even though it was statewide. This led to the 2005 recommendation that CF be added to the newborn screening panel.

For metabolics, Massachusetts pilots were introduced to study the benefit of tandem mass spec screening. It was a study, and we were using -- by using a study, we were able to begin to study the clinical utility of tandem mass spec, again in concert with clinical experts. We used consent.

These studies did not turn on a dime. It took time and collaborative effort. It took a continuation of initial efforts by other states, in order to bring in more numbers. It took collegiality, non-judgmental assessment. When things did need to be fixed, the states helped each other.

Next slide, please. Again, this is only a sampling of some of the continuations that were made possible by state to state sharing, by training courses, by some kit development. Funding was an issue, and unfortunately in the early days, some of these pilots' continuations were compounded by some unfounded and widely publicized criticisms.

Next slide, please. I don't want to ignore all of the other work that goes on behind the scenes pretty much consistently in order to keep programs going, up to date, and improved. Again, this is just a sampling, and again this particular slide focuses on the pilot phase or studies of markers. And as you can see, there's a wide range of activities in a wide range of states.

Most of the activities result in implementation. Some of the activities result in FDA clearance of kits. Some of the activities were set aside because it didn't work. This is a most essential, a basic

expectation for quality improvement services that we provide.

Next slide, please. There's more, and again this is just a sampling and just the beginning of things that are going on with sequencing, and it's also a set of studies and a set of implementations that states are taking on, that has -- that does not have inconsequential costs.

Next slide, please. Let's go back to the primary focus, to the studies of clinical merits, and states' willingness and capacity to perform pilot studies that address clinical merit. Again, this is identified research. Again, these were initiated, designed, and implemented by states working with their clinical partners.

In this case, CDC funding of the initial pilot generated the preliminary data and SCID was added to the RUSP in 2010. NIH funding of continuation pilots to generate larger numbers facilitated a faster generation

of national data, to support the RUSP recommendation.

But I think that again, looking at the outcomes of those SCIDs, was really quite a success story. We have to -- since we're doing studies, we have to be prepared for the idea that not every study will have implementation as an outcome. Clinical utility is not a given. It's something we hope for, but we're doing studies.

Next slide, please. Then we have the interest in LSDs, and I have to say some pretty serious issues relative to legislative mandates.

I'd go so far as to say that despite a pretty good track record of the states in bringing forward new conditions, the recent preponderance of legislative mandates appears to suggest a break in trust that the states and their clinical partners will do the right thing.

So politics has entered public

health. I happen to think that's unfortunate. There is a process that works.

Next slide, please. I do believe that states are very interested in doing the right thing and in doing it right. A few years ago, in response to a request for a statement -- excuse me, in response to a request for a statement of capabilities to run pilot newborn screening studies, three states, Massachusetts, New York and California joined together and submitted a single statement, recognizing the versatility in a consortium of states with demonstrated experience and expertise with pilot screening studies.

Our vision was a grassroots kind of state consortium, to allow innovative development of screening for sets of new conditions that piqued state newborn screening programs' interest.

Next slide, please. So here's a set of some interesting quotes from my colleagues. Clearly, we have to begin somewhere. Some

people like to test the waters and some people, some states like to swim in tested waters. That's okay. We have a strong history of sharing our experiences while improving.

There's frequently a lack of quality control and proficiency testing materials, which means that you have to be able to produce and verify your own materials. This is for early stage pilot studies.

Next slide, please. The biggest challenge was the absence of experience with newborn screening for LSDs by other states. Of course that's a big challenge, because we rely on data sharing and experience sharing. Our attorney also felt that all of the negative results should be sent to the hospitals for inclusion in the baby's medical records.

Since we were working offline from our LIMs, this became problematic for us. So this is some of the practicalities of implementation of early pilot studies.

Next slide, please. Budgets are

generally very tight. That's not news, which makes it difficult to hire staff with the proper expertise and design -- to design and carry out pilot studies, or while not generally a problem in our state, there's often a lack of clinical specialists to ensure that infants who screen positive will get the appropriate confirmatory testing and are properly diagnosed.

Next slide, please. We would have liked to have brought on SCID. These are some comments having to do with legislative mandates. But were forced to bring on something else. Or hospitals refused to participate. Only 50 percent of infants were screened, and we decided never to do a consented pilot again. We spent almost two years with no mass spec.

So that would be in contrast to the Massachusetts experience with consent, which has worked very well. Another state's experience with consent was a major challenge

for them.

Next slide, please. And finally, in addition to the challenges with the FDA rules and you might have noticed that some of the previous comments noted that most pilot studies begin with laboratory-developed tests, because one rarely has a kit to apply to a study of clinical merit.

We have the -- we have the new amendment to the Newborn Screening Saves Lives Act. Finally, this new kind of legislation, we're going to have to deal with it. It shows good intentions with challenging outcomes. But we'll make it work. We have in Massachusetts done consent-based studies, and it's worked for 15 years. Either that will work or something else will come forward.

We have a good service. It gets better through research, and getting better engenders the trust that we need to go forward. I think it's okay. I think the major problem that I see with this particular wording in the

Newborn Screening Saves Lives Act is the issue with the de-identified specimens, because everything else that we've described about the clinical studies for the pilot studies evaluating clinical merit were done with -- as identified research. Thank you very much.

MEMBER BOTKIN: Thank you Anne. So really excellent panel presentations. Gives, I think, a clear sense that there's a lot of excellent work going on here. Do we have time for any questions?

CHAIR BOCCHINI: Well, we're running behind, so if we can limit it to just one or two questions. I think at this point, based on the presentations, we've been given a very good idea of what's going on and what the potential is and where the problems are. So I think that moving forward, I think I commend the Committee, the Work Group for what's coming forward, and look forward to additional -- some recommendations and organization as we go forward.

But I think if there are any brief comments or questions at this point, because we are behind.

MEMBER BOTKIN: Let me just say from my perspective this wouldn't be a question now, but I think something we'll pick up with the Subcommittee is the question of how these different entities decide on what's up for a pilot study, and how those systems that are developing here and being funded can best coordinate with this committee, so that we can work as seamlessly together as possible.

CHAIR BOCCHINI: Great. I think that's the outcome that we're looking for, and it's very clear that the organizations are speaking together, and I think that's really good.

MEMBER BOTKIN: Yes sir, Don.

MEMBER BAILEY: I just wanted to thank Jeff and the whole panel for doing this. I think this is really important, and obviously the pilot studies are essential to moving

forward on any of these activities.

I think, you know, this will keep coming up as we talk about the matrix, and the feasibility phase of this Joe, in terms of the one, two and three rating and how the pilot studies fit in to when and how we do a three versus a two versus a one.

I was hoping you might be addressing that in the context of this presentation. But I think that will be something going forward. But I think clearly we're going to be in a position where a lot of conditions might meet the benefit criteria, but it's going to be very hard to implement. When and how we, you know, fit that into the whole system with pilot studies I think is going to be an important consideration.

Public Comments

CHAIR BOCCHINI: All right, thank you. And again, thank you for bringing us up to date on where we are with that. We have a few public comments. We have two public

comments by phone and then one in person. So we're going to start with Sarah Wilkerson, whose topic is timeliness in newborn screening. If you would identify yourself and indicate if you have any affiliations.

Operator, can we open Sarah Wilkerson's phone line?

OPERATOR: Sarah's line is now open.

CHAIR BOCCHINI: Thank you. Go ahead, Ms. Wilkerson.

MS. WILKERSON: Thank you. Can you hear me okay?

CHAIR BOCCHINI: Yes, we can.

MS. WILKERSON: Great, thanks. Thanks so much. I'm Sarah Wilkerson. I'm a mother and a member of the board of the Save Babies Through Screening Foundation. My son's story was featured in the *Milwaukee Journal Sentinel* a little over a year ago.

I've spoken to this group multiple times about my son Noah, who died at a few days old due to undiagnosed MCAD. His disorder was

not identified in time to save his life, due to the state lab in my home state of Colorado being closed over the weekend, adding unnecessary days to his test results.

I want to sincerely thank the Laboratory Standards and Procedures Subcommittee for all of their hard work over the last year or so, researching the issue of timeliness in newborn screening, and I'm so very pleased with the direction that this project has taken. The guidelines that have been created and refined are sorely needed to cover the basis, to set labs and hospitals on their way towards saving even more lives and staving off disabilities.

I understand that the Subcommittee will be presenting their guidelines to the Committee shortly, and I want to encourage the members of the Committee to vote to move them forward as a recommendation.

There have been many states across the country who have already preemptively

stepped up and done really tremendous things to clean up their policies on their own, which has been so amazing to watch, though many other states have not responded at all and could use this guidance from you.

My own state of Colorado is one that has yet to respond, for example. Many of you may remember that I was pregnant last time you saw or heard from me. I had my daughter in October, and she's doing very well, though her test results, which should have been fast-tracked through the system due to our known risk of MCAD, ended up taking a day longer than her brother Noah's test sample did.

Clearly, my state has gotten worse rather than better in regards to timeliness, though I did just learn that they were chosen for the NewSTEPs Collaborative Improvement and Innovation Network for Timeliness in Newborn Screening Program. So many thanks to the program directors for selecting them, and for also being similarly aggressive at helping

states improve.

Colorado aside, I continue to hear stories from other families and states across the country as well, where the courier system isn't used, batching happens, or other delays exist that can put children at risk. I believe that this best practice guideline for everyone to follow and hospitals and labs will really help.

Again, thank you so much for your hard work. I am so eager to hear the presentation later, and feel hopeful that it will meet the requirements of the Committee, so that this project can continue to move forward and help put this issue in the system to rest. Thank you.

CHAIR BOCCHINI: Thank you for your comments, Ms. Wilkerson, and congratulations on the birth of your daughter.

MS. WILKERSON: Thank you.

CHAIR BOCCHINI: And as you indicated, we will hear the final report from

the Subcommittee and look at the recommendations, and we should have a vote today. So thank you.

MS. WILKERSON: Great, thanks.

CHAIR BOCCHINI: Next we have Ms. Elisa Seeger, whose topic is ALD. Operator, can we open Ms. Seeger's line.

OPERATOR: The line is open.

CHAIR BOCCHINI: Thank you.

MS. SEEGER: Hello?

CHAIR BOCCHINI: Yes, we can hear you.

MS. SEEGER: Okay. My name is Elisa Seeger, and I am the founder of the Aidan Jack Seeger Foundation. On March 29, 2013, New York State signed Aidan's Law, in honor of my son, who lost his life to ALD in 2012. He was just seven years old. On December 30th of 2013, New York started testing all newborns for ALD.

In the first year of ALD testing ending December 31st of 2014, New York had identified nine boys and six girls with zero

false positives, giving these children and their families the information necessary to save their lives. The New York Newborn Screening Program has proven the efficacy of the ALD newborn screening test.

With approximately 250,000 babies tested in 2014, we can safely say the ALD newborn screening test is working and should be added in every state. Imagine that your son did not have the same chance as a baby born in New York. Imagine knowing that your zip code dictates whether your son will live or die.

I will forever be grateful to everyone in the New York State Newborn Screening Program that has made ALD testing not only possible but also a priority. Not only have they taken the step to be the first to test for ALD; they have worked diligently to make sure protocols are in place once a baby is diagnosed.

In the nine months preceding testing, the New York State Newborn Screening

Program researched and created management protocols consisting of identifying nine metabolic centers throughout New York State for initial referrals; identifying geneticists, neurologists and endocrinologists in each of the nine centers; created diagnostic guidelines, surveillance protocols, treatment initiation recommendations, parental educational materials and methods for long-term follow-up.

The ALD newborn screening manuscript has just been published, and is readily available for review. It is clear New York State has set the example every state can follow. The New York State Newborn Screening Program is willing to share their data so every state can test for ALD. We know that early diagnosis is the only way to save lives. Every 36 hours another baby will be born with ALD.

In just the last two weeks, in my limited interaction with the ALD world, a 45 year-old professor from Virginia died from ALD,

leaving behind his wife and three children. An 11 year-old boy from Arizona lost his battle to ALD on Monday, and with a diagnosis for his older brother, who also has ALD.

A family from Louisiana took their six year-old son in for evaluation, and were given a death sentence for their child, as he was too far progressed for treatment. All of these lives forever shattered, such as my own life, because of this disease. ALD is an epidemic, an epidemic that can be stopped with a simple test.

All of you sitting here today have the power to add ALD to the Recommended Uniform Screening Panel quickly. Please expedite the evidence review process and make the decision to add ALD. Please give all the future boys born with ALD the chance that Aidan and so many others did not have, the right to a normal, healthy life. Thank you for your time.

CHAIR BOCCHINI: Thank you Ms. Seeger for your presentation, and we appreciate

your input. As you know, we will hear an update from the Evidence Review Committee shortly about the status of the evidence review. Thank you.

Now here we have Dr. Amber Salzman, whose topic is ALD. Dr. Salzman.

DR. SALZMAN: My name is Dr. Amber Salzman, and I lead the Stop ALD Foundation. I come before you today in support of adding adrenoleukodystrophy to the Recommended Uniform Screening Panel, and in hope of accelerating the process to get it there.

Thank you for allowing me to speak today, and for the continued time and consideration you give to this very important matter. Many of you have heard my personal story that drives me to prevent others from unnecessarily experiencing the loss and heartache our family has.

I ask your indulgence in hearing it briefly again. My nephew Oliver was diagnosed with ALD at the age of seven, when it was too

late to intervene. He continued to decline and lost ability after ability, until he finally succumbed to the disease and we lost Oliver in a few short years.

My son Spencer was one year old at the time of my nephew's diagnosis, and thanks to the early warning, we were able to intervene. Spencer is now a healthy and charming 15 year-old taking Honors Bio, Advanced Math and swimming on his school's team.

I'm most proud of the huge commitment he has made to volunteer his time every week to help children with special needs. No day goes by that I do not think of the ultimate sacrifice Oliver made to serve as a screen for my son. With ALD newborn screening, all kids born with ALD will have an opportunity to be spared.

I have been attending committee meetings since we submitted the nomination to add ALD to the RUSP in mid-2012, and I'm

encouraged that the process has moved forward. However, I'm deeply saddened and alarmed by the knowledge that so many children have been born with ALD since that time, and have not been given the opportunity to avoid a devastating outcome.

Every 36 hours, another baby is born in the U.S. with ALD. If the baby is fortunate enough to be born in New York, where ALD screening is implemented, then their life may be spared. We must find a way to accelerate implementation of screening in the rest of the United States.

As I understand the new duties of the Committee, as outlined by Dr. Bocchini this morning, a decision needs to be made within nine months of a condition going to a Condition Review Group. Since ALD was moved to a Condition Review Group at the January 2014 meeting, it would be of great interest to learn what the proposed time line is for the ALD review to be completed.

The ALD newborn screening test and follow-up process works. It costs much less than caring for the children who are not diagnosed at birth. I speak on behalf of the many concerned foundations, individuals and scientific and medical professionals who are eager to help and support getting ALD added to the RUSP. Thank you for your prompt attention in getting this rapidly implemented.

CHAIR BOCCHINI: Thank you, Dr. Salzman for your comments. We certainly appreciate your continued support of this process. Now for this meeting, we've also received many written public comments, and so we want to thank those who presented and those who sent written comments to us, so that they understand that they are certainly considered and important to this Committee and to the work of the Committee.

So with that, I'm afraid we're behind schedule and so we need to take a break. And so what I propose, since we're behind, is

that we shorten the break to about ten minutes. So if everybody can be back in our chairs at ten minutes after 11, I think we'll get restarted. So thank you.

(Whereupon, the above-entitled matter went off the record at 10:56 a.m. and resumed at 11:12 a.m.)

Laboratory Procedures and Standards Subcommittee

CHAIR BOCCHINI: All right. Let's go ahead and get started. So we now have a presentation from the Laboratory Procedures and Standards Subcommittee. This is an update on the Timely Newborn Screening Project, and we have a vote scheduled for the final recommendations.

I think -- I was going to say I looked and the two chairs were empty. But both of the co-chairs, Kellie Kelm and Susan Tanksley are at the podium. So please start.

MEMBER KELM: Good morning. So we're here to provide you an update, and based

on the work of the Work Group and the Subcommittee, and we're going to start off with some slides, just providing the update to where we are now, and many of you remember this.

So a background on why timeliness in newborn screening is important. In order to effectively reduce disability, morbidity and mortality, newborn screening must happen before onset of symptoms. Newborn screening panels have changed, and include time-critical conditions. These are conditions that may manifest with acute symptoms in the first days of life, and they require immediate treatment to reduce risk of mortality and morbidity.

So the Discretionary Committee's Lab Standards and Procedures Subcommittee was tasked with investigating timeliness of newborn screening in the U.S. in September of 2013. The Committee received a public comment at that meeting, and based on that, we've moved forward with surveying states on current practices and reviewing guidelines and literature.

The media raised the issue nationally to the general public, the *Milwaukee Journal Sentinel* article in November of that year as well, raising the issue even higher. So this Discretionary Committee in January recommended or renewed the four recommendations from the initial report from 2006, 2005, that were these four.

Initial specimens should be collected at 24 to 48 hours of life. Specimens should be received in a laboratory within 24 hours of collection. Newborn screening results for time-critical conditions should be available within five days of life, and all results should be available within five days of collection.

So and at this January meeting, the Subcommittee was also tasked with these six items, to outline the system, investigate existing gaps and barriers, identify strategies to achieve the four goals, develop a list of critical conditions that require urgent follow-

up, to review the recommendations in light of new technologies and suggest revisions to the recommendations if needed.

So now I'm going to pass it over to Susan, who's going to talk about what we've done to meet those six tasks.

DR. TANKSLEY: Okay. So you've seen this diagram before, and this is just showing partners in the newborn screening system, and basically to reiterate that newborn screening is not done just at the state level in the state lab. It's not a lab and follow-up type issue.

It spans from the time a specimen is collected all the way through long-term treatment and follow-up. But it's also impacted by many other factors, such as advisory committees like this one, as well as payer sources and things like that. So we just need to keep all of those things in mind and partners as we continue to move forward.

One of the things that we did was to

outline the newborn screening system, and this diagram shows that process and all the different steps that are taken from the time a specimen is collected. So in the pre-analytical phase from when it's collected, all the way through the post-analytical, where you have that long-term follow-up and management.

Each of these steps can be measured discretely. But in order to be able to calculate some of these measures, we may have to put steps in place to actually make these queriable and be able to -- not just capture them, but be able to calculate them.

What am I doing here? All right, sorry. Okay. So as a subcommittee, we have a much larger subcommittee, but we developed a timeliness work group and the individuals are listed here, and included several individuals from APHL as well and HRSA, who spent a tremendous amount of time and effort on this. I want to thank them again for all of their work.

We had internal discussions within the Timeliness Work Group. We had discussions with clinical experts from hematology, endocrinology, pulmonology, and then we also had a huge amount of assistance from the Society of Inherited Metabolic Disorders, and they had a work group that put together a position statement related to this issue.

Oh sorry, full screen. All right. Sorry about that. Okay. So one of the first things that we did was to develop a discussion guide, and what we wanted to do was to be able to talk with states and gather information on what's the current status in regards to these recommendations.

So how well are you currently meeting those. What are the gaps and barriers that are preventing you from meeting those, and then what are some strategies or interventions that could be put in place or have been put in place that led to improvement?

We did this at both in-person

meetings. Two of those were at regional collaborative meetings. It was also done via webinars and some conference calls. Based on that information, APHL, with the help of the work group, put together a survey and that was fielded, and it was called the Newborn Screening Timeliness Survey. The full report is available in the briefing book, and that report was presented to you at the last meeting as well.

Now it's coming. All right. So one of the things we developed was a list of time-critical disorders.

So these are disorders that may present in the first week of life, with -- and so need to be reported as quickly as possible. Primary work on this was done by the Society of Inherited Metabolic Disorders, and we added to that with the endocrine disorder with congenital adrenal hyperplasia. So that's the only condition that was added to the work that the SIMD had put together.

As part of that survey, we received data from the states and all 50 states and one territory did respond to that survey. This is just a quick snapshot of the current status of those four recommendations. Each bar represents one state newborn screening program, and you can see the median values for those.

So the one that had the highest compliance at the time that the survey was fielded was the percent of initial specimens collected at 24 to 48 hours of life, with 82.2 percent being the median and the lowest was the percent of newborn training specimens being received within 24 hours of collection, with the median being 25 percent.

Okay. So some of the gaps and barriers that were pretty universal when you looked at the impact to all of those recommendations. One, which is still a huge issue and something that needs to be raised through education, is the lack of awareness of the urgency of newborn screening.

That's something that if you don't know it's urgent, then perhaps that doesn't make you want to do something faster. Regardless of where you are in the newborn screening systems, this is not just talking about laboratories and testing or not just the hospitals, but in regards to the entire system.

A lack of training and high turnover of staff performing dried blood spot collections. Batching by birthing facilities. You've heard that mentioned before. Simply geographic distance from the birthing facility to the newborn training laboratory. We'll give you one instance in Alaska.

Those specimens are transported to Oregon. That's done via courier, but there's not courier in all parts -- there's not a standard courier in all parts of Alaska.

So those have to be transported to the collection point in Alaska and then sent to Oregon. Lack of availability of courier overnight delivery services, operating hours of

the courier. So there are weekends -- there are some couriers who don't operate on weekends. There are some couriers who just don't operate on Sundays. There are holidays for standard couriers.

So unless you have a courier set up specifically for newborn screening, those will continue to be issues. Operating hours of the newborn screening program. You've heard that today already. Lengthy testing algorithms, where we're actually trying to avoid high false positive rates.

So we have to be careful that we don't negatively impact the system by just trying to be faster. So there are second tier or third tier algorithms that happen in the laboratory, that may be done to try to decrease your false positive rates. A higher false positive rate is going to negatively impact the rest of the system.

Lack of ability to collect complete data. That could be the demographic data

submitted on the forms when they come to the laboratory. That could also be the ability to collect data at each point in the system, so that we can actually measure -- accurately measure and try to improve based upon that.

There are also a lot of inefficiencies of the system, and I mention two of them there, where specimens have to be dry before they're transported. But if they're not dry at the time that courier comes, then they're going to have to wait an entire day before they come -- before they can be picked up.

Okay. So some of the common strategies for improvement, and the two highlighted in yellow were ones that pretty much were mentioned by almost everyone. One utilized the courier overnight delivery services, and to expand newborn training program operating hours. That's not only laboratory but also someone to call out those results, especially those for those critical

conditions.

Two, provide educational activities to birthing facility staff, the laboratory staff and to parents. Again, we're looking at systematic approaches here. Improving reporting and communication mechanisms. So electronic ordering and resulting is something that's vital here.

If the demographic information is there when the specimen is received at the laboratory, those specimens can be processed more rapidly as well. And again, getting the results out faster so that they can be acted on faster as well.

Focusing on CQI activities, both at facilities and at the laboratories and in the newborn screening programs. Just some of the things that can be done. Improving data collection, which we've already talked about, and then providing that feedback to facilities, and making sure that it's monitored.

So provide the information, but

what's done with that information? All right. Turn it back to Kellie.

MEMBER KELM: All right. So we had already presented our new recommendations at the last meeting, and they have had some slight tinkering for what we think is mainly clarity purposes. But I wanted to restate them here, and these are also the ones that are in the report that you have in the briefing book.

So as we had talked about before, we actually, in addition to sort of changing some of them in order to make sure that we focus on what the --- on the newborn as well as focusing on the conditions that are important, we changed the order in the order we thought to change and focus these recommendations where they needed to be.

So here we sort of grouped them as A, as the overall goals, and then B, sort of what we think of as technical or goals that need to be met in order to meet the ones above in A. So to achieve the goals of timely

diagnosis and treatment of screen conditions, and to avoid associated disability, morbidity and mortality, the following time frames should be achieved by newborn screening programs.

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

And B, in order to achieve these goals, number one, initial newborn screening specimens should be collected in the appropriate time frame for the newborn's condition, but no later than 48 hours after birth. Number two, newborn screening specimens should be received at the laboratory as soon as possible, ideally within 24 hours of

collection.

So issues that we need to work on as we move forward in order to help improve this -- improve the whole system, is to continue and expand our collaboration with the American Hospital Association and possibly the Joint Commission, to work on collection and transport inefficiencies at hospitals.

Also develop recommendations based on communication of newborn screening results, whether a presumptive positive or for normal to the family of the infected infant. We had a lot of feedback from the Work Group from the experts that we talked to about some issues with communication, and I think that that was something that we thought we couldn't address within this report.

But I think, you know, we heard needed a lot of work in order for us to really meet these time lines, as some of the communication pieces were still an issue. The continued need for improved standardization of

reporting procedures and statements.

We found out within, as we were working on the survey and moving forward, is obviously, you know, different terms, different definitions, different ways of reporting. You know, I think like what we did with case definitions. I mean I think a lot of standardization of terms and things, so that we can get the same data and move forward together, rather than states comparing apples and oranges and doing things differently.

So moving forward, these recommendations are goals for the systems to achieve the best outcomes for affected infants. As Susan said, this newborn screening is a system, and the parts must work together to achieve the best outcomes. So we must remove the gaps and mitigate the barriers, follow the examples of other states, get buy-in from everybody in the system.

Funding is an important piece for that, and it's critical that as we work to

improve timeliness that we achieve a balance, so that as Susan said, we don't negatively impact the system by moving to vote too fast, that we could impact other, you know, create other inefficiencies or issues.

So we do want to acknowledge the Work Group, the lots of help that we got from APHL, our Subcommittee, SMID and all the experts that we talked to. So I think that's it. I can go back and put the revised. And I should say that we did hear and we should specify that the -- that these goals are for the initial screen, the first screen and may not, you know, we can talk about.

But we didn't really touch on the second screen, those states that do second screens. So anyway. So I don't know if we have any discussion, comments, questions. So -- and I forgot to add. So the report that has gone through the Subcommittee is in a briefing book, and obviously the Committee has only had a few weeks to look at it.

If you have any other comments, concerns, edits that you see that are needed, Debi's offered to be the recipient of your emails. We would appreciate any feedback that the Committee could provide on the report that we have provided to you. So thank you.

CHAIR BOCCHINI: Well first, let me thank you both, because I think that this was a very formidable challenge here, and I think you balanced things very well and came up with a strategy to address these issues in a very nice way. So I think we've come to some very good conclusions in terms of suggested recommendations, and then have a plan for what else needs to be addressed in the future going forward.

So I appreciate your work and that of the Work Group and the Subcommittee. So thank you. So these are open for any discussion, first from the Committee and if not, we'll take -- okay, Jeff.

MEMBER BOTKIN: Now we had a little

bit of discussion about this, I think, at the last meeting. So maybe just to remind me what the thinking is. So these are recommendations that are really coming from us, largely to birthing facilities, health care, the newborn screening programs and sort of laboratory, that nexus of service there, and it hasn't so much included the primary care provider.

So the recommendation sort of ends once the call is made to the primary care provider. I guess I still have some concern about potential delays between that call and getting the family in for confirmatory testing, and to the extent that many primary care providers may not be adequately informed or incentivized to understand that this can be a very big deal.

So what are your thoughts on that issue? Is there an opportunity to speak to some of the primary care organization groups to enhance education about urgency in these contexts?

MEMBER KELM: So we hadn't thought about that. And I do think, and as I mentioned, I mean we heard from the experts on issues with communication and that piece missing, and then further along. So we didn't touch on that here, but I do think it was something we put as something that, you know, and I know we definitely had a lot more written in the report, that it definitely needs to be followed up on.

But I think that the obviously our task was mainly to work within this time frame, and I know that we have talked about needing more work for, for example, working potentially with hospital and birthing facility people, and that we didn't have those members in our group, and the same thing with follow-up.

So we didn't have any -- there were no recommended ideas about, for example, goals, timely goals for that. But I do think that that was something that came up several times, was that we needed to improve communication and

potentially work, once this process is done moving forward, the next steps.

CHAIR BOCCHINI: Okay. So I have Andrea and then Dieter.

MEMBER WILLIAMS: So I have two things. One, I was wondering whose responsibility is it to do the education at the point of the hospital, and if they fall outside of this guideline or this goal, who enforces it? What happens then?

DR. TANKSLEY: So there's a tremendous amount of education that's done by the newborn screening programs. I'm not sure how we expand that further. I think we do need to expand it past the sole responsibility of the newborn screening programs.

There are some hospitals that have really good education programs for their own staff. I've been at a hospital and I thought it was fantastic, and I thought wow, that would be a really good example for the entire nation. But how do you -- how do you set those things

up? How do you maybe set up some nationwide type education things?

I think you have to reach into some of those organizations like the AHA, in order to do that. We don't really have that inroads. I know APHL has begun some work with them. I think we need to further or expand some of those relationships, and we've talked in this group about having some Joint Commission measures perhaps.

But we've -- we haven't been able to get there yet. So if anyone has ideas about how we may expand those relationships and have those discussions, that would be very helpful.

MEMBER WILLIAMS: inaudible

DR. TANKSLEY: As far as enforcement, I mean there really -- there is not much enforcement. I mean it is a state-mandated, state-required test, state-run programs. So it really depends upon the state and what they have in their regulations. So if there's an enforcement within the regulations

of that state, they may be able to have some enforcement ability.

I'm from Texas, and we don't have that in our statute, where we can enforce that at this point. So that would be state by state, where there would be enforcement, unless there's something that's more like a Joint Commission standard.

CHAIR BOCCHINI: And so I think it's clear that there are a number of things that the Committee can tackle going forward, and that certainly we may need -- we certainly need to tackle with our partners, who are stakeholders in this process. It could be the Joint Commission, it could be others and so this -- these recommendations won't solve all the problems.

But I think they give a framework for how we believe that specimens should be obtained and sent and processed, so that we get the best outcome that's possible, given the current way things are done. Dieter.

MEMBER MATERN: You know, just to comment, a response to Dr. Botkin's question about whether we should have considered what the provider actually does with the information they receive from the newborn screening program.

But in my opinion, the laboratory that provides the results or communicates the results, and as stated here, immediately and about time-critical conditions, should include information that you really have to act immediately.

And so I don't know if there's anything in addition that needs to be done, except that really that that communication is clear, about action is immediately required.

CHAIR BOCCHINI: I was going to take two more comments. Carol and then Natasha, and then we need to see if we're ready for a vote.

DR. CAROL GREENE: Before the vote, I just wanted to be real specific about something that was mentioned just a moment ago.

To avoid any confusion, I propose that -- I'm a liaison, but I really think that the Committee needs to consider that number three should read "all initial newborn screening tests should be completed within seven days of life."

Otherwise, you're going to have in the preface that it's only relating to initial screens, and people will take it separately and they'll be confused. So it's been very clear language, and I think that would be in the recommendations that you vote on, and also in the paper, because I think that was the intent.

The other thing I would just add is -- and then I'll pass the microphone on, is within the context of the hospital, once these recommendations are published and once they're accepted by the Secretary, they are recommendations that are out there and I'm all in favor of JCAHO and more education.

But we should also empower people to take those recommendations and go to risk management, and the lawyers of the hospital

will make sure it happens.

MS. BONHOMME: No response to that. This is Natasha Bonhomme of Genetic Alliance. Thank you so much for presenting this. Again, this is such an important topic. One thing I wanted to at least go back to is, you know, here we're setting recommendations and have a policy national level. But education and newborn screening does happen at that local level. It's about what's happening in those nurseries.

So I really encourage you to, even if there wasn’t anyone on the group that pulled this together who had those contacts or relationships you felt with those different nursing groups, or the people who really are there who have the blood spot in their hand, and it's really up to them if it goes out today or tomorrow.

There are other people in the room who really have those relationships. Baby's

First Test has done a lot of work in AWHONN, in terms of presenting to nurses, presenting to their leadership around these issues.

There are a number of advocacy organizations who are doing this type of work, working with their hospitals to raise awareness around newborn screening at their hospital level. You know, this is something that can be added to that.

So I really encourage you to look, you know, depending on where these recommendations go, but look to those partners who are more at that grassroots level, because that's really where the bandwidth is. We know there's turnaround or turnover and there's a lot of issues there in terms of education.

But there are groups of people out there who are eager and looking to do this work. So --

CHAIR BOCCHINI: All right, thank you. So with that, do we have a motion to accept? And I think since you had indicated

that it was initial testing, I don't think that's a problem for adding.

DR. TANKSLEY: Okay. I was going to suggest -- so we actually refer to days of life on the first three, on A1, 2 and 3. So perhaps in A itself, that statement in yellow, we add something to refer to initial screens. So perhaps "should be achieved for initial screens by newborn screening programs."

CHAIR BOCCHINI: Okay, thank you. That's -- we'll accept that, yes.

MEMBER MATERN: I'm concerned about the definition of initial screen, because you also mentioned that there are second tier tests that are applied sometimes. So is the initial screen the initial specimen or the initial test?

DR. TANKSLEY: The initial screen would be the initial specimen, and yeah. Perhaps we just need to define that in the paper.

CHAIR BOCCHINI: Okay. Steve.

MEMBER McDONOUGH: Thank you, Mr. Chairman. I'd like to thank you for your excellent report and all the hard work you did. I really appreciate the information for clinicians on time-critical conditions. That's going to be very helpful in all the recommendations for improvement.

I move that this Committee make the following recommendations, basically as stated up there, with the additional language changes to clarify the initial specimen.

I also recommend that each state newborn screening program adopt the following objectives. By 2017, at least 95 percent or more of newborns will achieve these goals, which are time-critical conditions be communicated immediately to the provider, no later than five days of life. Presumptive positives are to be communicated within seven days, and all initial tests be completed within seven days.

By 2017, this Committee would

recommend that all state newborn screening programs report annually to the Maternal Child Health Bureau in progress in meeting these objectives, and make available to the public the timeliness performance of hospitals and birthing centers in their states.

I also recommend that this Committee recommends to the Secretary of Health and Human Services, that the Secretary develop a grant program to assist all state newborn screening programs in implementing the above objectives, or in assisting in cost for state newborn screening programs in implementing new recommendations from this Committee, once they've achieved timeliness objectives.

CHAIR BOCCHINI: So that's on the table. Dieter.

MEMBER MATERN: Yeah Steve, thank you. I have one question. You mentioned that the public health or the program should inform the hospitals and birthing centers about the timeliness of the submission of blood spots, I

guess. But I would then also add that the programs inform the hospitals about their ability to return the results in a timely fashion.

MEMBER McDONOUGH: I would be happy to incorporate the annual reporting of --- the Maternal Child Health Bureau, the performance of the public health labs in meeting the timeliness recommendations and objectives.

CHAIR BOCCHINI: So your comment was specifically that the public health labs inform the hospitals of the ability to meet --

MEMBER MATERN: So the way I understand it is the way it is right now in Minnesota, where the state twice a year provides information to the hospitals on how well they are or how well they're doing with respect to timely collection and submission to the laboratory of the samples. But we don't hear back as to how they're doing with respect to returning the results to us.

MEMBER BAILEY: So I support the

essence of Steve's motion here. I think -- I don't know what part of this has got more implementation and what more is our official recommendation. I like the idea of going beyond the recommendation to say here is what we're wanting to achieve long term, and I think less than 95 percent and by a certain date, you know and also --

So I like the concept behind it, and support all the suggestions you've made, Steve. I don't know if that -- again, I don't know if there's some of this that needs to be broken apart from implementation and recommendations. I would defer to you, Dr. Bocchini, on how you want to move on this. But I'm glad to second that, if you think that's -- it's appropriate to include all that in this.

CHAIR BOCCHINI: I think it's appropriate. If you second that, I'll divide it into two parts. So Part 1 will be specifically the recommendations with the modifications as indicated, to address the

issue of making sure that there's an understanding of initial specimen, and then the second will be -- so we can have two separate votes on -- so the second part on Steve's recommendations for setting guidelines and for what states should achieve.

So with that, with the second, then let's -- I guess we need to formally go around the table for a vote.

Is there additional discussion? Cathy, and then Charlie.

MEMBER WICKLUND: Yeah, this is Cathy, and I'm not objecting to Steven's comments or what he's suggesting. I'm having a hard time without seeing them and really thinking. It's a little extra information, I guess, that I don't know if I'm prepared to --

CHAIR BOCCHINI: Okay.

MEMBER WICKLUND: Yeah. I think that this should definitely be voted upon and kind of unpacked from that. But then I would like to see his recommendations. Oh nice,

okay. Thank you. Ask and ye shall receive. Yeah. Just wanting a little to think.

CHAIR BOCCHINI: Okay. So Charlie.

MEMBER HOMER: This may be more of an insider baseball question, but I guess I'm wondering if we're making a recommendation to the Secretary, what's the authority of the Secretary to exert these types of recommendations. In other words, for example in Medicaid, which I'm more familiar with, the Secretary can encourage the states to report a variety of things, but doesn't actually have the authority to do that.

So and maybe again, we could communicate our intent, we could make a recommendation. But I'm just trying to think if we'd like it to be accepted, if we can think through a mechanism that would probably facilitate the acceptance.

CHAIR BOCCHINI: So I think for Part 1, these recommendations are going to be the recommendations of the Committee. They're not

recommendations to the Secretary. They're recommendations of timeliness of collection of specimens and return of information that the Committee endorses.

So we're not asking the Secretary to weigh in on that. We're making those recommendations of the Committee. On the other hand, the issue about having the Secretary involved, and I like the fact that we need to nuance that the right way, because the Secretary cannot have states do that, if you can recommend that that happen.

So maybe we could vote on the recommendations now, and then look at the language of Steve's recommendation, hold that until we look at the language and then put it on the slide tomorrow morning as unfinished business, that we could then make sure everybody's comfortable that we're saying everything that everybody understands, and then make a decision concerning that. Is that fair? Did I answer your question?

MEMBER HOMER: Well, I think I take from that we don't actually have a clear mechanism yet, and we'll be thinking overnight between how we could frame this part in a way that would enable us to make a recommendation?

CHAIR BOCCHINI: For the second part.

MEMBER HOMER: For the second part of Steve's. So I don't want my comments to be taken as opposition to the content, to your concept, which I'm firmly supportive. But I just think if we want the Secretary to take action, we need a vehicle for it.

CHAIR BOCCHINI: Yeah I agree with you, and it's not taken in a negative way. We need to frame it in the right way, so that we're within what the purview of the Secretary is, as well as stating exactly what we want to have happen. So I agree. Coleen.

MEMBER BOYLE: Just some clarity on procedure, because what you said made me rethink a little bit. So for the first part,

the part that's before us, when we vote on this and if we accept it, is this something then we're asking the Secretary's endorsement of, or this is just Committee business? Okay. So do we lose some influence by not having an endorsement by the Secretary? Just clarity there.

CHAIR BOCCHINI: Well, I think we're certainly going to make the Secretary aware that this is a decision, that the Committee endorses these recommendations for timeliness of newborn screening, and what I felt was that was all we really needed to do. So that's why I set it up this way.

All right. Hearing no additional questions or comments, let's then proceed with a vote on the suggested recommendations for timely newborn screening. I've got to find my voting thing. I know Dr. Bailey doesn't like to always be the first one to --

MEMBER BAILEY: I'm very comfortable with this one.

CHAIR BOCCHINI: Oh, you're comfortable? Okay, all right, all right. All right. Then we'll go alphabetically, starting with Dr. Bailey.

MEMBER BAILEY: I vote to approve.

CHAIR BOCCHINI: Okay. I vote to approve. Jeff Botkin.

MEMBER BOTKIN: Approve.

CHAIR BOCCHINI: Coleen Boyle.

MEMBER BOYLE: Approve.

CHAIR BOCCHINI: Denise Dougherty.

MEMBER DOUGHERTY: Approve.

CHAIR BOCCHINI: Kellie Kelm.

MEMBER KELM: Approve.

CHAIR BOCCHINI: Charlie Homer.

MEMBER HOMER: Approve.

CHAIR BOCCHINI: Fred Lorey.

MEMBER LOREY: Approve.

CHAIR BOCCHINI: Michael Lu.

MEMBER LU: Approve.

CHAIR BOCCHINI: Steve McDonough.

MEMBER McDONOUGH: Approve.

CHAIR BOCCHINI: Dieter Matern.

MEMBER MATERN: Approve.

CHAIR BOCCHINI: Melissa Parisi.

MEMBER PARISI: Approve.

CHAIR BOCCHINI: Alexis Thompson.

MEMBER THOMPSON: Approve.

CHAIR BOCCHINI: Cathy Wicklund.

MEMBER WICKLUND: Approve.

CHAIR BOCCHINI: And Andrea Williams?

MEMBER WILLIAMS: Approve.

CHAIR BOCCHINI: Okay. So it's unanimous, and so we will take Part 2 as an open motion which has been seconded. We'll review the language so that we can make it clear, make sure everybody has a copy of it in the morning, and then we'll present it for further discussion and then a vote.

Evaluating Harms in Assessment of Net Benefits

Okay. So in the interest of time, I'm going to skip -- I want to just to kind of give an overview of the condition review

process as it stands now.

But I can do that at another time, to try and get us back a little bit closer to being on schedule. I'd like Nancy Green to come forward to make her presentation on "Evaluating Harms in the Assessment of Net Benefits: A Framework for Newborn Screening Condition Review."

Dr. Green is a professor of Pediatrics in the Division of Pediatric Hematology, Oncology Stem Cell Transplantation, Columbia University Medical Center, where she also serves as dean of Clinical Research Operations, and associate director of Columbia's NCATS-funded clinical translational science award.

She received her medical degree and her clinical training at Columbia University. From 2000 to 2007, she served at the March of Dimes as the national medical director there from 2002 to 2007. She returned to Columbia in 2007. Her federally funded research focuses

since that time have been on clinical translational behavioral aspects of therapies for sickle cell disease, policies and practices of population-based public health screening for newborns and genetic disorders. So Nancy, we'll turn this over to you.

DR. NANCY GREEN: Thank you very much, and I thank the Committee to allow me to make a presentation. So I want to start by saying that in evaluating the harms from newborn screening, this is not sort of a dour presentation.

It's really, you know, in the true nature of how the development of evidence review and decision-making was derived, that there was a balance of harms and benefits for the Committee to arrive at net benefit.

So it's really to sort of balance that consideration in a more balanced and complete way, an explicit way. So not to be dour. Is somebody advancing the slides, or am I doing this? The arrow at the bottom? This

one?

Sorry. I don't know my right from my left. Oh, okay. Thank you. Okay, thank you. Okay. Let's try this. Oh there it is. Okay, right, okay, and really to just have this as a -- to integrate the consideration of harms into the formal evidence review. Okay. So I would like to acknowledge my colleagues and co-conspirators in this.

Certainly Aaron Goldenberg, Anne Comeau, Nancy Rose, Susan Tanksley, Lisa Prosser, Jelili Ojodu and Jeff Botkin and of course Alex Kemper. So thank you all, and the process of considering the harms, most of us are from the -- actually I think it's called now the Condition Review Group, with input from this Committee leadership and also Dr. Botkin.

We began by reviewing the methodology for other established evidence review groups listed here, as well as leaders in the field of evidence review. So we made three decisions in the analysis of harms. One

is to define harms. That took a while actually, and it was broadly defined as any adverse impact.

So the events, burdens or risks that the primary consideration really needs to be the child, but that the family and social considerations would be included, and that the harms considered would not be all of the potential harms from screening, diagnosis and therapy, but it would really be those harms that arose beyond those from standard clinical presentation and care, and would include children who were deriving no direct benefit from newborn screening, or yeah.`

Okay. So certainly we considered physical burdens, increased risk of medical therapies such as with an earlier treatment if the condition were discovered earlier; potential harms from delayed diagnosis from false negative results; uncertainties of clinical diagnosis or clinical spectrum and certainly those considerations have come up

again and again in evidence review, and even potentially disparities in access.

For the families, really the harms would be largely psychosocial and logistic, for example, false positives. Okay. So the challenges to identifying harms are both generic and also particular to newborn screening, and many of these have been -- issues have been raised in previous evidence review and committee meetings.

So trials are usually designed to focus on medical benefits, they may have limited data on harms, either because those data are less available or they're less apparent, or that the trials are really more of a short-term focus, and then there are challenges that may have to do with subject recruitment and selectivity.

So we've heard about, for example, children who were diagnosed early because of an affected sibling or other family member with an adverse outcome, as we've heard earlier today.

There may be -- there are often constrained numbers and issues of sampling not only for sibs but in terms of the diversity.

And diversity, by that I mean the population who's being tested, but also the diversity of disease and the presentation. Okay. So the approach that we are taking, because this is in fact these -- we're not asking for the Committee to vote on this. This is an explanation of what's already in place through our evidence review process.

I want to make that very clear, that this is really formalizing the process for review of harms, and that we consider the impact of the number of children at risk, the severity of the harms, the likelihood of the harms and the timing.

We're not -- we decided not to look at opportunity costs like for newborn screening programs, because really that aspect is covered in public health assessments and other assessments by this Committee. And the

methodology that we're using is largely modeling, just like the benefits are being modeled, understanding that the, you know, the boundaries, upper and lower boundaries of modeling may be very broad, especially for harms where the data tend to be more scant.

We also like to propose that, you know, we have this robust discussion and presentations about pilots, and that to maybe make a plea for pilot studies, to really focus on gathering data in a systematic way about harms as well as benefits, and then certainly to identify areas of research that would be important to focus on going forward.

So the current status, as I said, these recommendations have already been incorporated into the Criteria Review Work Group. So we've written a manuscript. The Committee has received copies of that manuscript and we'd like your comments on that, final comments, and then we'd like to submit it to -- for a peer review publication.

So thank you for your attention, and I'd be happy to answer questions.

CHAIR BOCCHINI: Thank you, Nancy. Any questions or comments?

DR. NANCY GREEN: Jeff, did you want to comment, since you participated and were very helpful in helping, you know, throughout?

MEMBER BOTKIN: I'm not sure I have anything to add. Just to reinforce what I think you emphasized here, which are these are particularly challenging elements to the pilot process, to collect really any real data on and, you know, we have a fair amount of data on parents' reactions to false positive tests, those sorts of things.

I don't know how often we collect data on issues around some of the more higher risk problems, inappropriate interventions, for example. What do we know about SCID and how many kids perhaps have had inappropriate interventions based on their clinical condition? Those sorts of things, I think, are

just difficult to monitor.

So generally supporting the notion that the more data we can collect in this domain, the better we have, and then having this as part of the regular discussion process certainly is a real asset.

CHAIR BOCCHINI: Don.

MEMBER BAILEY: Yeah. Just so -- just thank you for taking this on. I think this is a really important topic, and just to editorialize a bit, it's near and dear to my heart. People, when I started proposing newborn screening for Fragile X, people kept saying here's why you shouldn't be doing that. Here are the harms that might occur for that.

And so I do think including an analysis of this, and we've talked about this in our Committee. I mean we do have this and we're thinking about net benefit of weighing, weighing benefits and harms. So I just would say that for us to think about this, that we have a very high standard for benefit. We

don't take speculative benefits as evidence.

So I don't think we should take speculative harms as evidence either, and we really need to make sure that if we're going to, you know, say well people might be worried about this or that might happen, that's not evidence. So I think what you're arguing is that we should be including data on harms, and we should be studying that as a part of this whole process.

With our Fragile X pilot project, we actually framed it in more of a clinical trial context. So we said this is the equivalent of a Phase 1 clinical trial, where we weren't trying to prove benefit of screening, but rather to see whether any of the adverse events that people have said might happen as a function of screening would really happen, postpartum depression or anxiety and so forth.

So I think thinking about these pilot studies, Michael, and as we're moving forward in terms of framing them in ways that

explicitly address the harms as well as the benefits would be really important.

CHAIR BOCCHINI: Thank you. Other comments? Jeff again and then --

MEMBER BOTKIN: Well, let me just reinforce -- I'm going to get myself in trouble with this one. But I just want to reinforce what Don had to say.

Because I think a lot of bioethics analysis, and here's where I'm going to lose my decoder ring. The speculative harms really in this domain have been considered quite significant, and you can point to things like, you know, the period of blissful ignorance of a child who has a condition, but you don't know it, and by doing newborn screening, you're going to alert parents to the fact that they've got a child with a condition, when they would have had some blissful ignorance for a while.

Well the studies show that that just doesn't exist. I mean parents don't like the notion of. So you can concoct a lot of risk

hypothetically and apply them here, when in fact you collect the data and they don't turn out to be significant risk. So just reinforcing your point.

CHAIR BOCCHINI: Melissa and then Coleen.

MEMBER PARISI: Quick question. I'm not finding the draft of the report in the briefing book. Could you send that around for us to review?

CHAIR BOCCHINI: All right, yeah, because the Committee needs to look at that and provide any input back to Nancy. So that was -- we'll make sure you have it.

MEMBER BOYLE: So Nancy, I guess just maybe a point of clarification. How would this have impact? Is this something perhaps new or adding to the evidence review process? How might this have influenced prior reviews, and should we be concerned about that?

DR. NANCY GREEN: Okay, thanks for that. That's an important question, Coleen. I

don't think that the issues have been ignored. They just haven't been systematically addressed. So, you know, having been part of the review group for some time, I think that the harms have arisen where there have been obvious data.

But just the explicit data and gaps, particularly the gaps probably or the magnitude, have not just been clear. But I don't think that we have to look back at missed opportunities for evaluation. I don't know if Alex has any comment about that. Thumbs up, says Alex. Okay.

DR. KEMPER: We looked at the harms all along the process, but we recognized, and really Nancy, I think, did a great job of putting this out, is that we had a very systematic approach to looking at benefits.

But we didn't have the same approach to presenting harms and especially the gaps in harms, or when we looked at a particular harm and it didn't exist, there was no way for us to

share it in sort of the formal way that we had done it.

So I think that Nancy, in partnership with Aaron, did a great job of just fleshing this out, so that we could be more systematic in how we reported it to you all on the Advisory Committee.

CHAIR BOCCHINI: Thank you. Other comments? Oh Charlie.

MEMBER HOMER: I guess a couple of things. To your earlier point Don, and on the heels of the U.S. Preventive Service Task Force presentation earlier, there is a presumption that while the vulnerable child syndrome data I agree is completely overstated and not consistently substantiated, I do think that standard public health practice about screening recommendations is that people who are healthy, you don't want --

I think I don't see any grounds for us to change our presumption, that the burden for an intervention such as the screening test

should be higher than not. I think that's not what you're saying, but it's getting a little close in there, in your comments.

So you know, I do think that the evidence around net benefit probably does need to be higher than the evidence about net harms. That's the main point. I also have a suspicion that it is going to be in the pilot work, in the sort of post-marketing surveillance concept, that we're going to really need to be looking at this more intensively.

So it's going to be informing that field more than any of the earlier ones. And then the other thing, looking at the U.S. Preventive Service Task Force presentation this morning, and Alex, you'll have to remind me on your evidence reviews. But they did have a formal mechanism in their diagrams of highlighting harms.

She said there was those curvy lines, and maybe if we incorporate something like that, if we haven't already in our design

for the evidence reviews, that will remind us of the importance of looking at that.

DR. NANCY GREEN: Right. The model for evidence review in this context came from that Task Force. So the harms are embedded in that net benefit concept, for each of those steps. Thanks Charlie.

DR. TARINI: Beth Tarini, AAP representative. I wanted to echo Charlie's comment about the overstatement, likely overstatement of the magnitude of the vulnerable child syndrome. As someone who was funded by the NIH to look at this, I think that to Nancy's point, which I hope people don't overlook, is that the magnitude has actually --

There was the issue of the qualitative piece of what are the actual harms, and identify them, as well as the magnitude of how pervasive or frequent these are, as well as the identification of even if it's a small subset of the population, we don't necessarily know -- that suffers these harms, we don't

actually know who they are. So we don't know the risk factors for that population.

And yet we do, I think in our discussions in the Committee, use a pseudo-magnitude discussion about harms when we discuss candidate nominations, to the extent that for an example, when deliberating about a condition I have seen at times people say well, there's the harm of false positives.

That comment is injected into the discussion, without an assessment of even a potential magnitude, even if you had confidence intervals. So it still, I think, influences this Committee, but unfortunately without any sort of magnitude on what we're talking about.

And so my overall point is to say I think it's important to quantify it to some degree, if only to help place it rightfully within the discussion, with its importance, wherever that importance may be.

CHAIR BOCCHINI: Okay. Other comments? If not, Nancy thank you, and this is

-- I certainly thank you for taking the lead on this, and this is just one of the contributions that you make to the Condition Work Group. So thank you.

DR. NANCY GREEN: Thank you.

Condition Review Update ALD

CHAIR BOCCHINI: All right. Next on the agenda, Alex Kemper is going to give us a Condition Review Update on ALD. Dr. Kemper is a general pediatrician and director of the Program on Health Services Research at Duke University.

His research focuses on the implementation and evaluation of screening programs for children, including newborn screening, screening for visual impairment and screening for lead poisoning.

Dr. Kemper is also associate editor for *Pediatrics*, the official journal of the American Academy of Pediatrics, and he now leads the Condition Review Work Group. Alex.

DR. KEMPER: Oops, I was changing

them around again. Thank you very much Dr. Bocchini, and I'm very happy to be able to provide this update on where we are with our review of X-linked adrenoleukodystrophy, and I have some very specific questions for the Advisory Committee as well, in terms of the scope of the review, in terms of what would most help inform the work that you all have to make related to decisions.

So again, I'm very lucky to work with a great group of people, who are all listed here, and in the interest of time, I won't read everyone's name. But I would like to note that Dr. Lorey and Dr. Bailey will be serving as the Committee representatives for this particular review. So we thank you in advance.

The last time, at the last meeting, I described a fair amount of information around what X-linked adrenoleukodystrophy is, and I don't want to, in the time that I have today, repeat all that, but instead focus again on

some of the particular issues that I'd like to raise.

So but just to help orient you, it's X-linked adrenoleukodystrophy is a peroxisomal disorder which affects the adrenal cortex and the central nervous system. It's got a broad phenotype spectrum, ranging in onset and severity from a childhood form to an adult form, and I'll give you -- be showing you a slide about this in a little bit.

Of course, it's the severe childhood form that we're most interested in, as it relates to newborn screening. Again, it's a disorder that primarily affects males, but I don't want it to be lost that female heterozygous carriers can develop symptoms in adulthood. It's the most common peroxisomal disorder.

The estimated incidence in the United States is about 1 in 21,000 newborn males, with about 1 in 14,000 newborn females being carriers. This is just a brief update

with where we are, in terms of the systematic evidence review. As is typical, we cast a wide net, looking for articles. You can see the key words that we used up there.

We developed these in partnership with a medical librarian. We're looking at PubMed, EMBASE and CINAHL. From database inception, we found a little over 1,300 relevant articles using our search that way. There's feedback, okay. Now I feel like I need longer arms.

We've taken that initial group of articles and screened them for relevance, bringing us down to 987, and then looking at that group there, there were 495 that were looked at for eligibility. When you compare those to our inclusion/exclusion criteria, you end up with about 170 original articles.

Now that number could change a little bit, based on some of the conversation that we're going to have in a little bit, again where I need your advice. And as usual, all

this screening happens with two independent reviewers, to make sure that we're not missing anything.

Again, I'd like to highlight some particular important issues related to adrenoleukodystrophy. Again, it's caused by a mutation in the ABCD1 gene, which encodes for the adrenoleukodystrophy protein. That protein facilitates transport of very long chain fatty acids into peroxisomes, and ultimately leads to the disorder.

There are more than 600 mutations that have been identified, and there's this nice registry of mutations. Most of them are unique, and there's challenges related to the genotype/ phenotype correlation, even within families, which makes this a bit difficult.

Screening can be accomplished in dried blood spots. Dr. Salzman talked a little bit about this before. There's a study that's being led by Dr. Matern, with looking at 100,000 anonymous dry blood spots. There's

been a prospective screening project that was done in Maryland with the Kennedy Krieger Institute, that looked at 5,000 newborns. Then of course there's the New York data. I'm just going to read the numbers, because I don't have them in a slide.

So between December 13th, 2013 and November 14th, 2014, about 205,000 dried blood spots were screened, and that identified 16 newborns, eight boys with adrenoleukodystrophy, four girls who were carriers, two with Zellweger Syndrome, which is a peroxisomal biogenesis disorder, so related to adrenoleukodystrophy in the peroxisomes, and then two additional peroxisomal biogenesis disorders.

That comprises the 16 newborns that were identified. Interestingly, there were no false positives within that cohort. It's been described, and again I don't have the primary data. We need to go back and interview the folk that are -- I'm doing it again. I'm going

to use this okay. They're going to hear me in the hallway soon.

So there were, and I think this is really interesting, that there were additional siblings and other family members who were diagnosed as part of the evaluation of those 16 babies, that were identified. I can't comment further on that though today.

Diagnosis is based again on mutation analysis measurements of the fatty acids in plasma, and head MRI. There's a score named the Loes score, which helps classify babies.

Treatment. Again, depends upon the particular form that you have, but can include stem cell transplant for those infants most severely affected. So this slide -- I'll move that so I can see my slides too -- breaks down the different forms of the disorder.

So there's -- you can think of there being cerebral adrenoleukodystrophy. There's the -- and then the other forms that can happen later in life. In terms of the cerebral

adrenoleukodystrophy, there's a childhood adolescent in an adult onset form.

In this slide, we have further broken things out by the progression, rapid versus slow; whether or not there's myelopathy, white matter lesions on MRI. Again, that's where the Loes score comes in, behavioral and cognitive disorders, whether or not there's a peripheral neuropathy, and then life expectancy.

And again, what I'd like to -- for you to remember from this slide is that the life expectancy with untreated cerebral adrenoleukodystrophy is within a few years after onset of symptoms.

Again, I talked a little bit about screening. It can be detected in dried blood spots. There are small pilot and validation studies, as well as the prospective work that's gone on in New York. The key things to keep in mind is that there does seem to be this very low false positive rate, that screening can be

done in a high throughput method.

I can't comment on sensitivity false negative rates, but again, that's not uncommon when we look at the screening test. What's interesting is if you look at the New York data, the number of cases that they detected matches what one would think would be the birth incidence. So that's certainly reassuring, and then there's this challenge related to clinical validity and confirmation after you've had a positive screen.

I'm going to be talking about that in a little bit, and screening is based on tandem mass spec. If you have any particular questions about how that works, I hope that you all ask Dr. Matern and not me.

So again, in terms of the screening, New York, Connecticut and New Jersey have legislation that's been approved. California has in process work related to beginning to screen babies for adrenoleukodystrophy, and Maryland also has proposed to add it. I

mentioned the work that's going on at the Mayo Clinic.

So these are some of the big questions that I have, and maybe I can either raise them and we could talk about it now, or I can finish my presentation. Dr. Bocchini, I'll leave it up to you. But the challenges that we have, and again, we want to be able to turn our evidence review back to you quickly, so you can go ahead and make a decision on it, is related to the primary targets of screening.

So I've already mentioned how screening can identify these peroxisomal disorders, and how much we should focus on looking at evidence relating to discovering those, as well as evidence regarding the benefits of either the later -- the forms that present later or of the carrier females. Related to that is what secondary targets would you like us to consider, and what would most help inform the Advisory Committee.

So this is what I propose, is that

first of all we will certainly summarize everything that we can find related to outcomes of screening, including the peroxisomal disorders and detection of carrier females, that kind of thing. But in terms of the benefits of detection, focusing on the identification of cerebral adrenoleukodystrophy and the Addison's that can present in early childhood.

But really to look at the other peroxisomal disorders detected through newborn screening that serve as a secondary target, and not focus on that in our review. And although again from screening we will be able to catalogue how many of these late onset cases would come to attention, not focusing on what the benefit of that would be in terms of detection through newborn screening.

Dr. Bocchini, can I -- do you want me to just keep going? I think that probably makes the most sense. Huh? Okay. So in terms of establishing the diagnosis, again there's

DNA diagnostic tests that can help certainly identify mutations in the ABCD1 gene.

Neuroimaging, which is from what I've understood from talking to experts and what I've read, will always be abnormal in those babies that are going to have this rapid neurologic decline, increased very long chain fatty acids in plasma, and then again, for the most severely affected males, the presence of other signs or symptoms related to neurologic problems, as well as looking for the presence of adrenal cortical insufficiency.

I don't want to focus on this, other than to say that there are algorithms that have been developed for the workup of pre-symptomatic babies suspected to have adrenoleukodystrophy, in terms of how frequently to monitor them and at what point they should go to stem cell transplantation if that's recommended.

Here's another somewhat more complicated slide, that again this is what's

recommended in Japan. But it's quite similar to the other slide that I put up, in terms of frequency of following and that kind of thing. Look over here to treatment.

There's stem cell transplantation, which appears to reduce the progression of neurologic degeneration when given early to severely affected boys with excellent adrenoleukodystrophy; adrenal cortisol replacement therapy for those children that appear to have adrenal cortical insufficiency.

There's been some work around gene therapy, but again it's really the stem cell transplantation that's the cornerstone of therapy. There's Lorenzo's Oil, which how many people have seen the movie. But it's a way to overcome the metabolic defect.

There are a fair number of studies out there looking at Lorenzo's Oil, and I think it's safe to say that it's controversial, that the benefits have been really mixed. And again, the key thing that we're going to be

talking about when we come back is the issue of transplantation. There's also some work that's been done with statin to reduce the very long chain of fatty acids.

I'd like now to show you some of the impact of stem cell transplantation in boys with the early stage cerebral adrenoleukodystrophy, and this was from a recent study that was published in *Lancet*. I apologize. The reference got cut off from the bottom of the slide, but they went back and looked at 283 boys who were not transplants, and then compared that to 19 who were transplanted, and then in further analysis, matched the 19 who were transplanted early with another group of boys who were similar in terms of their disease progression, but did not get transplantation.

I'm just going to show you the Kaplan-Meier survival curves, because I think that tells the story better than anything. This is the 283 boys in the study overall, but

when you separate out the 19 who got early transplantation versus 30 matched similar cases who were not transplanted, the survival is really, you know, markedly different.

So 95 percent survival up to ten years from the first abnormal MRI, down to, you know, half that or so for those babies that didn't get transplanted. So this is really a case where it appears, and again we're going to be coming through with more rigorously evaluated evidence, that early detection and transplantation can lead to dramatic differences in survival.

So I'd like to stop there and then get your advice about how you all would like us to move forward with those other questions that I brought up.

CHAIR BOCCHINI: Alex, you want to go back to that slide where you had those questions, and then we'll open this to the Committee for questions and/or comment.

DR. NANCY GREEN: Can I ask for a

clarification on Kaplan-Meier? My concern is that the kids who did well had sibling match transplants. So as some of us understand well, including the person who's nodding her head at the table, that you know, obviously not every kid has that option. So I think that has to be considered in the dramatic visual take home on this.

DR. KEMPER: No, I think that's very good. I think that again, I put the slide up to make people realize that, you know, this is the outcome that we'll be looking at for the childhood ALD is mortality, I think the primary outcome. But there are all sorts of issues about why did those children come to attention sooner than others, you know, and what were the unique features that allowed them to have a successful transplant.

So I think that there are a lot of open questions. I think that there's, you know, some nice data now coming out about screening, but there are all sorts of issues

that we'll have to explore when we come back later, as well as, you know, what it takes to establish the diagnosis and figure out who needs to get treated.

MEMBER McDONOUGH: Is there data out looking at the timing of stem cell transplant and cognitive outcome, if it's done in the newborn period or age two or four? Is there any, enough information out there about that?

DR. KEMPER: You know, so I hesitate to -- so we're still in the process of going through all this. There are stuff about cognitive outcomes and, you know, ability to, you know, participate in activities and those kinds of things. But I'd rather not present the data off the top of my head, especially without being able to tell you what the sample sizes are and the quality and so forth. So I'm going to plead the Fifth.

DR. CAROL GREENE: So my question was related and not to ask you to answer it, but something that the Committee, I think, will

need to consider, and that is not just survival, but the graph that you showed, I think you were very clear that both groups of children started with similar clinical symptoms and similar MRIs.

DR. KEMPER: That's how they were matched.

DR. CAROL GREENE: That's how they were matched, and then the question is not just survival, but what's the cognitive and neurological quality of life of those survivors, because that's been an issue in ALD. I think life is incredibly important, but I think the Committee will probably also want to know what kind of life.

The other thing is that if you think about, and when you present any data about earlier intervention, especially intervention like a bone marrow transplant, I think you're going to need to really pay careful attention and the Committee will want to know the percentages, because only some of the children

who have the disorder, who are identified by newborn screening, some of those children are destined to normal 40 year-old men, who then develop Addison's, and then get, you know, live to be 80 and never have neurologic disease.

Do you want to transplant with the risk of death from transplant, that person as a newborn? So the statistics will be very important here. As you pointed out, the lack of any genotype/phenotype correlation here makes the analysis incredibly complex, and the only other thing I wanted to say is I really appreciate the notion that DNA is a definitive diagnosis, and I know that the DNA for ALD is probably upwards of 99 percent.

But the definitive diagnosis, the gold standard to which you compare the DNA, when you say that the DNA is X percent sensitive, it's the blood. So it's the blood levels of the very long, and Dieter, correct me if I'm wrong. But you can make the diagnosis based on DNA without seeing the blood.

But if the blood says it's ALD and the DNA says it isn't, you're going to go looking for mutations in the regulatory region. So the blood is the definitive diagnosis, unless I hear otherwise from Dieter.

MEMBER MATERN: Dieter Matern. I think the role of the ABCD1 gene here is a little murky as it comes to newborn screening. New York uses the molecular approach as part of the screening, but they do not base the result off the molecular test, whether they're going to report this out or not.

Any child with a high LPC is reported out, and the molecular data is only helpful in kind of quicker getting to the final diagnosis of X-ALD versus another peroxisomal disorder. So and from a screening perspective, I don't think we need to consider really the molecular as part of the screening testing, and it really should be part of the follow-up after you do the plasma very long chain fatty acids.

Can I say something more? While

we're at it, just to put a plug in for this concern and I look at Dr. Kelm, neither the screening test looking for the LPCs, and there are right now I think three or four different methods published on how to do it, are FDA approved. They're all laboratory developed tests.

Very long chain fatty acid analysis, there's no FDA-approved test, and the ABCD1 gene is tested with a non-FDA approved laboratory developed test.

So all of this might be a moot point if you need FDA approval to run this, and finally, to consider also at maybe the next time, when you come with the final review, is that the LPCs can be measured by themselves from a blood spot, or they can be incorporated into the LSD screening.

MEMBER BOTKIN: Jeff Botkin. Are the New York, Connecticut and New Jersey programs collecting data in a reasonably comprehensive way, that will help the Committee

understand from their experience within a reasonable period of time?

DR. KEMPER: I've not spoken to them directly, but based on the New York publications, I'm hopeful that the answer is yes.

MEMBER HOMER: I guess I'm a little confused. So you have the question of what outcomes to look at and which population, right, which we had said we're talking about the cerebral, the bad stuff for young -- for children, right? That's what we were talking about. But then you said that the screening test can't differentiate; is that correct?

DR. KEMPER: So the screening test will identify the whole spectrum, right? I'm looking at Dr. Matern, who's going to help me with this as well. But the question is then, for example, if the screening test identifies let's say the carrier females, how much information does the Advisory Committee want back, based on the benefit of detecting those

carrier females?

So the reason I ask is because it could be a lot of work too, because you could argue that there's, you know, no particular benefit to those carrier infants in infancy, or you could look at it and see, you know, down the line what the benefit would be to their own health, or the potential health for their children, or for the carrier females that get picked up and somebody goes, you know, if they do, you know, workup the family to see if there's any other affected person in the family. Then you could see where that would identify other affected individuals.

So I'm just trying to figure out like where we should focus our effort on. So for example, if we just focus on the benefits of identifying the children with the cerebral adrenoleukodystrophy and describe to you the survival and the neurologic outcomes and all that kind of stuff, and then have a catalogue though of, you know, these are all the other

things that would also be picked up in the process of screening, is that sufficient?

MEMBER LOREY: Yeah. I just wanted to comment that since we already know a certain percentage of the female carriers will be symptomatic in one way or another, I don't know how we can avoid studying it.

DR. KEMPER: I'm not saying that it should avoid being studied prospectively. I'm just trying to look at -- and I would think it would be wrong for the research community not to look at the, you know, the outcomes in those children. I'm just trying to think of, for just purely the purposes of the evidence review, where that fits into things.

So, you know, I'm happy to explore that side of things, if you think that it would be useful. But given all the other components that have to be done, I'm just trying to figure out where, you know, where the --

MEMBER LOREY: Yeah, I agree, and the only reason I bring it up is because I

understand the one place they're screening in Europe, they're not screening the girls at all.

DR. KEMPER: Is that right? I didn't know that.

MEMBER LOREY: Yeah, so --

DR. KEMPER: I don't think logistically that could be done here. Dr. Green. I'm sorry.

MEMBER HOMER: Yeah, I'm sorry. Since I'm obviously not a clinical expert in this, I'm still a little confused. So leaving aside the females for the moment, so is the question for example if you do screening, let's just suppose that you do screening and you identify children with the cerebral form early, and that there's a net benefit due to treatment with stem cell transplant, and that by itself might suggest that this is a beneficial approach.

Seems like you would then -- what I was trying to get at is are there also other males, for example, that you're identifying

that you can't differentiate, and perhaps might not develop anything other than Addison's disease or other adult symptoms, and now you can't tell whether they're going to develop the cerebral form and therefore expose them to the risk of getting a stem cell transplant?

DR. KEMPER: Well there's -- again, I don't want to get too far ahead of where we are in terms of evidence review. So at the time that newborn males test positive, there are things that you can do to figure out whether or not they're going to have this neurologic form.

So there's the MRIs, which from everything I've read are -- and Dieter, you might want to comment on this as well -- are a good way to separate those children that really need to move on to transplantation versus those who don't. If you look at the protocols that I showed earlier, MRI is like built in there.

So if your question is, you know, is there risk that a child might get transplanted

who wouldn't otherwise need to be transplanted, I'm sure that risk exists. But hopefully if they follow the protocols, that you know, that would, you know, lead that to be close to zero.

My question, just for the process of evidence review, is that if you identify a male who may not develop adrenal problems until, you know, many years down the road, first of all I suspect that there's not going to be any evidence regarding the benefits of finding that kid earlier versus when they would have, you know, come to attention later.

But it's very easy for me to catalogue how often that might happen. But in terms of providing, you know, evidence or doing modeling around that, it just gets logistically very difficult. So I guess what I'm asking is is it okay with the Advisory Committee if I just catalogue the number of kids that would fall into that group, so that you would have that information to make decisions on, but really focus on the identification of the

children with the cerebral form, and you know, look at -- as well as the other positives, so we could figure out how many, you know, babies would get into the system.

But then of the ones with the cerebral form, you know, what would be the expected outcome of identifying them in the newborn period, versus when they present clinically. Is that -- I don't know if I answered your question.

MEMBER HOMER: Yeah. So it seems to me that that's the only group where you're going to be able to make determinative information, and the other stuff is generally informative, but isn't really going to --

DR. KEMPER: Yeah, and there are just all these like sort of one-off case reports. But it's just very hard to make a story out of it. In my heart of hearts, and I hope I'm not overstepping my bounds, it's going to be these issues of the cerebral adrenoleukodystrophy that are really going to

drive any decision by this body.

DR. CAROL GREENE: So speaking as a clinician who actually deals with the families and writes the orders and would be part of the follow-up protocol, first speaking as a geneticist, I would love to find all the families and be able to provide the genetic counseling. Speaking as a clinician more broadly, first of all forgetting the evidence review, the answer to Charlie's question is yes.

You cannot tell the difference at birth. You have to do an MRI to tell the difference. There are going to be, and I think we're going to hear from an expert in a moment. I'm sure that there are things that can make it more likely or less likely. If it's a truncating mutation, it's likely to be worse.

But we just heard a categorical statement that you cannot predict based on the DNA; you're going to have to do an MRI. To do an MRI on a six month old and a one year-old

and an 18 month old and a two year old and a two and a half year old, if that's the protocol, you sedate them. Sedation has risks, and the family is waiting.

So that's why we just heard eloquently about the need to understand what's the risks, okay? Maryland has already decided to go ahead. I've participated in discussions. I'm okay with it. I'm not going to be flipped out as a clinical geneticist getting a phone call that there's a positive screen.

But speaking very broadly, since you cannot tell at birth whether this person's going to be a 40 year-old with Addison's or nothing, then you have to look at the numbers and think about the risk. Otherwise, this Committee can't make a decision about what's the net benefit if they don't hear about the risk.

MR. MOSER: First of all this slide. I would put adrenal cortical replacement therapy as the number one issue. That's a

life-saving. You know, children with ALD, boys with ALD can die of Addison's disease from a simple fever. So I think that that's the number one treatment strategy.

And then regarding stem cell transplantation, you have to follow the boys, and I don't think the recommendation is MRI early on. I think it starts around age of two years, okay. This is -- I'm quoting the expert pediatric neurologist, Dr. Raymond and Dr. Fatimi and others. So and gene therapy is on the horizon. There are a number of transplants that have been done, and we're following the data on those.

So that you don't always have to have a perfect match for bone marrow transplantation. And then as far as the females, it's extremely important to identify them. You're not going to identify all of them. You're going to miss some. But you will -- with a little girl baby who has -- who's a carrier for ALD, you'll be able to do genetics

in the family and identify other affected males possibly.

So I'm available for any questions, and I'm sure that we all want to see ALD recommended universally. Thank you.

CHAIR BOCCHINI: Thank you.

DR. KEMPER: Say your name for the record.

MR. MOSER: Ann Moser.

DR. KEMPER: I was going to say it for you, but I didn't want to overstep my bounds.

CHAIR BOCCHINI: All right. Any other questions or comments? Don.

MEMBER BAILEY: Two things. Since Fred and I are responsible for the Committee's input, what's the timing of this Joe? Are we thinking of this in the next -- are we trying to shoot to vote in the next Committee meeting on this, is one question?

Then secondly, I think in terms of what would be helpful for us, I'd really love

to know the percentage of babies that need to have a treatment within the first year or two of life.

CHAIR BOCCHINI: So I think maybe you can answer the second question. I think the first question is that the Evidence Review Committee is working as hard as they can to try and get this done, but I'm not sure we've got a specific time set for presentation. So hopefully next meeting, but we're not sure that we can get it done by then.

MEMBER MATERN: Dieter Matern. I think one of the big advantages of this review is that you can actually get evidence from what is going on in New York, and I think it was mentioned earlier that maybe there's a publication already out about the first year.

I couldn't find it in PubMed. But I think looking at the follow-up algorithm and what happened with these patients that were identified, I think it's going to be extremely important, independent of whether it's X-ALD or

one of the other peroxisomal disorders.

Furthermore, among those centers in New York that are following these patients, they would also be the first ones who would make a diagnosis of ALD spectrum disease in any of the other conditions that you would expect to be picked up, and could confirm whether it was a false negative for those, although for X-ALD it might be more difficult to get to the false negative number.

MEMBER BOTKIN: Jeff Botkin, and I -- it doesn't look like you've done the public health impact survey stuff yet. But I'd wonder if you'd just make a comment or two about how easy this would be to bring onto existing platforms, etcetera.

DR. KEMPER: I have no idea.

MEMBER HOMER: I just want to make maybe a random comment related to the new legislation authorizing our Committee, because it's going to come up in this. The mandate for us to be quick, sometimes I think may result in

ultimately a delay in approvals, because if there's a study, for example like what's happening in New York in the field and we'd want a second year of data to really inform our decision, that might allow us to actually make a quicker recommendation than based on insufficient evidence to have to come up with a negative recommendation. Then it would be some time until we are able to put it back in the queue.

So I'm sure everyone knew that already, but I just wanted to kind of get that concern in the record.

CHAIR BOCCHINI: That's a good point, and that's part of the reason why we have to kind of go back and see what is necessary to have in place before a condition can get through the Nomination Prioritization Work Group. I think that's absolutely right, yeah.

Okay. Alex, I think you've had some feedback.

DR. KEMPER: Thank you.

CHAIR BOCCHINI: So thank you very much, and I thank everybody for their comments and questions. I think we're -- we did get behind, but I think all of the information that was presented this morning was really important, and I think that it was well worth getting behind for. So we're going to get everybody -- yes, Coleen.

MEMBER BOYLE: Could I just ask, oh sorry, clarity. I just don't know whether we had come to a decision about the suggestion Alex and the Review Group had put forward. So is the proposal that he made, in terms of focusing on the more serious outcomes of childhood onset versus the -- is that the way it's going to go?

CHAIR BOCCHINI: Well, I don't think we have a conclusion to that. But I think some of the comments that were made about adrenal insufficiency and the importance of recognizing that, and then determination -- at what age we

could determine cerebral versus non-cerebral, I think, needs to be in the mix.

I think we have two Committee members who are involved in the review, who can kind of flesh that out with the Condition Review Group, and then come back to the Committee if we have to address those in a little more detail. But I think -- I think we have enough for them to move forward, without a specific -- I think we've broadened it rather than shortened it, okay?

All right. Bring your lunch back here, and then we'll do our best to see if we can get started when we have a quorum.

(Whereupon, the above-entitled matter went off the record at 12:51 p.m. and resumed at 1:31 p.m.)

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

1:31 p.m.

CHAIR BOCCHINI: All right. We're ready to go ahead and start the session. Welcome back to the afternoon session of the first day of our sixth meeting of the Discretionary Advisory Committee. To start off, we need to take attendance. So let's do that. First, the members. Don Bailey.

MEMBER BAILEY: Here.

CHAIR BOCCHINI: All right, I'm here. Jeff Botkin.

MEMBER BOTKIN: Here.

CHAIR BOCCHINI: Coleen Boyle. Not back yet. Denise Dougherty.

MEMBER DOUGHERTY: Here.

CHAIR BOCCHINI: Charlie Homer.

MEMBER HOMER: Here.

CHAIR BOCCHINI: Kellie Kelm.

MEMBER KELM: Here.

CHAIR BOCCHINI: Fred's not back yet. Michael Lu.

MEMBER LU: Here.

CHAIR BOCCHINI: Steve McDonough.

MEMBER McDONOUGH: Here.

CHAIR BOCCHINI: Dieter Matern. Not back yet. Melissa Parisi.

MEMBER PARISI: Here.

CHAIR BOCCHINI: Alexis Thompson.

MEMBER THOMPSON: Here.

CHAIR BOCCHINI: Cathy Wicklund.

MEMBER WICKLUND: Here.

CHAIR BOCCHINI: Andrea Williams.

MEMBER WILLIAMS: Here.

CHAIR BOCCHINI: And Debi Sarkar.

MS. SARKAR: Here.

CHAIR BOCCHINI: And then the organizational representatives, Freddie Chen.

DR. CHEN: Here.

CHAIR BOCCHINI: Beth Tarini.

DR. TARINI: Here.

CHAIR BOCCHINI: Michael Watson.

DR. WATSON: Here.

CHAIR BOCCHINI: Nancy Rose.

DR. NANCY ROSE: Here.

CHAIR BOCCHINI: Debbie Badawi.

DR. BADAWI: Here.

CHAIR BOCCHINI: Susan Tanksley.

DR. TANKSLEY: Here.

CHAIR BOCCHINI: Chris Kus. Adam Kanis. Natasha Bonhomme.

MS. BONHOMME: Here.

CHAIR BOCCHINI: Siobhan Dolan.

PARTICIPANT: Here.

CHAIR BOCCHINI: Cate Walsh Vockley?

DR. VOCKLEY: Here.

CHAIR BOCCHINI: And Carol Greene. Not back yet. Okay. Oh, Dieter made it. Okay. All right.

(Laughter.)

CHAIR BOCCHINI: So you're implying that you were late enough that you missed the roll call? Is that what it was? Maybe that's how that happened, okay. Okay. We can strike that from the record.

(Laughter.)

Cost and Cost Effectiveness Analysis

CHAIR BOCCHINI: So we're going to

start the afternoon session with Dr. Scott Grosse presenting data on cost and cost effectiveness analysis, and as you know, this has become a much more important part of all federal committee activities, and certainly this has become very important to the ACIP, of which I've been a member for the past four years.

What I've seen happen is that we started off by years ago indicating that we were making a decision about what was best for patients, and cost was not an issue. Now, as we've gotten to the point where we have vaccines that are not all cost-saving, but do have some cost to the public, that we now have incorporated cost and cost effectiveness into our decision-making process.

It's not the primary thing that motivates a decision, but it's considered, and it has played a role in some of the recent decisions that the ACIP has made. So I think it is an important aspect, and as we've already

discussed, this has certainly become part of our mission, to include cost and cost effectiveness analysis in the decisions that we make.

So we're pleased to have Scott here. Scott is a senior health economist at the National Center on Birth Defects and Developmental Disabilities for the CDC. And so he's worked with others in the Condition Work Group, Review Work Group, and has been very helpful to us over the past months, as we've worked through our process of modifying our decision matrix.

So Scott, we'll turn this over to you, and let you get started. Thank you.

DR. GROSSE: Okay. I'd like to thank Dr. Lu and the Committee for inviting me. Can you hear me now? Can you hear me? Now? Now? Okay. Okay, thank you.

Okay. Acknowledgments from colleagues who've given me some assistance on this presentation. Glossary, what is cost?

Cost means different things to different people. For an economist, cost refers to resources used up or foregone. There are direct costs, which is what do you do when you're actually providing care. Indirect cost is the foregone value of economic production, because someone is sick or has died.

Cost analysis or a partial economic evaluation, you can look at what is the cost caused by a disease, or what is the cost of an intervention, such as a screening program. That's then in contrast, you have a full economic evaluation, where you put the cost together with outcomes.

So cost effectiveness analysis, you look at what is the cost and what is the health outcomes. Cost benefit analysis is similar, except all outcomes are put in dollar terms, monetary terms. You have a single metric of dollars.

Economic cost, as I said, is the value of resources that are used up, and it

doesn't matter who pays for it. If you have an in-kind cost, it's still a cost. You value the donated services or time at what the opportunity cost is, which is the value that they could have been doing if they were doing something else.

In contrast, you have financial cost for the accounting cost. What is the budget? So which costs, economic cost or financial cost depends on the perspective of the analysis, which depends on the audience that you're trying to inform. You have variable and fixed costs, general principles.

As long as you are covering your variable costs, you're at least breaking even. But fixed costs, which do not vary with the level of output, needs to be taken into account for long-term sustainability.

Marginal cost and incremental cost are similar but slightly different. Marginal cost is when you do more of the same thing, how does your average cost change? Incremental

cost is when you do something different like -- so a marginal cost, if you test more specimens for a given assay, how does your cost change? Incremental cost is when you're testing for a new condition using a new test, how does that alter your costs?

How to estimate costs in the health care arena. For direct costs, the micro-costing is when you measure the value of ingredients, the labor, time, equipment, consumables such as reagents. You have to calculate what are the quantities and what is the unit cost of each to calculate the total cost. An alternative is cost accounting data if you have a cost accounting system in place.

Now there's an indirect way which is not -- I'm sorry. It's different than indirect cost. This is indirect estimation of direct cost. Actually, the term indirect cost, productivity losses, there's controversy about that terminology too.

But charges. It's very common to

use information on how much a hospital or a clinic or a drug company charges for a particular service. The problem is charges in this country bear very little relationship to cost. There is a relationship, but it's very inexact.

On average, charges are more than twice what the estimated cost is, sometimes five times more or even more. It depends; it's very variable. So if you have just charged, it's hard to actually know what the cost is, although there are cost to charge ratios.

It's very common to use these schedules, such as the National Medicare fee schedule as a proxy even for pediatric cost, because it's something that's standard. Average payment. If you have claims data from multiple payers, you can calculate what is the average reimbursement, with the idea that providers are not going to continue providing a service if they're getting reimbursed from all payers, less than it's costing them to provide

the service.

There's no single gold standard measure of cost. There's different ways of trying to estimate it. So how do you estimate the incremental cost of adding a new test using dried blood spots? Fixed cost, collecting the specimen, the laboratory, transporting the specimen, that doesn't change when you add disorders. It's only the cost associated with the new condition.

So you have the laboratory staff, equipment, reagents, the space and utilities that are required for the additional space. Then short term follow up and tracking. The downstream costs to health care systems and families are harder to assess. There's the cost for the clinical follow-up from the reporting of the laboratory results.

You need to bring in the family and the additional time spent with that family, long-term management. But for long-term management, you have to -- it's only the

difference between the management that would come with screening and costs without screening. If a condition is going to be identified in the absence of screening, just delayed, then it's the difference in the management cost.

Whereas if a disorder is not identified in the absence of screening, then all of that long-term management cost would have to be included. So but the bottom line is the cost of expansion of newborn screening is more than just the laboratory cost.

I'm going to give an example, testing for LSDs, such as MPS I. A state that did an analysis of the cost of testing for LSD, which is not named, with calculated for 100,000 births per year, an average 1.2 screens per infant. So one screen state. But that doesn't mean it's just 1.0 screens, as everyone knows.

So in order to use -- assuming they're using the full injection tandem mass spectrometry, you'd have to purchase or lease

three of these instruments, along with the ancillary equipment, and they calculated the cost as $1.2 million, which is higher than some estimates because the ancillary equipment adds to the total cost.

So you can use standard accounting formula to calculate the cost of depreciation. That's about $160,000 per year, plus maintenance cost, plus cost of lab upgrades that were needed to include these tandem mass specs. So the total cost of equipment per year is roughly $330,000, and then labor cost is roughly the same amount of money.

For the incremental cost for a given disorder, it's the cost of the reagent. So the testing for LSDs, whether you test for one LSD or five LSDs, it's roughly the same. So it's the reagents, which is about a dollar per specimen, or -- so the total cost to screen for one LSD is a little less than $8. Each additional LSD would be $1.20 extra in laboratory cost.

So you cannot answer the question in isolation of what is the cost to screen for MPS I. It all depends. How many other LSDs are you screening for? Then there's the cost of the diagnostic testing. So if there's a complicated algorithm, which varies from state to state, but in general those --

So the screening algorithm varies. So where you set the cutoffs, the technology used is going to influence the number of infants who get referred for diagnostic testing, and then within the diagnostic testing, there are different protocols. So how many were used at the cutoffs on these diagnostic tests, the first -- the enzyme, the IDUA enzyme activity assay, the GAG assay.

Those are trying to rule out most of the positives. Once you've -- and the cost of that is between 200 and 600 dollars per specimen, according to the Public Health System Impact Assessment Fact Sheet that you have in your briefing book.

So the total cost, depending upon how many get tested, could be anywhere from $2,000 to $27,000 for 100,000 infants screened. Then you'll have a small number that do need DNA testing, the gene sequencing for the IDUA gene, and that could add anywhere from two to eight thousand dollars.

So the total cost works out to anywhere from five cents to 35 cents for infant. Now you'll note that that's substantially less than the $1.20 for the screening test. So even at 35 cents, that's assuming a high, relatively high rate of false positives. Many people say well, there's such a high rate of false positives with this testing. That's too much of a burden.

But even at the upper end of the estimate of false positives or pseudodeficiency genes, it's still low compared to the cost of the initial screening. SCID. We've been working with the Washington Department of Health to analyze their costs. They published

or they did a report. They analyzed the cost of doing the TREC assays.

A little over $8 per infant, two screen state. So it's less than $8 per screen. Some labs have reported $6 per specimen. For the short-term follow-up, they calculate on average one hour of staff time for each positive screening result. That's sort of a generous estimate. So you say including all the costs, the fringe benefits, the supervision, it's about maybe $50 per positive screen.

That's a lot of money, but considering the number of positive screens that need to be followed up, that added two cents per infant tested. The cost of flow cytometry testing, about $250, including the phlebotomy and the clinical interpretation done at the university medical center. So the total screening cost, including the diagnostic testing, $8.17.

That's when Washington added SCID.

They raised the fee by $8.17, based on this analysis they had done. But states differ. States differ in terms of the technology used, what -- how much follow-up is done inside versus contracted out. Some states pay for the cost of the confirmatory and diagnostic testing; others don't.

Florida, there was a recent article published by Kubiak et al., quoting the Florida Department of Health, which raised their fee by $16.67 to cover the cost of SCID testing. No breakdown provided, but that included costs for co-location and referral center contracts, as well as the laboratory and short-term follow-up costs.

There's both -- now you notice these analyses have been from the financial cost, from the perspective of the department of health in a state. From an economics perspective, you want to include not just the costs, whether it's measured financially or economic costs to the screening program, but

also what are the costs to the clinical system, comparing the management of the disorders identified through newborn screening, versus not newborn screening.

This is from a paper that Lisa Prosser published in 2010, a cost effectiveness analysis of newborn screening for MCAD deficiency. With MCAD, there are maybe a third of the children would not be diagnosed in the absence of newborn screening. They'd be asymptomatic, and so there's some additional costs of diagnosis and follow-up, some savings in cost of treatment because of voided hospitalizations.

So they calculated the estimated, the net difference in treatment costs. The exact numbers are not important, but the principle is that if you're looking at the total impact of adding a condition, you want to look not just at the screening cost but also the downstream costs.

Now we're going to go beyond the

cost of implementation, to considering what is the balance of costs and benefits, which is -- the term "value" is shorthand. There are many different words that people use that are often used interchangeably. People will say oh, that's cost effective. It's cost saving.

Dr. Bocchini's familiar with the difference. His service on the ACIP has given him a lot of exposure to these terms and estimates. Cost beneficial, positive ROI. The terms are not interchangeable. They have different meanings. Each is associated with a different analytic method, and the choice of the method should depend on the purpose of your analysis and your audience or stakeholders.

So the three major economic evaluation methods, there's cost effectiveness analysis, which asks what approach costs less per unit of health gained? There's a subtype of cost effectiveness analysis that's also called cost utility analysis, where you calculate the cost for quality adjusted life

year, cost for QALY.

Then there's cost-benefit analysis, which as I mentioned everything is put in the dollar terms, and the question is the monetary benefit to society greater than the cost. If the monetary benefit exceeds the cost, then there's net benefit and you get the green light, saying yes, this is something that's worth doing.

Budget impact analysis is a financial analysis. You look at what is the expected change in the financial expenditures for a given health care system or payer for a given time period?

It may be one year, it may be ten years. It's from the budget holder perspective. Your state Medicaid program, Medicare, they use a ten-year perspective. Congressional Budget Office mandates that. It could be your state government as a whole.

The budget impact analysis is what is the net impact on the budget over this

defined time period that you would expect as a result of doing something.

Something may have positive budgeting, but the total budgetary costs increase But from a societal perspective, it may actually be cost saving, and that's fairly common. The reason is that many of the benefits may accrue to other payers, other health care systems.

So if you're going to do a budget impact analysis, it's also good to look at an economic analysis from the societal perspective. So cost effectiveness or cost benefit analysis? Which method to use depends on your audience. In the medical field, medical journals almost always prefer cost effectiveness analysis.

By tradition, the health field, putting an explicit dollar value on lives or life years saved, is considered not good form. Now implicitly when you do a cost effectiveness analysis and you calculate the cost, say it's

$100,000 per life year saved, and you make a decision on that basis, you are implicitly putting a dollar value on health. But because it's not explicit, that is considered more acceptable.

Outside of health, cost-benefit analysis is the norm. In other areas of public policy, in the economics discipline, cost effectiveness analysis is quite rare. I never studied cost effectiveness analysis in graduate school. It's only when I came to work at the CDC that I had to learn how to do cost effectiveness analysis.

So cost-benefit analysis is the norm in most areas of public policy, transportation, environmental protection. And so when people in newborn screening or public health insist on using cost effectiveness analysis, they're putting health at a disadvantage relative to other areas of public policy, where dollars are used as the metric and where legislators are commonly expecting to find that.

Value is in the eyes of the stakeholder. For some stakeholders, only health outcomes matter. For example, Medicare coverage decisions are based on medical necessity. That's in their authorizing legislation. They do not consider cost effectiveness. Others are interested in the budget impact.

So Medicaid programs are very interested, what is the impact going to be on our budget? They're concerned with is it affordable? Something may be highly cost effective, but if there's a high outlay, they say no, we can't afford it. So affordability and value are not interchangeable. Something may be affordable because of the low cost, and if there's no major change in infrastructure required, there's low cost in absolute terms, and intervention may very well be approved.

If an intervention is perceived as difficult or expensive, then considerations of cost effectiveness or cost-benefit may become

more influential. A low cost intervention may be considered, may be assumed to be better value than an expensive intervention, but that's not necessarily the case.

There is an example I came across last week. Aaron Carroll on his blog talked of comparing lung cancer screening with treatment for chronic Hepatitis C virus infection in prisoners. The cost of lung cancer, the CT lung cancer screening is about $100 per visit. It's pretty inexpensive. The cost of this new drug treatment for chronic Hepatitis C, which I'm sure many of you have heard about, is roughly 80, 90 thousand dollars for a single course of treatment.

That's expensive. Many payers are balking at that, and say no, it's not affordable. But which one provides better value for the money? That's a different question which we'll get back to a little later.

So how do decision-makers use

economic evaluations? Within newborn screening, the traditional approach is to consider health outcomes and cost as separate criteria. First, you look at clinical benefit. Then you look at cost. Or you can assess the balance of cost and outcomes, as net benefit or a cost effectiveness ratio.

But then you have to decide how are you going to use that information? Are you going to use it as a decision rule. That is, if the cost for QALY is less than $50,000, then it's cost effective. If it's not, it's over, then it's not cost effective. Or you can consider it as just one criterion among multiple decision criteria.

Instead of studying the absolute threshold, you consider in a range. So also instead of using these cost estimates as a criterion for deciding whether something is approved or not. Thank you. Gentlemen and a skull. You can use economic findings to guide prioritization in implementation, rather than

as a decision is it approved or not approved.

And economic analyses or decision analyses can be used to identify gaps in research. We don't really know whether something is cost effective. This is the information that we need in order to make that decision. How do other advisory committees? We heard the U.S. Preventive Services Task Force does not consider cost effectiveness.

The Community Guide at CDC has a stratified process. They make the decision whether something is recommended based on the evidence of effectiveness. But if something is recommended, then they do a systematic review of economic evaluations, and then use that information to inform public health decision-makers, to guide the prioritization among the recommended services.

And then the ACIP, which you heard about from Dr. Bocchini, the ACIP now requires that any new vaccine or new application of vaccine that is proposed have an economic

analysis as part of the submission. The nominator has to submit a cost effectiveness or a cost-benefit analysis before it will be considered.

That is reviewed by health economists at CDC. It's reviewed by the committee members as part of the decision-making process. So the slide from Lisa Prosser, Lisa works with the ACIP. She provides training for ACIP members on economic evaluation. So they do their evidence review. There's the public comment and the vote.

The cost effectiveness is one of five major sets of criteria. It's not the only one, but it's considered. Here's an example of how it has been considered in the influenza vaccination. It used to be that influenza was only recommended for older adults and for infants, which had the lowest cost effectiveness ratio.

Over time, all age groups have had it recommended. I think was it adults, 1949

were the last group to be added?

A cost ratio of over $100,000 per QALY. That's highlighted in yellow. People traditionally use $50,000 for QALY. It is a decision rule. But that was in the 1990's, never adjusted for inflation. So increasingly people are using $100,000, as equivalent to what 50,000 used to be worth.

We've heard the term cost saving. Cost saving means the total costs are lower. The expression is an ounce of prevention worth a pound of cure. Many people misunderstand or misinterpret that as meaning that prevention should be cheaper. That's not what the expression says. It's worth that means value, not lower cost.

Some preventive services, like the traditional childhood immune vaccines were cost saving. Folic acid fortification is incredibly cost saving, like $100 of what it costs for every dollar spent on fortification. Smoking cessation is cost saving from a societal

perspective, not necessarily for a health plan, but societally it is.

Most preventive services though, including most screenings, are not cost saving. So then you have to assess the value. Is the early detection of disease worth the extra cost to the health care system, compared to standard of care? So skip that.

Partial economic evaluations are a valuable component of a full economic evaluation. Before you can do a full economic evaluation you need to know what is the cost of the disease that you're studying, what is the cost of the intervention? You then have a model, a decision analytic model, which projects the total health outcomes and total costs, based on the components that go into that.

Very important principle. First you need evidence of effectiveness. If you don't have evidence of effectiveness, why even talk about cost effectiveness, because if it's not

effective, it's not cost effective. You might be surprised how often cost effectiveness analyses get published in medical journals for interventions which do not have good evidence of effectiveness.

There are actually more of those than there are of the ones for effective interventions. I did a review for Genetics and Medicine last year, which -- where somebody had done a systematic review of economic evaluations and genetic testing. Out of 50-odd, only six were Tier 1 tests with high quality evidence of effectiveness.

Another problem is that we often have conflicting estimates of effectiveness, like mammography screening for breast cancer. What percentage of deaths, breast cancer deaths are prevented by mammography? There's one well often cited economic analysis which concluded there was a very low cost effectiveness ratio, and they were assuming 40 percent of all deaths were avoided.

The consensus now is 15 to 20 percent, and some think it's even less than that. The fewer the percentage of deaths avoided, the higher the cost effectiveness ratio. So you can get very different estimates depending on what your assumptions are.

Newborn screening for CAH. Traditionally, it was assumed that in the absence of newborn screening, 12 percent of infants with salt-wasting CH would die, you know, a society like the United States. We did a systematic evidence review and it was probably two percent. So obviously that's going to affect your estimate of the cost effectiveness of screening.

So full economic evaluation, first you start with evidence of effectiveness. Then you have to define who's your audience. Is this going to be a societal economic analysis or a budget impact analysis? Are you going to take long-term or short-term perspective?

You have to define the different

interventions you're comparing, which for example with newborn screening, it's often not newborn screening versus no screening. There are often different screening strategies. We don't talk about universal versus targeted screening anymore, but there are different screening strategies in terms of the cutoffs.

So you may consider multiple interventions. How much is it worth the extra case, to increase sensitivity from 97 percent to 99 percent? You'll get more cases detected, but what is the extra cost? So you select the cost and health outcomes. You can do a decision analysis without cost, then add costs.

Cost effectiveness analysis, you calculate the total cost and total health outcomes for each of the interventions. You exclude an intervention, any intervention which costs more and is less effective. You don't calculate that cost effectiveness ratio. It's dominated. For the non-dominated strategies, you calculate the incremental cost

effectiveness ratio, comparing one strategy to the next most effective.

Decision rules. I mentioned the $50,000 for QALY, which is an arbitrary rule. It was never based on anything more than convenience. Range of values may be reasonable instead of a single value. But what economists like to do is compare revealed preferences. What have decision-makers decided other interventions are worth? What is the cost effectiveness ratio for something which has been approved?

They say well, looking at that, if they're willing to spend 100 or 200 thousand dollars for QALY for this, then why not for this? The problem is there's a huge range among decisions, services that are covered. Also the problem with doing that is your cost effectiveness ratio depends on your comparison.

So if you're comparing, say testing for Lynch Syndrome in cancer patients, to no testing. You may get one cost effectiveness

ratio. But if you compare doing universal testing versus using family history, the Bethesda criteria, you'll get a very different cost effectiveness ratio. So the comparator matters.

I mentioned funded services may have a very wide range of cost effectiveness ratios. Treatments for rare diseases, including lysosomal storage disorders, often have cost effectiveness ratios greater than $1 million for QALY, and I'll give an example I think in the next slide.

So orphan drugs to treat rare disorders very commonly cost say 200, 300 thousand dollars per person per year. Cystic fibrosis, the new breakthrough drug that the President mentioned in his State of the Union address, it's targeted at four percent of patients with a specific mutation. It costs roughly $300,000 per year.

It's curative, but it's not life-saving, since the risk of death is fairly low

until people get older. So what is the cost per QALY of that drug? I have not seen that, but it's probably over a million dollars per QALY. Pompe disease, very similar. In Europe, it's been estimated at roughly $1.3 million per QALY for treating someone with Pompe disease using ERT.

Hemophilia A, mean cost on average is $150,000 per year. If you have an inhibitor, roughly seven percent of hemophilia patients, Hemophilia A patients, develop an inhibitor, where they develop an antibody against the clotting factor. The cost for those patients is roughly $500,000 per year. Yet that's -- those treatments are all covered.

So public health, we tend to assume the cost effectiveness ratio is going to be less. Now I'm coming back to that lung cancer screening versus Hepatitis C drug treatment. There was a study published last year, the National Lung Screening trial. There was a cost effectiveness analysis in the *New England*

Journal of Medicine.

For smokers, current or former smokers over age 55 who undergo this screening and then followed up for ten years, current smokers, the ICER was $43,000 per QALY. For former smokers, over $600,000 per QALY.

The new guidelines, the new coverage announced by Medicare, all current or former smokers, assuming they've had at least 30 pack years, and they've quit within the past 15 years, will be covered, and these subjects in the trial had exactly the same criteria. So the cost effectiveness is highly variable.

So for severe, for chronic Hepatitis C virus infection is controversial. A cost effectiveness analysis of a 12 week course of treatment for prisoners calculated that the cost was roughly 25 to 28 thousand dollars per QALY. So very costly intervention, but highly cost effective. So which -- what comparison are you going to use?

Cost-benefit analysis, everything's

in dollars. I'm sorry for the formatting. It's different on my computer than what shows on this one. There are two approaches to evaluating cost-benefit analysis. I'm going to skip the former. The one that's used by most economists, the regulatory analysis is willingness to pay, and you ask what is the average willingness to pay to avoid an ill -- a poor outcome, such as death?

That's called value of statistical life. It's much higher than any other estimate of health. For example, if you look at how much people would lose if they died, in terms of earnings. This is higher, typically six to nine million dollars. Most federal agencies now use a figure of $9 million for every death avoided. So if you're looking at an analysis of preventing air pollution or road deaths, each avoided death is typically going to be valued at $9 million.

It's based on economic analysis of occupational fatalities relative to

compensating wage differentials, and then extrapolated to other areas. I'm just saying that's what's the norm in the public policy arena.

Washington State has been doing cost-benefit analysis of newborn screening expansion since 2002. By law, any regulation in the state of Washington has to have a cost-benefit analysis before it can be approved.

The Washington Department of Health developed its own capacity. They've had their own internal economist, John Thompson, who did his Ph.D. at the School of Public Health, has also participated in and has become adept at developing these spreadsheet models.

Their most recent one they did for SCID in 2012 used a value statistical life of $7.7 million. They also -- some of their analyses they did a cost effectiveness analysis in parallel to the cost-benefit analysis. So if you don't put the dollar value on the avoided deaths, and you just calculate number

of deaths in terms of life years, and cost, you can calculate the cost per life year saved. No QALYs; it was just survival.

So we're currently working with APHL, the Washington APHL and CDC is collaborating on a model, an updated spreadsheet model of testing for SCID, which is going to be customized. Well, it's going to be disseminated so other states can use it and customize it for their purposes, with their own state parameters.

It's going to have both the cost effectiveness and cost-benefit. So I'm going to skip over these slides in the interest of time. There's various steps you need to go through in order to calculate the net costs or cost savings. The bottom line, it's cost effective, and net monetary benefit, both.

So lessons learned from the Washington experience and from other studies. Modeling cost effectiveness analysis or cost benefit, the full economic evaluation, is

resource-intensive. CDC did a cost effectiveness analysis of screening for CCHD. That took -- it was a two year process. APHL has now taken ten months to adapt an existing model from Washington, and it's not quite complete.

Those were for conditions where there's already a very good evidence base. For candidate disorders, where you don't have previously published cost effectiveness models and systematic evidence reviews, it's going to be much more challenging.

Lisa Prosser can't be here today. There's a panel on cost effectiveness which she sits on that's meeting today. She said in her experience, 18 months is a minimum to do a decent quality cost effectiveness analysis. So that's, I think, the last slide.

CHAIR BOCCHINI: Scott, thank you very much. That was a great presentation, and as you indicated, those of us on the CDC ACIP Work Group have been able to have a couple of

talks by again, senior economists such as yourself, and they've been excellent. But I do say that about two weeks after the conference, I wish they were sitting right next to me again.

(Laughter.)

CHAIR BOCCHINI: So let's open this up for questions, comments from the Committee. I think this is a really good start to us really trying to tackle what we need to do and what we could do in a nine-month time frame, to assess the impact of a condition being added to the RUSP. So let's open with any questions or comments on the Committee. Steve.

MEMBER McDONOUGH: Thank you for your excellent presentation. What type of information is there about cost to society, families on level of disability of their child?

Some conditions don't result in life and death; they result in a moderate disability or a mild disability, and you look at divorce rates and then accounting for childbirth,

chronic disease and attention to other siblings and stuff like that. What information is out there on that cost?

DR. GROSSE: Okay, great question. The usual approach is to look at the medical costs and educational costs of treating disability, and then the decrement in quality-adjusted life years. So Lisa and I have published an article where we quantified estimates of the loss in QALYs for different types of developmental disabilities associated with newborn screening conditions or infectious diseases.

There's a lot of variability in the estimates. There's not a single true number. So what our conclusion was any analysis that's doing this should use a range to reflect the uncertainty, rather than putting everything on a single point estimate.

In terms of spillover effects on other family members, that is growing in attention. Lisa has published a couple of

papers addressing that issue. It's hard, because of the lack of good evidence. I did work with another colleague on a survey of families with children with spina bifida, and tried to quantify some of those.

The problem is there's inconsistent estimates from different studies. Is it that families with children with a disabling condition have a higher rate of divorce? Not necessarily. There are some studies like Down's Syndrome, there actually may be a lower rate of divorce, compared to other conditions. So it's very hard to quantify that.

MEMBER BOTKIN: Jeff Botkin. I guess I'm thinking about the cost-benefit analysis of a cost effectiveness analysis for this Committee. There's sort of a general question --

DR. GROSSE: What's the return on investment?

MEMBER BOTKIN: -- about how often do these analyses provide sort of fundamentally

different perspectives on the issues. You know, are there circumstances in which this sort of additional analysis would have perhaps led us to a very different decision about a condition or not? So -- and I don't know whether you're suggesting that this ought to become part of our regular -- maybe that's a question too.

Should this become a regular part of this Committee's workflow, and perhaps the basic question, how often do you think it would make a big difference with the kind of analysis we're already doing?

DR. GROSSE: Okay. First, as an economist, my job is not to make the decision. It's to provide information to the decision-makers. The ACIP has wrestled with this. I think the meningococcal immunization was delayed, in part because of that cost issue. Would you like to address that?

But I think more often, the economic analysis will help by providing evidence

supporting an expansion. So that the idea of doing this model for SCID screening is there's still a lot of states that are not screening for SCID. Why? It's complicated. It requires an investment of resources, doing something different.

Showing that it's highly cost effective compared to other public health expenditures can help provide an argument or justification for the investment of resources for those states to add SCID. That's why we talk about economic evaluations, not necessarily just to make a decision it's something worth doing, but to help in the prioritization.

MEMBER BOYLE: I'm just going to emphasize that point. Last week at Don Bailey's meeting, I can quote him because he said it out loud.

But he made -- the person who runs the newborn screening laboratory made the point that it wasn't until he actually brought the

dollars and cents to the legislature that he actually is getting them to move, actually showing them the return on investment there. So it does work, at least based on what he told us.

DR. GROSSE: Yeah.

MEMBER HOMER: I guess a couple of questions. One is a broader one, which is interesting in that Congress specifically prohibited CMS from considering cost in making its decisions. Well, it seems like Congress directed us to include cost in our consideration. So is there a judgment about maybe is that -- I don't know. It's an interesting reflection about the role of public health versus private health, even though the dollars are all coming from public sources.

Anyhow, that might suggest that a continued imbalance between our investments in health care versus health will accelerate if this process continues. I was struck by your brief comment, and maybe I misinterpreted it,

that said the cost effectiveness, if I'm using the terms right, of screening for most metabolic diseases is --

DR. GROSSE: No, screening cancer.

MEMBER HOMER: No, but you gave a figure of over a million dollars per QALY.

DR. GROSSE: That's treatment for certain rare diseases.

MEMBER HOMER: Okay.

DR. GROSSE: Not all. I just gave a few examples, three different examples.

MEMBER HOMER: Okay.

DR. GROSSE: Orphan drugs for rare disorders are typically very expensive.

MEMBER HOMER: Sure.

DR. GROSSE: And if you look at the cost per person per year of the treatment, and then you calculate how many quality-adjusted life years are saved as a result, your ratio is typically very high, not uncommonly more than $1 million.

MEMBER HOMER: Okay, and therefore -

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DR. GROSSE: That's revealed preference, that society considers it worth spending that money for treating those conditions. I'm not making a value judgment. The economic analysis, this is how much we're spending. This is the health outcome. The health gain in saying our -- do decision-makers consider that to be good value?

MEMBER HOMER: I'm sorry, so could you then contrast that with the old and arbitrary standard of sort of 50 to 100 thousand dollars is the rough, the dollars per QALY that people consider more or less cost effective? That's where I was a little confused, because when you have that figure and then the million dollars, I'm going huh.

DR. GROSSE: So the point is that there's not a single value that decision-makers are saying we're willing to spend $100,000 per QALY. Anything less than 100,000 we should spend, we should pay for. If it's more than

$100,000, like CT lung cancer screening for former smokers, then we shouldn't pay for that. Well, that's not how our society has made those decisions.

MEMBER HOMER: But I guess if part of what the purpose of doing the cost effectiveness analysis is to introduce some element of rationality to our priority-setting process, then if -- because I'm assuming that's part of what we want to do, right? I think --

DR. GROSSE: I don't -- this Committee is not going to introduce rationality into the U.S. health care system.

(Laughter.)

MEMBER HOMER: No, but we could help prioritize recommendations to the Secretary based on -- based on that.

DR. GROSSE: Okay. Within that very limited optimization, not global optimization.

MEMBER HOMER: Yeah.

DR. GROSSE: But also if it's a screening test which is easy to do, low cost

may be considered sufficient. If it costs $1 per infant to screen for a condition using existing instruments, existing -- yeah. People say why not, typically? I'm not recommending that. I'm just saying that's typically how people will respond. If it's a completely new process, new technology that requires investing in that, the standard, the bar is going to be higher.

So I'm saying a cost effectiveness analysis is going to be more influential in the latter than in the former.

MEMBER HOMER: True. I mean that's -- if you're sitting in business, in part you're doing cash flow versus your profit and loss statement. So your cash -- I mean you've got to be putting more money up front, and maybe you don't have it in the bank in the legislature's allocation.

So you can't afford it that year, even though the net return is going to be good over time. Maybe that's another way of framing

that.

MEMBER BOYLE: I guess I go back to the -- I mean just following up on Charlie's conversation, I go back to the SCID example, and I think it's nicely summarized in your slide. I mean it really is.

I mean look at the cost of early versus late treatment. It's like a no-brainer, and for anyone who -- no. Any state who's trying to consider the costs here, you know, without even the human part of it, the financial costs just make a tremendous difference.

So I mean I think that it really can help accelerate the implementation of this. Maybe not everything's going to be as black and white as SCID. But maybe they will be, or at least it will help persuade. For me, looking at this is very persuasive.

DR. GROSSE: But I'd like to call Yao Ding, who's sitting in the first row. He's the cost effectiveness fellow at APHL who's

leading the modeling efforts.

MEMBER BOYLE: And the fact that we have this model now that people -- that states can actually plug in with their values I think is terrific.

MEMBER LU: Scott, you mentioned that it takes about 18 months to do a good cost effectiveness analysis, and Congress asked us to take cost analysis into our consideration, but also gave us nine months to go from nomination to a decision. What can reasonably be done in the nine month period?

DR. GROSSE: Partial economic evaluation.

MEMBER LU: What does that mean?

DR. GROSSE: Calculating what is the cost of implementation from a budget perspective? Not doing a global economic analysis for the whole health care system. But you can say okay, how much is it going to cost a state to implement screening for Condition X? Not just the reagent cost, because reagent cost

is often a relatively small part of the total.

But the whole cost of whatever, changing the laboratory, expanding the space, acquiring the instruments, training -- recruiting and training staff, making sure you've got enough follow-up staff, making sure you've got the referral process in place for the diagnostic centers. What is the cost of all of that? That you can do within nine months.

MEMBER PARISI: I just had -- first of all, thank you for explaining some things that were kind of fuzzy for me, particularly with regard to this cost for treatment of over a million dollars for rare diseases, and sort of in response, Charlie, to your comment as well about that seeming crazy.

The point about the willingness to pay component I think is really important, and I've heard pharmaceutical company representatives say we charge these really high amounts for these drugs for rare diseases

because we can, and because society and insurers in general are willing to pay, A, because they are rare and there aren't that many individuals, and because by virtue of having such a rare condition, it's sort of like we owe it to these individuals with these rare disorders to provide treatment for them, and therefore we're willing to pay these, you know, really extreme costs.

It's also expensive to develop new drugs for a small population. So it's for me, I think, having this comment about willingness to pay is really key for some of these rare diseases.

DR. GROSSE: And that's thanks to Dr. Lu. We had some conversation before this meeting. He asked me to include that in this presentation.

DR. WATSON: Thank you. So unique to genetic disorders are two features, later onset or at least a split between early onset and later onset. Certainly in many that are in

the pipeline right now, and then the fact that when you have Mendelian conditions, you have lots of other family members, that it's rarely factored into genetic testing cost effectiveness.

So I'm wondering what your views are related to newborn screening? Is it always the individual and their benefit that is going to be part of the calculation, or would you extend it further? Because the rarer the disease the more -- when you find one person, you will find more people with the condition in that inheritance group.

DR. GROSSE: For autosomal dominant disorders, the norm is to include the cascade testing of family members. Like for Lynch Syndrome, identifying a patient with colorectal cancer who happens to have a mutation on one of those 4 MMR genes, that doesn't -- that's not cost effective, because they've already had their cancer.

For identifying the family members,

then it becomes cost effective, depending upon how many family members you identify, and whether they agree to undergo the prophylactic screening.

DR. WATSON: So you touch on a third rail then, which is different from colon cancer, in that reproductive decision-making may come from knowing that something's segregating in your family, and people have rarely wanted to include that in cost analyses because it's politically ugly to think they're calculated.

DR. GROSSE: No comment.

DR. TANKSLEY: Is this on? Susan Tanksley. I wanted to follow up on Dr. Lu's question and Scott's response, and it's -- I mean that's only half of the equation, right. So if you know how much it's going to cost to implement, that's one thing, and that's a question that's often asked.

But from a public health lab perspective, we found it much more beneficial

to be able to say what is the cost avoidance if you're doing the screening, and that was very successful for SCID implementation in Texas. We were able to get it implemented, basically because the Medicaid program found, through a cost-benefit analysis, that it was actually much, much more beneficial to screen than to not screen.

That was just looking at 50 percent, 60 percent of our population, not the entire population.

DR. GROSSE: Using charges rather than costs or payments.

DR. TANKSLEY: Using charges.

DR. GROSSE: I think they had for -- I saw the data. She shared the data with me. We'll talk later.

DR. TANKSLEY: Well, it worked. It's often -- it's often hard. It's hard to find that data. It's really, really hard to identify what is the cost avoidance. But anyway, I really appreciate your talk.

DR. GROSSE: When Lisa Prosser, Lisa quoted the 18 month figure, that's assuming you're going to do a systematic evidence review to find the parameters to include in your model. So at the end stage, that's a model that peer -- that could be published in a peer review journal.

If you're just interested in doing sort of a quick back of the envelope calculation for internal purposes without publication, that can take much less time.

But I don't think this Committee could use that kind of an analysis for its work. So one of the suggestions you might consider is within that nine month time period, you could do that cost of implementation analysis or the CRW could do that.

But you could also in parallel they should be working on developing a full economic evaluation, which would not be to inform the Committee's decision, but to help inform the state implementation process, which will take

place after a condition is added to the RUSP.

But of course, that's going to require resources. I don't think the CRW would be able to do that with its existing funding.

MEMBER BOTKIN: Jeff Botkin. So as we think about fostering pilot studies here, as a way of acquiring a better evidence base for making these sorts of decisions, can we -- should we be thinking in terms of incorporating routinely economic considerations in the data collection, so that these sorts of analyses can be promoted?

DR. GROSSE: In terms of the -- yes, brief.

DR. BADAWI: Debbie Badawi. Is the thought then that these -- as you do your framework for or if there is a cost-benefit analysis done for conditions that are nominated to the work group, that there would be a similar -- a model, then, that states could plug into to figure their costs, because obviously different states are going to have

different costs, depending on the specialists available, births, all that.

DR. GROSSE: Correct. That's exactly the goal of the SCID model, is something that different states can then adapt. Some states have one screen or two screens. There's going to be different estimates about the prevalence costs.

MEMBER BOYLE: In that model what -- and the hardest part -- obviously, it's all difficult to get, I'm assuming. But the hardest data to get is the cost offset. Is that right?

DR. GROSSE: Uh-huh, yes.

MEMBER BOYLE: Yeah. Could that be the modeling piece of it? So the other pieces are easy to get, easier. Could you actually model that and have some, you know, have some parameters on that? So at least the Committee could get a sense of what that impact could be.

DR. GROSSE: Actually, these estimates are conservative. The actual

difference in cost is likely to be larger than this, because the cost estimates are coming from -- do not necessarily include all the costs of the hospitalizations for infections before an infant is diagnosed.

So there's some missing there. Also, it's not clear how much after the transplant these are covered. Also, the number of deaths avoided by SCID is probably understated here, because it's based primarily on post-transplant deaths. But there are a lot of infants with SCID who die without a diagnosis or die of infections before they're eligible for a transplant.

So what this analysis does, and we're in the process of revising this; that's why this is a draft -- please do not cite these numbers -- is that even with relatively conservative assumptions, it is still highly cost effective.

CHAIR BOCCHINI: Again Scott, thank you very much. A great presentation.

(Applause.)

CHAIR BOCCHINI: All right. Now we're going to take a short break, and then the subcomittees will meet. So I'm going to turn this over to Debi, so that she can give us some instructions as to where each subcommittee will meet and how to get there.

MS. SARKAR: Okay. So the Education and Training Subcommittee, they are going to be meeting in this room. The Lab Subcommittee and the Follow-up and Treatment Subcommittee will be meeting in the Parklawn Building, which is across the street at 5600 Fishers Lane. What I'm going to ask everyone is in about ten minutes, if you guys could all meet me upstairs by the elevators, I can walk everybody over.

When we get to the Parklawn Building, we'll need to have your driver's license out, so that you can go through security. After that, we will have HRSA staff take you to your respective meeting rooms. So thank you very much.

CHAIR BOCCHINI: Okay. So this will conclude the first day of our meeting. I want to thank everybody for their input, and I want to remind everybody that we're going to start promptly at 9:00 a.m. tomorrow, that following public comments, we will address the second motion that is still open, and then we'll go into the MPS I review, okay.

(Whereupon, the above-entitled matter went off the record at 2:38 p.m.)