

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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DISCRETIONARY ADVISORY COMMITTEE ON HERITABLE  
DISORDERS IN NEWBORNS AND CHILDREN

+ + + + +

MEETING

+ + + + +

THURSDAY  
FEBRUARY 12, 2015

+ + + + +

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

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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

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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.

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1 CHAIR BOCCHINI: Charlie Homer.  
2 MEMBER HOMER: Here.  
3 CHAIR BOCCHINI: Kellie Kelm.  
4 MEMBER KELM: Here.  
5 CHAIR BOCCHINI: Fred Lorey is on  
6 his way. Michael Lu.  
7 MEMBER LU: Here.  
8 CHAIR BOCCHINI: Steve McDonough.  
9 MEMBER McDONOUGH: Here.  
10 CHAIR BOCCHINI: Dieter Matern.  
11 MEMBER MATERN: Here.  
12 CHAIR BOCCHINI: Melissa Parisi.  
13 MEMBER PARISI: Here.  
14 CHAIR BOCCHINI: Alexis Thompson.  
15 MEMBER THOMPSON: Here.  
16 CHAIR BOCCHINI: Cathy Wicklund.  
17 MEMBER WICKLUND: Here.  
18 CHAIR BOCCHINI: Andrea Williams.  
19 MEMBER WILLIAMS: Here.  
20 CHAIR BOCCHINI: And Debi Sarkar.  
21 MS. SARKAR: Here.  
22 CHAIR BOCCHINI: And then our

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

4 DR. CHEN: Here.

5 CHAIR BOCCHINI: American Academy of  
6 Pediatrics, Beth Tarini.

7 DR. TARINI: Here.

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

10 DR. WATSON: Here.

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

13 DR. NANCY -ROSE: Here.

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

17 DR. BADAWI: Here.

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

20 DR. TANKSLEY: Here.

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

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1 Kus.

2 DR. KUS: Here.

3 CHAIR BOCCHINI: Department of  
4 Defense, Adam Kanis.

5 DR. KANIS: Here.

6 CHAIR BOCCHINI: Genetic Alliance,  
7 Natasha Bonhomme.

8 MS. BONHOMME: Here.

9 CHAIR BOCCHINI: March of Dimes,  
10 Siobhan Dolan.

11 DR. DOLAN: Here.

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

14 DR. VOCKLEY: Here.

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

17 DR. GREENE: Here.

18 Opening Remarks

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

22 Let's see. For my opening remarks,

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

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

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

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1 added to the work of the Committee.

2 But the bill, now law, allows the  
3 Committee's work to continue uninterrupted. So  
4 we should have a seamless change from the  
5 discretionary committee to the Secretary's  
6 committee. And so on our meeting in May, May  
7 11th and 12th, we will resume as the  
8 Secretary's advisory committee. So this would  
9 be the last meeting of the discretionary  
10 committee.

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

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

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1 appropriate transition.

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 aspects.

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

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

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

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

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

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

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

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

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

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

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

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

19 MEMBER DOUGHERTY: I think that's --  
20 so they'll start considering issues maybe in  
21 2018? That's my guess, but you never know with  
22 Congress.

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

7 MEMBER DOUGHERTY: Joe?

8 CHAIR BOCCHINI: Yes.

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

13 CHAIR BOCCHINI: If you can answer  
14 that.

15 MS. SARKAR: Unfortunately no.

16 CHAIR BOCCHINI: Charlie.

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

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

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

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

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

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

22 CHAIR BOCCHINI: Yes sir.

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

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

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

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

22                   MS. SARKAR:        I just want to add

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

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

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

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

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

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

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

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

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

12 Approval of September 2014 Meeting Minutes

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

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

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

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

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

7 (Laughter.)

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

10 (No response.)

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

16 (No response.)

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

19 MEMBER BAILEY: Yes.

20 CHAIR BOCCHINI: Yes for me. Jeff  
21 Botkin.

22 MEMBER BOTKIN: Yes.

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1 CHAIR BOCCHINI: Colleen Boyle?  
2 MEMBER BOYLE: Yes.  
3 CHAIR BOCCHINI: Denise Dougherty?  
4 MEMBER DOUGHERTY: Yes.  
5 CHAIR BOCCHINI: Kellie Kelm.  
6 MEMBER KELM: Yes.  
7 CHAIR BOCCHINI: Charlie Homer.  
8 MEMBER HOMER: Yes.  
9 CHAIR BOCCHINI: Fred Lorey.  
10 MEMBER LOREY: Yes.  
11 CHAIR BOCCHINI: Michael Lu.  
12 MEMBER LU: Yes.  
13 CHAIR BOCCHINI: Steve McDonough.  
14 MEMBER McDONOUGH: Yes.  
15 CHAIR BOCCHINI: Dieter Matern.  
16 MEMBER MATERN: Yes.  
17 CHAIR BOCCHINI: Melissa Parisi.  
18 MEMBER PARISI: Yes.  
19 CHAIR BOCCHINI: Alexis Thompson.  
20 MEMBER THOMPSON: Yes.  
21 CHAIR BOCCHINI: Cathy Wicklund.  
22 MEMBER WICKLUND: Yes.

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1 CHAIR BOCCHINI: And Andrea  
2 Williams.

3 MEMBER WILLIAMS: Yes.

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

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

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

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

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

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

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

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1 Thanks for inviting me to speak to you today.

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

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

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

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

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

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

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

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

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

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

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1 evidence-based recommendations.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 Force does the following steps to arrive at a  
2 recommendation.

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

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

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

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1 populations, which directly assess the effects  
2 on health outcomes.

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

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

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

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

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

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

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

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

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

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

22 And so with A and B recommendations,

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

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

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

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1 C, D and the I statement.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22          Also, you know, I was interested in

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 CHAIR BOCCHINI: Charlie Homer.

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

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

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

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

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

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

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

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

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

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

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

17 CHAIR BOCCHINI: Thank you.  
18 Melissa.

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

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1 I think that was just in that second band.

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

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

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

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

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1 are now being put upon us.

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

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

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

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

22 So from that perspective do you find

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

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

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

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

22 DR. KEMPER: Alex Kemper, and now

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 And I doubt they're going to bring

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1 any money this way, but that would be a better  
2 question for Iris, Iris "Moneybags" Mabry.

3 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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1 know, a partner, for example, AARP.

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

8 MEMBER THOMPSON: Payers?

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

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

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

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

8 CHAIR BOCCHINI: Freddie.

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

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

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1 and that would be not ideal, not disastrous.

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

9 CHAIR BOCCHINI: Denise.

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

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

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

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

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

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

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

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

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

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

22 (Applause.)

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1 Pilot Study Work Group Update

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

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

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

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

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

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

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

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

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

22 So this is a little bit of an aside,

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

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

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

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1 have been de-identified or not.

2 As folks know, the vast majority of  
3 research on dried blood spots is with de-  
4 identified blood spots. So that brings it  
5 under IRB oversight, brings it under the rest  
6 of the regulations. Also, this first section  
7 says that Sections 46.1168 and 116(d) of Title  
8 45 shall not apply.

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

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

22 So two caveats here just to point

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

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

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

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

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

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

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

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

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

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

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

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

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

21 (No response.)

22 MEMBER BOTKIN: Okay, not at the

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1 moment, but stay on the line.

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

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

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

22 Also Kathy Swoboda, formerly at Utah

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

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

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

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

9 So Carla Cuthbert from CDC will be  
10 our first speaker.

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

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

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

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

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

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

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

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

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

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1 to fund two-year implementation activities. In  
2 2011 and '12, we supported Michigan and  
3 Minnesota. In 2013 and '14, Oklahoma, Virginia  
4 and Georgia were the recipients of our  
5 activities. In the fall of 2015, we don't know  
6 yet. We are looking forward to being able to  
7 support another group of states.

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

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1 other public health community members.

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

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

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

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

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

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

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

4 This slide is just to give you an  
5 idea of how long we have been doing this. This  
6 has been happening for about 35 years, since  
7 1978, when the first program rolled out for our  
8 congenital hyperthyroidism. This is also to  
9 give you an indication, but things don't happen  
10 at the flick of a switch. We need to be very  
11 much prepared, and we need to know what is  
12 being considered, so that we can start  
13 developing the level of expertise that we need  
14 within the branch, to provide quality assurance  
15 materials.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22                  DR. CUTHBERT:        Well, it will impact

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

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

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

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

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

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

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

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

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

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

22 Sorry. So we have a model of

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

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

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

22 As I said, we have a sources slot

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

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

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

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

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

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

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

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

22 All right, yes, okay. So this is

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

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

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

22 What I'm going to try to cover

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 collection of data in pilots.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 I think if you look -- I'm going to  
7 page through this. So that gives us a total of  
8 57 conditions potentially being identified out  
9 of newborn screening. As we go to begin to  
10 look at really where this seems to be going,  
11 here's a quick, another 16 that are pretty well  
12 on the launch pad. Some have issues of the  
13 paradigm that justifies newborn screening for a  
14 particular condition like Fragile X, where a  
15 lot of data still needs to be generated.

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

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1 potentially.

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

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

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

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1 deal with everything that's coming up.

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

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

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

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

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

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

19 So there will be a meeting on March  
20 9th. There will be information forthcoming  
21 afterwards, where we're really going to discuss  
22 a lot of these issues as they relate to the

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

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

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

16 MS. SARKAR: I can.

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

19 DR. COMEAU: Hello.

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

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

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1 on.

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

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

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

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1 people, and what I say I own.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 expectation for quality improvement services  
2 that we provide.

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

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

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

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1 of national data, to support the RUSP  
2 recommendation.

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

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

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

22 So politics has entered public

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

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

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

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

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

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

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

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

22 Next slide, please. Budgets are

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

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

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

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1 for them.

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

9 We have the -- we have the new  
10 amendment to the Newborn Screening Saves Lives  
11 Act. Finally, this new kind of legislation,  
12 we're going to have to deal with it. It shows  
13 good intentions with challenging outcomes. But  
14 we'll make it work. We have in Massachusetts  
15 done consent-based studies, and it's worked for  
16 15 years. Either that will work or something  
17 else will come forward.

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

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

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

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

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

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

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

18          MEMBER BOTKIN: Yes sir, Don.

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

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1 forward on any of these activities.

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

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

18 Public Comments

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

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

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

8 OPERATOR: Sarah's line is now open.

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

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

13 CHAIR BOCCHINI: Yes, we can.

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

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

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

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

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

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

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

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

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

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1 states improve.

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

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

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

20 MS. WILKERSON: Thank you.

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

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

4 MS. WILKERSON: Great, thanks.

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

8 OPERATOR: The line is open.

9 CHAIR BOCCHINI: Thank you.

10 MS. SEEGER: Hello?

11 CHAIR BOCCHINI: Yes, we can hear  
12 you.

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

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

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

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

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

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

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

11 The ALD newborn screening manuscript  
12 has just been published, and is readily  
13 available for review. It is clear New York  
14 State has set the example every state can  
15 follow. The New York State Newborn Screening  
16 Program is willing to share their data so every  
17 state can test for ALD. We know that early  
18 diagnosis is the only way to save lives. Every  
19 36 hours another baby will be born with ALD.

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

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1 leaving behind his wife and three children. An  
2 11 year-old boy from Arizona lost his battle to  
3 ALD on Monday, and with a diagnosis for his  
4 older brother, who also has ALD.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 Laboratory Procedures and Standards  
9 Subcommittee

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

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

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

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

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

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

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

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

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

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

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

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

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

22 One of the things that we did was to

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

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

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

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

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

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

22           We did this at both in-person

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 conditions.

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

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

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

22 So provide the information, but

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

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

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

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

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

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

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

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1 collection.

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

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

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

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1 reporting procedures and statements.

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

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

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

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

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

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

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

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

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

22           MEMBER BOTKIN: Now we had a little

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 MEMBER WILLIAMS: inaudible

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 will make sure it happens.

2

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

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

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

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

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

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

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

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

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

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

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

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

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

22 CHAIR BOCCHINI: Okay. Steve.

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

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

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

22                  By 2017, this Committee would

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

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

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

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

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

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

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

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

22 MEMBER BAILEY: So I support the

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

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

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

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

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

10 Is there additional discussion?  
11 Cathy, and then Charlie.

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

18 CHAIR BOCCHINI: Okay.

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

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

3                   CHAIR BOCCHINI:   Okay.    So Charlie.

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

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

20                   CHAIR BOCCHINI:   So I think for Part  
21      1, these recommendations are going to be the  
22      recommendations of the Committee.    They're not

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

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

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

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

6                   CHAIR BOCCHINI: For the second  
7 part.

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

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

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

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

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

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

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

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

5 MEMBER BAILEY: I vote to approve.

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

8 MEMBER BOTKIN: Approve.

9 CHAIR BOCCHINI: Coleen Boyle.

10 MEMBER BOYLE: Approve.

11 CHAIR BOCCHINI: Denise Dougherty.

12 MEMBER DOUGHERTY: Approve.

13 CHAIR BOCCHINI: Kellie Kelm.

14 MEMBER KELM: Approve.

15 CHAIR BOCCHINI: Charlie Homer.

16 MEMBER HOMER: Approve.

17 CHAIR BOCCHINI: Fred Lorey.

18 MEMBER LOREY: Approve.

19 CHAIR BOCCHINI: Michael Lu.

20 MEMBER LU: Approve.

21 CHAIR BOCCHINI: Steve McDonough.

22 MEMBER McDONOUGH: Approve.

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1 CHAIR BOCCHINI: Dieter Matern.

2 MEMBER MATERN: Approve.

3 CHAIR BOCCHINI: Melissa Parisi.

4 MEMBER PARISI: Approve.

5 CHAIR BOCCHINI: Alexis Thompson.

6 MEMBER THOMPSON: Approve.

7 CHAIR BOCCHINI: Cathy Wicklund.

8 MEMBER WICKLUND: Approve.

9 CHAIR BOCCHINI: And Andrea  
10 Williams?

11 MEMBER WILLIAMS: Approve.

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

19 Evaluating Harms in Assessment of Net Benefits

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

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1 process as it stands now.

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

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

17 She received her medical degree and  
18 her clinical training at Columbia University.  
19 From 2000 to 2007, she served at the March of  
20 Dimes as the national medical director there  
21 from 2002 to 2007. She returned to Columbia in  
22 2007. Her federally funded research focuses

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

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

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

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

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1 one?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 just difficult to monitor.

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

7 CHAIR BOCCHINI: Don.

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

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

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1 don't take speculative benefits as evidence.

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

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

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

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

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

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

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

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

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

5 CHAIR BOCCHINI: Melissa and then  
6 Coleen.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5 DR. NANCY GREEN: Thank you.

6 Condition Review Update ALD

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

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

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

22 DR. KEMPER: Oops, I was changing

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18           Screening can be accomplished in  
19 dried blood spots. Dr. Salzman talked a little  
20 bit about this before. There's a study that's  
21 being led by Dr. Matern, with looking at  
22 100,000 anonymous dry blood spots. There's

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

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

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

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

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

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

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

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

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

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

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

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

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1 done in a high throughput method.

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

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

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

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

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

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

22 So this is what I propose, is that

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. NANCY GREEN: Can I ask for a

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22          Can I say something more? While

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

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

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

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

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1 understand from their experience within a  
2 reasonable period of time?

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

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

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

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1 carrier females?

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

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

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

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

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

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

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

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

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

5 MEMBER LOREY: Yeah, so --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 drive any decision by this body.

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

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

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

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

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

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

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

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

5 And then regarding stem cell  
6 transplantation, you have to follow the boys,  
7 and I don't think the recommendation is MRI  
8 early on. I think it starts around age of two  
9 years, okay. This is -- I'm quoting the expert  
10 pediatric neurologist, Dr. Raymond and Dr.  
11 Fatimi and others. So and gene therapy is on  
12 the horizon. There are a number of transplants  
13 that have been done, and we're following the  
14 data on those.

15 So that you don't always have to  
16 have a perfect match for bone marrow  
17 transplantation. And then as far as the  
18 females, it's extremely important to identify  
19 them. You're not going to identify all of  
20 them. You're going to miss some. But you will  
21 -- with a little girl baby who has -- who's a  
22 carrier for ALD, you'll be able to do genetics

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1 in the family and identify other affected males  
2 possibly.

3 So I'm available for any questions,  
4 and I'm sure that we all want to see ALD  
5 recommended universally. Thank you.

6 CHAIR BOCCHINI: Thank you.

7 DR. KEMPER: Say your name for the  
8 record.

9 MR. MOSER: Ann Moser.

10 DR. KEMPER: I was going to say it  
11 for you, but I didn't want to overstep my  
12 bounds.

13 CHAIR BOCCHINI: All right. Any  
14 other questions or comments? Don.

15 MEMBER BAILEY: Two things. Since  
16 Fred and I are responsible for the Committee's  
17 input, what's the timing of this Joe? Are we  
18 thinking of this in the next -- are we trying  
19 to shoot to vote in the next Committee meeting  
20 on this, is one question?

21 Then secondly, I think in terms of  
22 what would be helpful for us, I'd really love

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1 to know the percentage of babies that need to  
2 have a treatment within the first year or two  
3 of life.

4 CHAIR BOCCHINI: So I think maybe  
5 you can answer the second question. I think  
6 the first question is that the Evidence Review  
7 Committee is working as hard as they can to try  
8 and get this done, but I'm not sure we've got a  
9 specific time set for presentation. So  
10 hopefully next meeting, but we're not sure that  
11 we can get it done by then.

12 MEMBER MATERN: Dieter Matern. I  
13 think one of the big advantages of this review  
14 is that you can actually get evidence from what  
15 is going on in New York, and I think it was  
16 mentioned earlier that maybe there's a  
17 publication already out about the first year.

18 I couldn't find it in PubMed. But I  
19 think looking at the follow-up algorithm and  
20 what happened with these patients that were  
21 identified, I think it's going to be extremely  
22 important, independent of whether it's X-ALD or

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1 one of the other peroxisomal disorders.

2 Furthermore, among those centers in  
3 New York that are following these patients,  
4 they would also be the first ones who would  
5 make a diagnosis of ALD spectrum disease in any  
6 of the other conditions that you would expect  
7 to be picked up, and could confirm whether it  
8 was a false negative for those, although for X-  
9 ALD it might be more difficult to get to the  
10 false negative number.

11 MEMBER BOTKIN: Jeff Botkin, and I -  
12 - it doesn't look like you've done the public  
13 health impact survey stuff yet. But I'd wonder  
14 if you'd just make a comment or two about how  
15 easy this would be to bring onto existing  
16 platforms, etcetera.

17 DR. KEMPER: I have no idea.

18 MEMBER HOMER: I just want to make  
19 maybe a random comment related to the new  
20 legislation authorizing our Committee, because  
21 it's going to come up in this. The mandate for  
22 us to be quick, sometimes I think may result in

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1 ultimately a delay in approvals, because if  
2 there's a study, for example like what's  
3 happening in New York in the field and we'd  
4 want a second year of data to really inform our  
5 decision, that might allow us to actually make  
6 a quicker recommendation than based on  
7 insufficient evidence to have to come up with a  
8 negative recommendation. Then it would be some  
9 time until we are able to put it back in the  
10 queue.

11 So I'm sure everyone knew that  
12 already, but I just wanted to kind of get that  
13 concern in the record.

14 CHAIR BOCCHINI: That's a good  
15 point, and that's part of the reason why we  
16 have to kind of go back and see what is  
17 necessary to have in place before a condition  
18 can get through the Nomination Prioritization  
19 Work Group. I think that's absolutely right,  
20 yeah.

21 Okay. Alex, I think you've had some  
22 feedback.

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1 DR. KEMPER: Thank you.

2 CHAIR BOCCHINI: So thank you very  
3 much, and I thank everybody for their comments  
4 and questions. I think we're -- we did get  
5 behind, but I think all of the information that  
6 was presented this morning was really  
7 important, and I think that it was well worth  
8 getting behind for. So we're going to get  
9 everybody -- yes, Coleen.

10 MEMBER BOYLE: Could I just ask, oh  
11 sorry, clarity. I just don't know whether we  
12 had come to a decision about the suggestion  
13 Alex and the Review Group had put forward. So  
14 is the proposal that he made, in terms of  
15 focusing on the more serious outcomes of  
16 childhood onset versus the -- is that the way  
17 it's going to go?

18 CHAIR BOCCHINI: Well, I don't think  
19 we have a conclusion to that. But I think some  
20 of the comments that were made about adrenal  
21 insufficiency and the importance of recognizing  
22 that, and then determination -- at what age we

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1       could determine cerebral versus non-cerebral, I  
2       think, needs to be in the mix.

3               I think we have two Committee  
4       members who are involved in the review, who can  
5       kind of flesh that out with the Condition  
6       Review Group, and then come back to the  
7       Committee if we have to address those in a  
8       little more detail. But I think -- I think we  
9       have enough for them to move forward, without a  
10      specific -- I think we've broadened it rather  
11      than shortened it, okay?

12              All right. Bring your lunch back  
13      here, and then we'll do our best to see if we  
14      can get started when we have a quorum.

15              (Whereupon, the above-entitled  
16      matter went off the record at 12:51 p.m. and  
17      resumed at 1:31 p.m.)

18

19

20

21

A F T E R N O O N   S E S S I O N

22

1:31 p.m.

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1 CHAIR BOCCHINI: All right. We're  
2 ready to go ahead and start the session.  
3 Welcome back to the afternoon session of the  
4 first day of our sixth meeting of the  
5 Discretionary Advisory Committee. To start  
6 off, we need to take attendance. So let's do  
7 that. First, the members. Don Bailey.

8 MEMBER BAILEY: Here.

9 CHAIR BOCCHINI: All right, I'm  
10 here. Jeff Botkin.

11 MEMBER BOTKIN: Here.

12 CHAIR BOCCHINI: Coleen Boyle. Not  
13 back yet. Denise Dougherty.

14 MEMBER DOUGHERTY: Here.

15 CHAIR BOCCHINI: Charlie Homer.

16 MEMBER HOMER: Here.

17 CHAIR BOCCHINI: Kellie Kelm.

18 MEMBER KELM: Here.

19 CHAIR BOCCHINI: Fred's not back  
20 yet. Michael Lu.

21 MEMBER LU: Here.

22 CHAIR BOCCHINI: Steve McDonough.

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1 MEMBER McDONOUGH: Here.

2 CHAIR BOCCHINI: Dieter Matern. Not  
3 back yet. Melissa Parisi.

4 MEMBER PARISI: Here.

5 CHAIR BOCCHINI: Alexis Thompson.

6 MEMBER THOMPSON: Here.

7 CHAIR BOCCHINI: Cathy Wicklund.

8 MEMBER WICKLUND: Here.

9 CHAIR BOCCHINI: Andrea Williams.

10 MEMBER WILLIAMS: Here.

11 CHAIR BOCCHINI: And Debi Sarkar.

12 MS. SARKAR: Here.

13 CHAIR BOCCHINI: And then the  
14 organizational representatives, Freddie Chen.

15 DR. CHEN: Here.

16 CHAIR BOCCHINI: Beth Tarini.

17 DR. TARINI: Here.

18 CHAIR BOCCHINI: Michael Watson.

19 DR. WATSON: Here.

20 CHAIR BOCCHINI: Nancy Rose.

21 DR. NANCY ROSE: Here.

22 CHAIR BOCCHINI: Debbie Badawi.

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1 DR. BADAWI: Here.

2 CHAIR BOCCHINI: Susan Tanksley.

3 DR. TANKSLEY: Here.

4 CHAIR BOCCHINI: Chris Kus. Adam  
5 Kanis. Natasha Bonhomme.

6 MS. BONHOMME: Here.

7 CHAIR BOCCHINI: Siobhan Dolan.

8 PARTICIPANT: Here.

9 CHAIR BOCCHINI: Cate Walsh Vockley?

10 DR. VOCKLEY: Here.

11 CHAIR BOCCHINI: And Carol Greene.  
12 Not back yet. Okay. Oh, Dieter made it.  
13 Okay. All right.

14 (Laughter.)

15 CHAIR BOCCHINI: So you're implying  
16 that you were late enough that you missed the  
17 roll call? Is that what it was? Maybe that's  
18 how that happened, okay. Okay. We can strike  
19 that from the record.

20 (Laughter.)

21 Cost and Cost Effectiveness Analysis

22 CHAIR BOCCHINI: So we're going to

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1 start the afternoon session with Dr. Scott  
2 Grosse presenting data on cost and cost  
3 effectiveness analysis, and as you know, this  
4 has become a much more important part of all  
5 federal committee activities, and certainly  
6 this has become very important to the ACIP, of  
7 which I've been a member for the past four  
8 years.

9 What I've seen happen is that we  
10 started off by years ago indicating that we  
11 were making a decision about what was best for  
12 patients, and cost was not an issue. Now, as  
13 we've gotten to the point where we have  
14 vaccines that are not all cost-saving, but do  
15 have some cost to the public, that we now have  
16 incorporated cost and cost effectiveness into  
17 our decision-making process.

18 It's not the primary thing that  
19 motivates a decision, but it's considered, and  
20 it has played a role in some of the recent  
21 decisions that the ACIP has made. So I think  
22 it is an important aspect, and as we've already

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1 discussed, this has certainly become part of  
2 our mission, to include cost and cost  
3 effectiveness analysis in the decisions that we  
4 make.

5 So we're pleased to have Scott here.  
6 Scott is a senior health economist at the  
7 National Center on Birth Defects and  
8 Developmental Disabilities for the CDC. And so  
9 he's worked with others in the Condition Work  
10 Group, Review Work Group, and has been very  
11 helpful to us over the past months, as we've  
12 worked through our process of modifying our  
13 decision matrix.

14 So Scott, we'll turn this over to  
15 you, and let you get started. Thank you.

16 DR. GROSSE: Okay. I'd like to  
17 thank Dr. Lu and the Committee for inviting me.  
18 Can you hear me now? Can you hear me? Now?  
19 Now? Okay. Okay, thank you.

20 Okay. Acknowledgments from  
21 colleagues who've given me some assistance on  
22 this presentation. Glossary, what is cost?

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1 Cost means different things to different  
2 people. For an economist, cost refers to  
3 resources used up or foregone. There are  
4 direct costs, which is what do you do when  
5 you're actually providing care. Indirect cost  
6 is the foregone value of economic production,  
7 because someone is sick or has died.

8 Cost analysis or a partial economic  
9 evaluation, you can look at what is the cost  
10 caused by a disease, or what is the cost of an  
11 intervention, such as a screening program.  
12 That's then in contrast, you have a full  
13 economic evaluation, where you put the cost  
14 together with outcomes.

15 So cost effectiveness analysis, you  
16 look at what is the cost and what is the health  
17 outcomes. Cost benefit analysis is similar,  
18 except all outcomes are put in dollar terms,  
19 monetary terms. You have a single metric of  
20 dollars.

21 Economic cost, as I said, is the  
22 value of resources that are used up, and it

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1 doesn't matter who pays for it. If you have an  
2 in-kind cost, it's still a cost. You value the  
3 donated services or time at what the  
4 opportunity cost is, which is the value that  
5 they could have been doing if they were doing  
6 something else.

7 In contrast, you have financial cost  
8 for the accounting cost. What is the budget?  
9 So which costs, economic cost or financial cost  
10 depends on the perspective of the analysis,  
11 which depends on the audience that you're  
12 trying to inform. You have variable and fixed  
13 costs, general principles.

14 As long as you are covering your  
15 variable costs, you're at least breaking even.  
16 But fixed costs, which do not vary with the  
17 level of output, needs to be taken into account  
18 for long-term sustainability.

19 Marginal cost and incremental cost  
20 are similar but slightly different. Marginal  
21 cost is when you do more of the same thing, how  
22 does your average cost change? Incremental

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1 cost is when you do something different like --  
2 so a marginal cost, if you test more specimens  
3 for a given assay, how does your cost change?  
4 Incremental cost is when you're testing for a  
5 new condition using a new test, how does that  
6 alter your costs?

7 How to estimate costs in the health  
8 care arena. For direct costs, the micro-  
9 costing is when you measure the value of  
10 ingredients, the labor, time, equipment,  
11 consumables such as reagents. You have to  
12 calculate what are the quantities and what is  
13 the unit cost of each to calculate the total  
14 cost. An alternative is cost accounting data  
15 if you have a cost accounting system in place.

16 Now there's an indirect way which is  
17 not -- I'm sorry. It's different than indirect  
18 cost. This is indirect estimation of direct  
19 cost. Actually, the term indirect cost,  
20 productivity losses, there's controversy about  
21 that terminology too.

22 But charges. It's very common to

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1 use information on how much a hospital or a  
2 clinic or a drug company charges for a  
3 particular service. The problem is charges in  
4 this country bear very little relationship to  
5 cost. There is a relationship, but it's very  
6 inexact.

7 On average, charges are more than  
8 twice what the estimated cost is, sometimes  
9 five times more or even more. It depends; it's  
10 very variable. So if you have just charged,  
11 it's hard to actually know what the cost is,  
12 although there are cost to charge ratios.

13 It's very common to use these  
14 schedules, such as the National Medicare fee  
15 schedule as a proxy even for pediatric cost,  
16 because it's something that's standard.  
17 Average payment. If you have claims data from  
18 multiple payers, you can calculate what is the  
19 average reimbursement, with the idea that  
20 providers are not going to continue providing a  
21 service if they're getting reimbursed from all  
22 payers, less than it's costing them to provide

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1 the service.

2 There's no single gold standard  
3 measure of cost. There's different ways of  
4 trying to estimate it. So how do you estimate  
5 the incremental cost of adding a new test using  
6 dried blood spots? Fixed cost, collecting the  
7 specimen, the laboratory, transporting the  
8 specimen, that doesn't change when you add  
9 disorders. It's only the cost associated with  
10 the new condition.

11 So you have the laboratory staff,  
12 equipment, reagents, the space and utilities  
13 that are required for the additional space.  
14 Then short term follow up and tracking. The  
15 downstream costs to health care systems and  
16 families are harder to assess. There's the  
17 cost for the clinical follow-up from the  
18 reporting of the laboratory results.

19 You need to bring in the family and  
20 the additional time spent with that family,  
21 long-term management. But for long-term  
22 management, you have to -- it's only the

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1 difference between the management that would  
2 come with screening and costs without  
3 screening. If a condition is going to be  
4 identified in the absence of screening, just  
5 delayed, then it's the difference in the  
6 management cost.

7           Whereas if a disorder is not  
8 identified in the absence of screening, then  
9 all of that long-term management cost would  
10 have to be included. So but the bottom line is  
11 the cost of expansion of newborn screening is  
12 more than just the laboratory cost.

13           I'm going to give an example,  
14 testing for LSDs, such as MPS I. A state that  
15 did an analysis of the cost of testing for LSD,  
16 which is not named, with calculated for 100,000  
17 births per year, an average 1.2 screens per  
18 infant. So one screen state. But that doesn't  
19 mean it's just 1.0 screens, as everyone knows.

20           So in order to use -- assuming  
21 they're using the full injection tandem mass  
22 spectrometry, you'd have to purchase or lease

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1 three of these instruments, along with the  
2 ancillary equipment, and they calculated the  
3 cost as \$1.2 million, which is higher than some  
4 estimates because the ancillary equipment adds  
5 to the total cost.

6 So you can use standard accounting  
7 formula to calculate the cost of depreciation.  
8 That's about \$160,000 per year, plus  
9 maintenance cost, plus cost of lab upgrades  
10 that were needed to include these tandem mass  
11 specs. So the total cost of equipment per year  
12 is roughly \$330,000, and then labor cost is  
13 roughly the same amount of money.

14 For the incremental cost for a given  
15 disorder, it's the cost of the reagent. So the  
16 testing for LSDs, whether you test for one LSD  
17 or five LSDs, it's roughly the same. So it's  
18 the reagents, which is about a dollar per  
19 specimen, or -- so the total cost to screen for  
20 one LSD is a little less than \$8. Each  
21 additional LSD would be \$1.20 extra in  
22 laboratory cost.

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1           So you cannot answer the question in  
2 isolation of what is the cost to screen for MPS  
3 I. It all depends. How many other LSDs are  
4 you screening for? Then there's the cost of  
5 the diagnostic testing. So if there's a  
6 complicated algorithm, which varies from state  
7 to state, but in general those --

8           So the screening algorithm varies.  
9 So where you set the cutoffs, the technology  
10 used is going to influence the number of  
11 infants who get referred for diagnostic  
12 testing, and then within the diagnostic  
13 testing, there are different protocols. So how  
14 many were used at the cutoffs on these  
15 diagnostic tests, the first -- the enzyme, the  
16 IDUA enzyme activity assay, the GAG assay.

17           Those are trying to rule out most of  
18 the positives. Once you've -- and the cost of  
19 that is between 200 and 600 dollars per  
20 specimen, according to the Public Health System  
21 Impact Assessment Fact Sheet that you have in  
22 your briefing book.

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1           So the total cost, depending upon  
2           how many get tested, could be anywhere from  
3           \$2,000 to \$27,000 for 100,000 infants screened.  
4           Then you'll have a small number that do need  
5           DNA testing, the gene sequencing for the IDUA  
6           gene, and that could add anywhere from two to  
7           eight thousand dollars.

8           So the total cost works out to  
9           anywhere from five cents to 35 cents for  
10          infant.       Now you'll note that that's  
11          substantially less than the \$1.20 for the  
12          screening test.   So even at 35 cents, that's  
13          assuming a high, relatively high rate of false  
14          positives.   Many people say well, there's such  
15          a high rate of false positives with this  
16          testing.   That's too much of a burden.

17          But even at the upper end of the  
18          estimate of false positives or pseudodeficiency  
19          genes, it's still low compared to the cost of  
20          the initial screening.   SCID.   We've been  
21          working with the Washington Department of  
22          Health to analyze their costs.   They published

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1 or they did a report. They analyzed the cost  
2 of doing the TREC assays.

3 A little over \$8 per infant, two  
4 screen state. So it's less than \$8 per screen.  
5 Some labs have reported \$6 per specimen. For  
6 the short-term follow-up, they calculate on  
7 average one hour of staff time for each  
8 positive screening result. That's sort of a  
9 generous estimate. So you say including all  
10 the costs, the fringe benefits, the  
11 supervision, it's about maybe \$50 per positive  
12 screen.

13 That's a lot of money, but  
14 considering the number of positive screens that  
15 need to be followed up, that added two cents  
16 per infant tested. The cost of flow cytometry  
17 testing, about \$250, including the phlebotomy  
18 and the clinical interpretation done at the  
19 university medical center. So the total  
20 screening cost, including the diagnostic  
21 testing, \$8.17.

22 That's when Washington added SCID.

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1 They raised the fee by \$8.17, based on this  
2 analysis they had done. But states differ.  
3 States differ in terms of the technology used,  
4 what -- how much follow-up is done inside  
5 versus contracted out. Some states pay for the  
6 cost of the confirmatory and diagnostic  
7 testing; others don't.

8 Florida, there was a recent article  
9 published by Kubiak et al., quoting the Florida  
10 Department of Health, which raised their fee by  
11 \$16.67 to cover the cost of SCID testing. No  
12 breakdown provided, but that included costs for  
13 co-location and referral center contracts, as  
14 well as the laboratory and short-term follow-up  
15 costs.

16 There's both -- now you notice these  
17 analyses have been from the financial cost,  
18 from the perspective of the department of  
19 health in a state. From an economics  
20 perspective, you want to include not just the  
21 costs, whether it's measured financially or  
22 economic costs to the screening program, but

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1 also what are the costs to the clinical system,  
2 comparing the management of the disorders  
3 identified through newborn screening, versus  
4 not newborn screening.

5 This is from a paper that Lisa  
6 Prosser published in 2010, a cost effectiveness  
7 analysis of newborn screening for MCAD  
8 deficiency. With MCAD, there are maybe a third  
9 of the children would not be diagnosed in the  
10 absence of newborn screening. They'd be  
11 asymptomatic, and so there's some additional  
12 costs of diagnosis and follow-up, some savings  
13 in cost of treatment because of voided  
14 hospitalizations.

15 So they calculated the estimated,  
16 the net difference in treatment costs. The  
17 exact numbers are not important, but the  
18 principle is that if you're looking at the  
19 total impact of adding a condition, you want to  
20 look not just at the screening cost but also  
21 the downstream costs.

22 Now we're going to go beyond the

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1 cost of implementation, to considering what is  
2 the balance of costs and benefits, which is --  
3 the term "value" is shorthand. There are many  
4 different words that people use that are often  
5 used interchangeably. People will say oh,  
6 that's cost effective. It's cost saving.

7 Dr. Bocchini's familiar with the  
8 difference. His service on the ACIP has given  
9 him a lot of exposure to these terms and  
10 estimates. Cost beneficial, positive ROI. The  
11 terms are not interchangeable. They have  
12 different meanings. Each is associated with a  
13 different analytic method, and the choice of  
14 the method should depend on the purpose of your  
15 analysis and your audience or stakeholders.

16 So the three major economic  
17 evaluation methods, there's cost effectiveness  
18 analysis, which asks what approach costs less  
19 per unit of health gained? There's a subtype  
20 of cost effectiveness analysis that's also  
21 called cost utility analysis, where you  
22 calculate the cost for quality adjusted life

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1 year, cost for QALY.

2 Then there's cost-benefit analysis,  
3 which as I mentioned everything is put in the  
4 dollar terms, and the question is the monetary  
5 benefit to society greater than the cost. If  
6 the monetary benefit exceeds the cost, then  
7 there's net benefit and you get the green  
8 light, saying yes, this is something that's  
9 worth doing.

10 Budget impact analysis is a  
11 financial analysis. You look at what is the  
12 expected change in the financial expenditures  
13 for a given health care system or payer for a  
14 given time period?

15 It may be one year, it may be ten  
16 years. It's from the budget holder  
17 perspective. Your state Medicaid program,  
18 Medicare, they use a ten-year perspective.  
19 Congressional Budget Office mandates that. It  
20 could be your state government as a whole.

21 The budget impact analysis is what  
22 is the net impact on the budget over this

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1 defined time period that you would expect as a  
2 result of doing something.

3           Something may have positive  
4 budgeting, but the total budgetary costs  
5 increase. But from a societal perspective, it  
6 may actually be cost saving, and that's fairly  
7 common. The reason is that many of the  
8 benefits may accrue to other payers, other  
9 health care systems.

10           So if you're going to do a budget  
11 impact analysis, it's also good to look at an  
12 economic analysis from the societal  
13 perspective. So cost effectiveness or cost  
14 benefit analysis? Which method to use depends  
15 on your audience. In the medical field,  
16 medical journals almost always prefer cost  
17 effectiveness analysis.

18           By tradition, the health field,  
19 putting an explicit dollar value on lives or  
20 life years saved, is considered not good form.  
21 Now implicitly when you do a cost effectiveness  
22 analysis and you calculate the cost, say it's

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1       \$100,000 per life year saved, and you make a  
2       decision on that basis, you are implicitly  
3       putting a dollar value on health. But because  
4       it's not explicit, that is considered more  
5       acceptable.

6               Outside of health, cost-benefit  
7       analysis is the norm. In other areas of public  
8       policy, in the economics discipline, cost  
9       effectiveness analysis is quite rare. I never  
10      studied cost effectiveness analysis in graduate  
11      school. It's only when I came to work at the  
12      CDC that I had to learn how to do cost  
13      effectiveness analysis.

14             So cost-benefit analysis is the norm  
15      in most areas of public policy, transportation,  
16      environmental protection. And so when people  
17      in newborn screening or public health insist on  
18      using cost effectiveness analysis, they're  
19      putting health at a disadvantage relative to  
20      other areas of public policy, where dollars are  
21      used as the metric and where legislators are  
22      commonly expecting to find that.

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1 Value is in the eyes of the  
2 stakeholder. For some stakeholders, only  
3 health outcomes matter. For example, Medicare  
4 coverage decisions are based on medical  
5 necessity. That's in their authorizing  
6 legislation. They do not consider cost  
7 effectiveness. Others are interested in the  
8 budget impact.

9 So Medicaid programs are very  
10 interested, what is the impact going to be on  
11 our budget? They're concerned with is it  
12 affordable? Something may be highly cost  
13 effective, but if there's a high outlay, they  
14 say no, we can't afford it. So affordability  
15 and value are not interchangeable. Something  
16 may be affordable because of the low cost, and  
17 if there's no major change in infrastructure  
18 required, there's low cost in absolute terms,  
19 and intervention may very well be approved.

20 If an intervention is perceived as  
21 difficult or expensive, then considerations of  
22 cost effectiveness or cost-benefit may become

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1 more influential. A low cost intervention may  
2 be considered, may be assumed to be better  
3 value than an expensive intervention, but  
4 that's not necessarily the case.

5 There is an example I came across  
6 last week. Aaron Carroll on his blog talked of  
7 comparing lung cancer screening with treatment  
8 for chronic Hepatitis C virus infection in  
9 prisoners. The cost of lung cancer, the CT  
10 lung cancer screening is about \$100 per visit.  
11 It's pretty inexpensive. The cost of this new  
12 drug treatment for chronic Hepatitis C, which  
13 I'm sure many of you have heard about, is  
14 roughly 80, 90 thousand dollars for a single  
15 course of treatment.

16 That's expensive. Many payers are  
17 balking at that, and say no, it's not  
18 affordable. But which one provides better  
19 value for the money? That's a different  
20 question which we'll get back to a little  
21 later.

22 So how do decision-makers use

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1 economic evaluations? Within newborn  
2 screening, the traditional approach is to  
3 consider health outcomes and cost as separate  
4 criteria. First, you look at clinical benefit.  
5 Then you look at cost. Or you can assess the  
6 balance of cost and outcomes, as net benefit or  
7 a cost effectiveness ratio.

8 But then you have to decide how are  
9 you going to use that information? Are you  
10 going to use it as a decision rule. That is,  
11 if the cost for QALY is less than \$50,000, then  
12 it's cost effective. If it's not, it's over,  
13 then it's not cost effective. Or you can  
14 consider it as just one criterion among  
15 multiple decision criteria.

16 Instead of studying the absolute  
17 threshold, you consider in a range. So also  
18 instead of using these cost estimates as a  
19 criterion for deciding whether something is  
20 approved or not. Thank you. Gentlemen and a  
21 skull. You can use economic findings to guide  
22 prioritization in implementation, rather than

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1 as a decision is it approved or not approved.

2 And economic analyses or decision  
3 analyses can be used to identify gaps in  
4 research. We don't really know whether  
5 something is cost effective. This is the  
6 information that we need in order to make that  
7 decision. How do other advisory committees?  
8 We heard the U.S. Preventive Services Task  
9 Force does not consider cost effectiveness.

10 The Community Guide at CDC has a  
11 stratified process. They make the decision  
12 whether something is recommended based on the  
13 evidence of effectiveness. But if something is  
14 recommended, then they do a systematic review  
15 of economic evaluations, and then use that  
16 information to inform public health decision-  
17 makers, to guide the prioritization among the  
18 recommended services.

19 And then the ACIP, which you heard  
20 about from Dr. Bocchini, the ACIP now requires  
21 that any new vaccine or new application of  
22 vaccine that is proposed have an economic

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1 analysis as part of the submission. The  
2 nominator has to submit a cost effectiveness or  
3 a cost-benefit analysis before it will be  
4 considered.

5 That is reviewed by health  
6 economists at CDC. It's reviewed by the  
7 committee members as part of the decision-  
8 making process. So the slide from Lisa  
9 Prosser, Lisa works with the ACIP. She  
10 provides training for ACIP members on economic  
11 evaluation. So they do their evidence review.  
12 There's the public comment and the vote.

13 The cost effectiveness is one of  
14 five major sets of criteria. It's not the only  
15 one, but it's considered. Here's an example of  
16 how it has been considered in the influenza  
17 vaccination. It used to be that influenza was  
18 only recommended for older adults and for  
19 infants, which had the lowest cost  
20 effectiveness ratio.

21 Over time, all age groups have had  
22 it recommended. I think was it adults, 1949

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1 were the last group to be added?

2 A cost ratio of over \$100,000 per  
3 QALY. That's highlighted in yellow. People  
4 traditionally use \$50,000 for QALY. It is a  
5 decision rule. But that was in the 1990's,  
6 never adjusted for inflation. So increasingly  
7 people are using \$100,000, as equivalent to  
8 what 50,000 used to be worth.

9 We've heard the term cost saving.  
10 Cost saving means the total costs are lower.  
11 The expression is an ounce of prevention worth  
12 a pound of cure. Many people misunderstand or  
13 misinterpret that as meaning that prevention  
14 should be cheaper. That's not what the  
15 expression says. It's worth that means value,  
16 not lower cost.

17 Some preventive services, like the  
18 traditional childhood immune vaccines were cost  
19 saving. Folic acid fortification is incredibly  
20 cost saving, like \$100 of what it costs for  
21 every dollar spent on fortification. Smoking  
22 cessation is cost saving from a societal

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1 perspective, not necessarily for a health plan,  
2 but societally it is.

3 Most preventive services though,  
4 including most screenings, are not cost saving.  
5 So then you have to assess the value. Is the  
6 early detection of disease worth the extra cost  
7 to the health care system, compared to standard  
8 of care? So skip that.

9 Partial economic evaluations are a  
10 valuable component of a full economic  
11 evaluation. Before you can do a full economic  
12 evaluation you need to know what is the cost of  
13 the disease that you're studying, what is the  
14 cost of the intervention? You then have a  
15 model, a decision analytic model, which  
16 projects the total health outcomes and total  
17 costs, based on the components that go into  
18 that.

19 Very important principle. First you  
20 need evidence of effectiveness. If you don't  
21 have evidence of effectiveness, why even talk  
22 about cost effectiveness, because if it's not

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1 effective, it's not cost effective. You might  
2 be surprised how often cost effectiveness  
3 analyses get published in medical journals for  
4 interventions which do not have good evidence  
5 of effectiveness.

6 There are actually more of those  
7 than there are of the ones for effective  
8 interventions. I did a review for Genetics and  
9 Medicine last year, which -- where somebody had  
10 done a systematic review of economic  
11 evaluations and genetic testing. Out of 50-  
12 odd, only six were Tier 1 tests with high  
13 quality evidence of effectiveness.

14 Another problem is that we often  
15 have conflicting estimates of effectiveness,  
16 like mammography screening for breast cancer.  
17 What percentage of deaths, breast cancer deaths  
18 are prevented by mammography? There's one well  
19 often cited economic analysis which concluded  
20 there was a very low cost effectiveness ratio,  
21 and they were assuming 40 percent of all deaths  
22 were avoided.

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1           The consensus now is 15 to 20  
2 percent, and some think it's even less than  
3 that. The fewer the percentage of deaths  
4 avoided, the higher the cost effectiveness  
5 ratio. So you can get very different estimates  
6 depending on what your assumptions are.

7           Newborn screening for CAH.  
8 Traditionally, it was assumed that in the  
9 absence of newborn screening, 12 percent of  
10 infants with salt-wasting CH would die, you  
11 know, a society like the United States. We did  
12 a systematic evidence review and it was  
13 probably two percent. So obviously that's  
14 going to affect your estimate of the cost  
15 effectiveness of screening.

16           So full economic evaluation, first  
17 you start with evidence of effectiveness. Then  
18 you have to define who's your audience. Is  
19 this going to be a societal economic analysis  
20 or a budget impact analysis? Are you going to  
21 take long-term or short-term perspective?

22           You have to define the different

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1 interventions you're comparing, which for  
2 example with newborn screening, it's often not  
3 newborn screening versus no screening. There  
4 are often different screening strategies. We  
5 don't talk about universal versus targeted  
6 screening anymore, but there are different  
7 screening strategies in terms of the cutoffs.

8 So you may consider multiple  
9 interventions. How much is it worth the extra  
10 case, to increase sensitivity from 97 percent  
11 to 99 percent? You'll get more cases detected,  
12 but what is the extra cost? So you select the  
13 cost and health outcomes. You can do a  
14 decision analysis without cost, then add costs.

15 Cost effectiveness analysis, you  
16 calculate the total cost and total health  
17 outcomes for each of the interventions. You  
18 exclude an intervention, any intervention which  
19 costs more and is less effective. You don't  
20 calculate that cost effectiveness ratio. It's  
21 dominated. For the non-dominated strategies,  
22 you calculate the incremental cost

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1 effectiveness ratio, comparing one strategy to  
2 the next most effective.

3 Decision rules. I mentioned the  
4 \$50,000 for QALY, which is an arbitrary rule.  
5 It was never based on anything more than  
6 convenience. Range of values may be reasonable  
7 instead of a single value. But what economists  
8 like to do is compare revealed preferences.  
9 What have decision-makers decided other  
10 interventions are worth? What is the cost  
11 effectiveness ratio for something which has  
12 been approved?

13 They say well, looking at that, if  
14 they're willing to spend 100 or 200 thousand  
15 dollars for QALY for this, then why not for  
16 this? The problem is there's a huge range  
17 among decisions, services that are covered.  
18 Also the problem with doing that is your cost  
19 effectiveness ratio depends on your comparison.

20 So if you're comparing, say testing  
21 for Lynch Syndrome in cancer patients, to no  
22 testing. You may get one cost effectiveness

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1 ratio. But if you compare doing universal  
2 testing versus using family history, the  
3 Bethesda criteria, you'll get a very different  
4 cost effectiveness ratio. So the comparator  
5 matters.

6 I mentioned funded services may have  
7 a very wide range of cost effectiveness ratios.  
8 Treatments for rare diseases, including  
9 lysosomal storage disorders, often have cost  
10 effectiveness ratios greater than \$1 million  
11 for QALY, and I'll give an example I think in  
12 the next slide.

13 So orphan drugs to treat rare  
14 disorders very commonly cost say 200, 300  
15 thousand dollars per person per year. Cystic  
16 fibrosis, the new breakthrough drug that the  
17 President mentioned in his State of the Union  
18 address, it's targeted at four percent of  
19 patients with a specific mutation. It costs  
20 roughly \$300,000 per year.

21 It's curative, but it's not life-  
22 saving, since the risk of death is fairly low

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1       until people get older.    So what is the cost  
2       per QALY of that drug?    I have not seen that,  
3       but it's probably over a million dollars per  
4       QALY.    Pompe disease, very similar.    In Europe,  
5       it's been estimated at roughly \$1.3 million per  
6       QALY for treating someone with Pompe disease  
7       using ERT.

8                Hemophilia A, mean cost on average  
9       is \$150,000 per year.    If you have an  
10      inhibitor, roughly seven percent of hemophilia  
11      patients, Hemophilia A patients, develop an  
12      inhibitor, where they develop an antibody  
13      against the clotting factor.    The cost for  
14      those patients is roughly \$500,000 per year.  
15      Yet that's -- those treatments are all covered.

16               So public health, we tend to assume  
17      the cost effectiveness ratio is going to be  
18      less.    Now I'm coming back to that lung cancer  
19      screening versus Hepatitis C drug treatment.  
20      There was a study published last year, the  
21      National Lung Screening trial.    There was a  
22      cost effectiveness analysis in the *New England*

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1       *Journal of Medicine.*

2                   For smokers, current or former  
3 smokers over age 55 who undergo this screening  
4 and then followed up for ten years, current  
5 smokers, the ICER was \$43,000 per QALY. For  
6 former smokers, over \$600,000 per QALY.

7                   The new guidelines, the new coverage  
8 announced by Medicare, all current or former  
9 smokers, assuming they've had at least 30 pack  
10 years, and they've quit within the past 15  
11 years, will be covered, and these subjects in  
12 the trial had exactly the same criteria. So  
13 the cost effectiveness is highly variable.

14                   So for severe, for chronic Hepatitis  
15 C virus infection is controversial. A cost  
16 effectiveness analysis of a 12 week course of  
17 treatment for prisoners calculated that the  
18 cost was roughly 25 to 28 thousand dollars per  
19 QALY. So very costly intervention, but highly  
20 cost effective. So which -- what comparison  
21 are you going to use?

22                   Cost-benefit analysis, everything's

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1 in dollars. I'm sorry for the formatting.  
2 It's different on my computer than what shows  
3 on this one. There are two approaches to  
4 evaluating cost-benefit analysis. I'm going to  
5 skip the former. The one that's used by most  
6 economists, the regulatory analysis is  
7 willingness to pay, and you ask what is the  
8 average willingness to pay to avoid an ill -- a  
9 poor outcome, such as death?

10 That's called value of statistical  
11 life. It's much higher than any other estimate  
12 of health. For example, if you look at how  
13 much people would lose if they died, in terms  
14 of earnings. This is higher, typically six to  
15 nine million dollars. Most federal agencies  
16 now use a figure of \$9 million for every death  
17 avoided. So if you're looking at an analysis  
18 of preventing air pollution or road deaths,  
19 each avoided death is typically going to be  
20 valued at \$9 million.

21 It's based on economic analysis of  
22 occupational fatalities relative to

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1 compensating wage differentials, and then  
2 extrapolated to other areas. I'm just saying  
3 that's what's the norm in the public policy  
4 arena.

5 Washington State has been doing  
6 cost-benefit analysis of newborn screening  
7 expansion since 2002. By law, any regulation  
8 in the state of Washington has to have a cost-  
9 benefit analysis before it can be approved.

10 The Washington Department of Health  
11 developed its own capacity. They've had their  
12 own internal economist, John Thompson, who did  
13 his Ph.D. at the School of Public Health, has  
14 also participated in and has become adept at  
15 developing these spreadsheet models.

16 Their most recent one they did for  
17 SCID in 2012 used a value statistical life of  
18 \$7.7 million. They also -- some of their  
19 analyses they did a cost effectiveness analysis  
20 in parallel to the cost-benefit analysis. So  
21 if you don't put the dollar value on the  
22 avoided deaths, and you just calculate number

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1 of deaths in terms of life years, and cost, you  
2 can calculate the cost per life year saved. No  
3 QALYs; it was just survival.

4 So we're currently working with  
5 APHL, the Washington APHL and CDC is  
6 collaborating on a model, an updated  
7 spreadsheet model of testing for SCID, which is  
8 going to be customized. Well, it's going to be  
9 disseminated so other states can use it and  
10 customize it for their purposes, with their own  
11 state parameters.

12 It's going to have both the cost  
13 effectiveness and cost-benefit. So I'm going  
14 to skip over these slides in the interest of  
15 time. There's various steps you need to go  
16 through in order to calculate the net costs or  
17 cost savings. The bottom line, it's cost  
18 effective, and net monetary benefit, both.

19 So lessons learned from the  
20 Washington experience and from other studies.  
21 Modeling cost effectiveness analysis or cost  
22 benefit, the full economic evaluation, is

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1 resource-intensive. CDC did a cost  
2 effectiveness analysis of screening for CCHD.  
3 That took -- it was a two year process. APHL  
4 has now taken ten months to adapt an existing  
5 model from Washington, and it's not quite  
6 complete.

7 Those were for conditions where  
8 there's already a very good evidence base. For  
9 candidate disorders, where you don't have  
10 previously published cost effectiveness models  
11 and systematic evidence reviews, it's going to  
12 be much more challenging.

13 Lisa Prosser can't be here today.  
14 There's a panel on cost effectiveness which she  
15 sits on that's meeting today. She said in her  
16 experience, 18 months is a minimum to do a  
17 decent quality cost effectiveness analysis. So  
18 that's, I think, the last slide.

19 CHAIR BOCCHINI: Scott, thank you  
20 very much. That was a great presentation, and  
21 as you indicated, those of us on the CDC ACIP  
22 Work Group have been able to have a couple of

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1 talks by again, senior economists such as  
2 yourself, and they've been excellent. But I do  
3 say that about two weeks after the conference,  
4 I wish they were sitting right next to me  
5 again.

6 (Laughter.)

7 CHAIR BOCCHINI: So let's open this  
8 up for questions, comments from the Committee.  
9 I think this is a really good start to us  
10 really trying to tackle what we need to do and  
11 what we could do in a nine-month time frame, to  
12 assess the impact of a condition being added to  
13 the RUSP. So let's open with any questions or  
14 comments on the Committee. Steve.

15 MEMBER McDONOUGH: Thank you for  
16 your excellent presentation. What type of  
17 information is there about cost to society,  
18 families on level of disability of their child?

19 Some conditions don't result in life  
20 and death; they result in a moderate disability  
21 or a mild disability, and you look at divorce  
22 rates and then accounting for childbirth,

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1 chronic disease and attention to other siblings  
2 and stuff like that. What information is out  
3 there on that cost?

4 DR. GROSSE: Okay, great question.  
5 The usual approach is to look at the medical  
6 costs and educational costs of treating  
7 disability, and then the decrement in quality-  
8 adjusted life years. So Lisa and I have  
9 published an article where we quantified  
10 estimates of the loss in QALYs for different  
11 types of developmental disabilities associated  
12 with newborn screening conditions or infectious  
13 diseases.

14 There's a lot of variability in the  
15 estimates. There's not a single true number.  
16 So what our conclusion was any analysis that's  
17 doing this should use a range to reflect the  
18 uncertainty, rather than putting everything on  
19 a single point estimate.

20 In terms of spillover effects on  
21 other family members, that is growing in  
22 attention. Lisa has published a couple of

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1 papers addressing that issue. It's hard,  
2 because of the lack of good evidence. I did  
3 work with another colleague on a survey of  
4 families with children with spina bifida, and  
5 tried to quantify some of those.

6 The problem is there's inconsistent  
7 estimates from different studies. Is it that  
8 families with children with a disabling  
9 condition have a higher rate of divorce? Not  
10 necessarily. There are some studies like  
11 Down's Syndrome, there actually may be a lower  
12 rate of divorce, compared to other conditions.  
13 So it's very hard to quantify that.

14 MEMBER BOTKIN: Jeff Botkin. I  
15 guess I'm thinking about the cost-benefit  
16 analysis of a cost effectiveness analysis for  
17 this Committee. There's sort of a general  
18 question --

19 DR. GROSSE: What's the return on  
20 investment?

21 MEMBER BOTKIN: -- about how often  
22 do these analyses provide sort of fundamentally

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1 different perspectives on the issues. You  
2 know, are there circumstances in which this  
3 sort of additional analysis would have perhaps  
4 led us to a very different decision about a  
5 condition or not? So -- and I don't know  
6 whether you're suggesting that this ought to  
7 become part of our regular -- maybe that's a  
8 question too.

9           Should this become a regular part of  
10 this Committee's workflow, and perhaps the  
11 basic question, how often do you think it would  
12 make a big difference with the kind of analysis  
13 we're already doing?

14           DR. GROSSE: Okay. First, as an  
15 economist, my job is not to make the decision.  
16 It's to provide information to the decision-  
17 makers. The ACIP has wrestled with this. I  
18 think the meningococcal immunization was  
19 delayed, in part because of that cost issue.  
20 Would you like to address that?

21           But I think more often, the economic  
22 analysis will help by providing evidence

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1 supporting an expansion. So that the idea of  
2 doing this model for SCID screening is there's  
3 still a lot of states that are not screening  
4 for SCID. Why? It's complicated. It requires  
5 an investment of resources, doing something  
6 different.

7 Showing that it's highly cost  
8 effective compared to other public health  
9 expenditures can help provide an argument or  
10 justification for the investment of resources  
11 for those states to add SCID. That's why we  
12 talk about economic evaluations, not  
13 necessarily just to make a decision it's  
14 something worth doing, but to help in the  
15 prioritization.

16 MEMBER BOYLE: I'm just going to  
17 emphasize that point. Last week at Don  
18 Bailey's meeting, I can quote him because he  
19 said it out loud.

20 But he made -- the person who runs  
21 the newborn screening laboratory made the point  
22 that it wasn't until he actually brought the

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1 dollars and cents to the legislature that he  
2 actually is getting them to move, actually  
3 showing them the return on investment there.  
4 So it does work, at least based on what he told  
5 us.

6 DR. GROSSE: Yeah.

7 MEMBER HOMER: I guess a couple of  
8 questions. One is a broader one, which is  
9 interesting in that Congress specifically  
10 prohibited CMS from considering cost in making  
11 its decisions. Well, it seems like Congress  
12 directed us to include cost in our  
13 consideration. So is there a judgment about  
14 maybe is that -- I don't know. It's an  
15 interesting reflection about the role of public  
16 health versus private health, even though the  
17 dollars are all coming from public sources.

18 Anyhow, that might suggest that a  
19 continued imbalance between our investments in  
20 health care versus health will accelerate if  
21 this process continues. I was struck by your  
22 brief comment, and maybe I misinterpreted it,

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1 that said the cost effectiveness, if I'm using  
2 the terms right, of screening for most  
3 metabolic diseases is --

4 DR. GROSSE: No, screening cancer.

5 MEMBER HOMER: No, but you gave a  
6 figure of over a million dollars per QALY.

7 DR. GROSSE: That's treatment for  
8 certain rare diseases.

9 MEMBER HOMER: Okay.

10 DR. GROSSE: Not all. I just gave a  
11 few examples, three different examples.

12 MEMBER HOMER: Okay.

13 DR. GROSSE: Orphan drugs for rare  
14 disorders are typically very expensive.

15 MEMBER HOMER: Sure.

16 DR. GROSSE: And if you look at the  
17 cost per person per year of the treatment, and  
18 then you calculate how many quality-adjusted  
19 life years are saved as a result, your ratio is  
20 typically very high, not uncommonly more than  
21 \$1 million.

22 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

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1       \$100,000, like CT lung cancer screening for  
2       former smokers, then we shouldn't pay for that.  
3       Well, that's not how our society has made those  
4       decisions.

5                   MEMBER HOMER:     But I guess if part  
6       of what the purpose of doing the cost  
7       effectiveness analysis is to introduce some  
8       element of rationality to our priority-setting  
9       process, then if -- because I'm assuming that's  
10      part of what we want to do, right? I think --

11                   DR. GROSSE:       I don't -- this  
12      Committee is not going to introduce rationality  
13      into the U.S. health care system.

14                   (Laughter.)

15                   MEMBER HOMER:     No, but we could help  
16      prioritize recommendations to the Secretary  
17      based on -- based on that.

18                   DR. GROSSE:     Okay. Within that very  
19      limited optimization, not global optimization.

20                   MEMBER HOMER:     Yeah.

21                   DR. GROSSE:     But also if it's a  
22      screening test which is easy to do, low cost

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1 may be considered sufficient. If it costs \$1  
2 per infant to screen for a condition using  
3 existing instruments, existing -- yeah. People  
4 say why not, typically? I'm not recommending  
5 that. I'm just saying that's typically how  
6 people will respond. If it's a completely new  
7 process, new technology that requires investing  
8 in that, the standard, the bar is going to be  
9 higher.

10 So I'm saying a cost effectiveness  
11 analysis is going to be more influential in the  
12 latter than in the former.

13 MEMBER HOMER: True. I mean that's  
14 -- if you're sitting in business, in part  
15 you're doing cash flow versus your profit and  
16 loss statement. So your cash -- I mean you've  
17 got to be putting more money up front, and  
18 maybe you don't have it in the bank in the  
19 legislature's allocation.

20 So you can't afford it that year,  
21 even though the net return is going to be good  
22 over time. Maybe that's another way of framing

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1 that.

2 MEMBER BOYLE: I guess I go back to  
3 the -- I mean just following up on Charlie's  
4 conversation, I go back to the SCID example,  
5 and I think it's nicely summarized in your  
6 slide. I mean it really is.

7 I mean look at the cost of early  
8 versus late treatment. It's like a no-brainer,  
9 and for anyone who -- no. Any state who's  
10 trying to consider the costs here, you know,  
11 without even the human part of it, the  
12 financial costs just make a tremendous  
13 difference.

14 So I mean I think that it really can  
15 help accelerate the implementation of this.  
16 Maybe not everything's going to be as black and  
17 white as SCID. But maybe they will be, or at  
18 least it will help persuade. For me, looking  
19 at this is very persuasive.

20 DR. GROSSE: But I'd like to call  
21 Yao Ding, who's sitting in the first row. He's  
22 the cost effectiveness fellow at APHL who's

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1 leading the modeling efforts.

2 MEMBER BOYLE: And the fact that we  
3 have this model now that people -- that states  
4 can actually plug in with their values I think  
5 is terrific.

6 MEMBER LU: Scott, you mentioned  
7 that it takes about 18 months to do a good cost  
8 effectiveness analysis, and Congress asked us  
9 to take cost analysis into our consideration,  
10 but also gave us nine months to go from  
11 nomination to a decision. What can reasonably  
12 be done in the nine month period?

13 DR. GROSSE: Partial economic  
14 evaluation.

15 MEMBER LU: What does that mean?

16 DR. GROSSE: Calculating what is the  
17 cost of implementation from a budget  
18 perspective? Not doing a global economic  
19 analysis for the whole health care system. But  
20 you can say okay, how much is it going to cost  
21 a state to implement screening for Condition X?  
22 Not just the reagent cost, because reagent cost

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1 is often a relatively small part of the total.

2 But the whole cost of whatever,  
3 changing the laboratory, expanding the space,  
4 acquiring the instruments, training --  
5 recruiting and training staff, making sure  
6 you've got enough follow-up staff, making sure  
7 you've got the referral process in place for  
8 the diagnostic centers. What is the cost of  
9 all of that? That you can do within nine  
10 months.

11 MEMBER PARISI: I just had -- first  
12 of all, thank you for explaining some things  
13 that were kind of fuzzy for me, particularly  
14 with regard to this cost for treatment of over  
15 a million dollars for rare diseases, and sort  
16 of in response, Charlie, to your comment as  
17 well about that seeming crazy.

18 The point about the willingness to  
19 pay component I think is really important, and  
20 I've heard pharmaceutical company  
21 representatives say we charge these really high  
22 amounts for these drugs for rare diseases

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1 because we can, and because society and  
2 insurers in general are willing to pay, A,  
3 because they are rare and there aren't that  
4 many individuals, and because by virtue of  
5 having such a rare condition, it's sort of like  
6 we owe it to these individuals with these rare  
7 disorders to provide treatment for them, and  
8 therefore we're willing to pay these, you know,  
9 really extreme costs.

10 It's also expensive to develop new  
11 drugs for a small population. So it's for me,  
12 I think, having this comment about willingness  
13 to pay is really key for some of these rare  
14 diseases.

15 DR. GROSSE: And that's thanks to  
16 Dr. Lu. We had some conversation before this  
17 meeting. He asked me to include that in this  
18 presentation.

19 DR. WATSON: Thank you. So unique  
20 to genetic disorders are two features, later  
21 onset or at least a split between early onset  
22 and later onset. Certainly in many that are in

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1 the pipeline right now, and then the fact that  
2 when you have Mendelian conditions, you have  
3 lots of other family members, that it's rarely  
4 factored into genetic testing cost  
5 effectiveness.

6 So I'm wondering what your views are  
7 related to newborn screening? Is it always the  
8 individual and their benefit that is going to  
9 be part of the calculation, or would you extend  
10 it further? Because the rarer the disease the  
11 more -- when you find one person, you will find  
12 more people with the condition in that  
13 inheritance group.

14 DR. GROSSE: For autosomal dominant  
15 disorders, the norm is to include the cascade  
16 testing of family members. Like for Lynch  
17 Syndrome, identifying a patient with colorectal  
18 cancer who happens to have a mutation on one of  
19 those 4 MMR genes, that doesn't -- that's not  
20 cost effective, because they've already had  
21 their cancer.

22 For identifying the family members,

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1 then it becomes cost effective, depending upon  
2 how many family members you identify, and  
3 whether they agree to undergo the prophylactic  
4 screening.

5 DR. WATSON: So you touch on a third  
6 rail then, which is different from colon  
7 cancer, in that reproductive decision-making  
8 may come from knowing that something's  
9 segregating in your family, and people have  
10 rarely wanted to include that in cost analyses  
11 because it's politically ugly to think they're  
12 calculated.

13 DR. GROSSE: No comment.

14 DR. TANKSLEY: Is this on? Susan  
15 Tanksley. I wanted to follow up on Dr. Lu's  
16 question and Scott's response, and it's -- I  
17 mean that's only half of the equation, right.  
18 So if you know how much it's going to cost to  
19 implement, that's one thing, and that's a  
20 question that's often asked.

21 But from a public health lab  
22 perspective, we found it much more beneficial

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1 to be able to say what is the cost avoidance if  
2 you're doing the screening, and that was very  
3 successful for SCID implementation in Texas.  
4 We were able to get it implemented, basically  
5 because the Medicaid program found, through a  
6 cost-benefit analysis, that it was actually  
7 much, much more beneficial to screen than to  
8 not screen.

9 That was just looking at 50 percent,  
10 60 percent of our population, not the entire  
11 population.

12 DR. GROSSE: Using charges rather  
13 than costs or payments.

14 DR. TANKSLEY: Using charges.

15 DR. GROSSE: I think they had for --  
16 I saw the data. She shared the data with me.  
17 We'll talk later.

18 DR. TANKSLEY: Well, it worked.  
19 It's often -- it's often hard. It's hard to  
20 find that data. It's really, really hard to  
21 identify what is the cost avoidance. But  
22 anyway, I really appreciate your talk.

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1 DR. GROSSE: When Lisa Prosser, Lisa  
2 quoted the 18 month figure, that's assuming  
3 you're going to do a systematic evidence review  
4 to find the parameters to include in your  
5 model. So at the end stage, that's a model  
6 that peer -- that could be published in a peer  
7 review journal.

8 If you're just interested in doing  
9 sort of a quick back of the envelope  
10 calculation for internal purposes without  
11 publication, that can take much less time.

12 But I don't think this Committee  
13 could use that kind of an analysis for its  
14 work. So one of the suggestions you might  
15 consider is within that nine month time period,  
16 you could do that cost of implementation  
17 analysis or the CRW could do that.

18 But you could also in parallel they  
19 should be working on developing a full economic  
20 evaluation, which would not be to inform the  
21 Committee's decision, but to help inform the  
22 state implementation process, which will take

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1 place after a condition is added to the RUSP.

2 But of course, that's going to  
3 require resources. I don't think the CRW would  
4 be able to do that with its existing funding.

5 MEMBER BOTKIN: Jeff Botkin. So as  
6 we think about fostering pilot studies here, as  
7 a way of acquiring a better evidence base for  
8 making these sorts of decisions, can we --  
9 should we be thinking in terms of incorporating  
10 routinely economic considerations in the data  
11 collection, so that these sorts of analyses can  
12 be promoted?

13 DR. GROSSE: In terms of the -- yes,  
14 brief.

15 DR. BADAWI: Debbie Badawi. Is the  
16 thought then that these -- as you do your  
17 framework for or if there is a cost-benefit  
18 analysis done for conditions that are nominated  
19 to the work group, that there would be a  
20 similar -- a model, then, that states could  
21 plug into to figure their costs, because  
22 obviously different states are going to have

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1 different costs, depending on the specialists  
2 available, births, all that.

3 DR. GROSSE: Correct. That's  
4 exactly the goal of the SCID model, is  
5 something that different states can then adapt.  
6 Some states have one screen or two screens.  
7 There's going to be different estimates about  
8 the prevalence costs.

9 MEMBER BOYLE: In that model what --  
10 and the hardest part -- obviously, it's all  
11 difficult to get, I'm assuming. But the  
12 hardest data to get is the cost offset. Is  
13 that right?

14 DR. GROSSE: Uh-huh, yes.

15 MEMBER BOYLE: Yeah. Could that be  
16 the modeling piece of it? So the other pieces  
17 are easy to get, easier. Could you actually  
18 model that and have some, you know, have some  
19 parameters on that? So at least the Committee  
20 could get a sense of what that impact could be.

21 DR. GROSSE: Actually, these  
22 estimates are conservative. The actual

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1 difference in cost is likely to be larger than  
2 this, because the cost estimates are coming  
3 from -- do not necessarily include all the  
4 costs of the hospitalizations for infections  
5 before an infant is diagnosed.

6 So there's some missing there.  
7 Also, it's not clear how much after the  
8 transplant these are covered. Also, the number  
9 of deaths avoided by SCID is probably  
10 understated here, because it's based primarily  
11 on post-transplant deaths. But there are a lot  
12 of infants with SCID who die without a  
13 diagnosis or die of infections before they're  
14 eligible for a transplant.

15 So what this analysis does, and  
16 we're in the process of revising this; that's  
17 why this is a draft -- please do not cite these  
18 numbers -- is that even with relatively  
19 conservative assumptions, it is still highly  
20 cost effective.

21 CHAIR BOCCHINI: Again Scott, thank  
22 you very much. A great presentation.

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1 (Applause.)

2 CHAIR BOCCHINI: All right. Now  
3 we're going to take a short break, and then the  
4 subcommittees will meet. So I'm going to turn  
5 this over to Debi, so that she can give us some  
6 instructions as to where each subcommittee will  
7 meet and how to get there.

8 MS. SARKAR: Okay. So the Education  
9 and Training Subcommittee, they are going to be  
10 meeting in this room. The Lab Subcommittee and  
11 the Follow-up and Treatment Subcommittee will  
12 be meeting in the Parklawn Building, which is  
13 across the street at 5600 Fishers Lane. What  
14 I'm going to ask everyone is in about ten  
15 minutes, if you guys could all meet me upstairs  
16 by the elevators, I can walk everybody over.

17 When we get to the Parklawn  
18 Building, we'll need to have your driver's  
19 license out, so that you can go through  
20 security. After that, we will have HRSA staff  
21 take you to your respective meeting rooms. So  
22 thank you very much.

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1                   CHAIR BOCCHINI:   Okay.   So this will  
2                   conclude the first day of our meeting.   I want  
3                   to thank everybody for their input, and I want  
4                   to remind everybody that we're going to start  
5                   promptly at 9:00 a.m. tomorrow, that following  
6                   public comments, we will address the second  
7                   motion that is still open, and then we'll go  
8                   into the MPS I review, okay.

9                   (Whereupon,        the        above-entitled  
10                  matter went off the record at 2:38 p.m.)

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