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Advisory Committee on

Heritable Disorders in Newborns and Children

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I failed to recognize yesterday, when we were going around the table, the fact that Dr. Carol Greene, who is the President of SIMD, has replaced Barbara Burton. And Carol has been at this committee meeting always. And so, we welcome her to a place around the table representing SIMD.

We're going to move ahead now and hear the report of the Evidence Review on the bilirubin issue. And Dr. John Co will now present the Evidence Review Group's report on the candidate nomination of hyperbilirubinemia.

Dr. Co, good morning.

DR. CO: Thank you. Thank you for having me down from sunny Boston today.

This group has heard the preliminary evidence review of this topic in January. We're presenting our interim review today. A paper on the CCHD is in progress. And we've had an extensive discussion just now about the progress on the methods piece of this.

In terms of the key authors, I want to highlight Alex and Danielle. They were very good at keeping all of us on track, particularly me, as the new person on the group for this review. Lisa, obviously, had an extensive role in the economic analyses, Jim and, of course, the rest of the staff, particularly Alex, who helped shepherd me through the

interviews with the experts.

In terms of neonatal hyperbilirubinemia, we know that there are multiple etiologies for this very common condition in newborns. It's a detectable risk factor for both acute bilirubin encephalopathy as well as chronic bilirubin encephalopathy, also known as kernicterus. We'll be talking about these -- the definitions of these conditions in a few minutes.

The primary concern for evaluating this condition is to prevent the neurotoxic effects which arise

In terms of current clinical practice guidelines, the AAP released a set of guidelines most recently in 2004 for the prevention and management of hyperbilirubinemia in kids -- or newborns, excuse me, greater than or equal to 35 weeks gestational age.

The main recommendations from this report, as well as from the clarifications five years subsequent, were to promote and support successful breastfeeding; perform systematic assessment before discharge, measurement of pre-discharge of bilirubin levels, either with total serum bilirubin or trans-cutaneous individually or in combination with clinical risk factor assessment to help assess risk for developing subsequent hyperbilirubinemia; provide early and focused follow-up based on risk assessment, based on pre-discharge screening and other risk factors; and when indicated, treat newborns with phototherapy or

exchange transfusion to decrease bilirubin, ultimately the key conditions that we're about to talk about today.

In terms of relevant evidence reviews, USPSTF recommendation that was released in 2009 was based on a review of six years of evidence from 2001 to 2007 containing 18 papers. That review concluded that the evidence about the benefits and the harms of screening was lacking and could not determine the balance of benefits and harms of screening newborn infants to prevent kernicterus or chronic bilirubin encephalopathy. And they concluded that the evidence was insufficient to recommend screening.

Our review consisted of 20 years of evidence -- or papers, plus an additional one because we started in 2010, so we threw in 2011 just to be thorough. It ultimately included six times the number of papers, due to our broader set of questions in this review.

In terms of case definitions, neonatal hyperbilirubinemia redefined as a total serum bilirubin greater than 95th percentile for age in hours in term and near-term newborns. I will say that it took quite a bit of time to arrive at agreement on this case definition. And we would also note that near-term infants comprise about 10 percent of births and are in addition to other pre-term infants more likely to develop and suffer sequelae from this condition.

Acute bilirubin encephalopathy we've defined as advanced manifestations of bilirubin toxicity in the first weeks of life, loss of Moro, extensor hypertonia, high-pitched cry. And also of note is that, in the literature, some authors use this term to describe less severe symptoms, although we did not, for the purpose of this report.

In terms of chronic bilirubin encephalopathy, or kernicterus, this describes a persistent improvement of brain damage from bilirubin toxicity characterized by these four areas: movement disorder, auditory dysfunction, ocular motor impairment and dental enamel hypoplasia.

This is our conceptual framework for thinking about screening. And on the left, you can see our general population of newborns. Here is the system which I'll go into some detail on in a minute. And the end result is, we hope, the reduced rate of our key conditions of acute bilirubin encephalopathy, kernicterus and improving overall morbidity and other outcomes.

The screening, obviously, takes place early, as well as risk assessment. There are harms for testing or identification. In terms of treatment, obviously, you could treat kids that -- you want to treat kids with hyperbilirubinemia to prevent the continuum of continuing, really, to encephalopathy, both acute and chronic.

In terms of key questions for condition, we have listed four

here, which we thought were most key for this discussion today. Is neonatal hyperbilirubinemia well-defined? When does it appear clinically? And what are known risk factors?

What characterizes both acute and chronic bilirubin encephalopathy? What evidence describes the relationships among neonatal hyperbilirubinemia and these two conditions and as neonatal hyperbilirubinemia associated with more subtle adverse outcomes, other than the two conditions we mentioned.

In terms of the condition of hyperbilirubinemia, the reported incidents of bilirubin levels above 30 milligrams per deciliter ranges anywhere from 3 to 12 per 100,000, or close to one in 10,000. Estimated incidents of ADE is approximately less than one per 200,000 live births. And the estimated incidents of kernicterus, or CBE, ranges anywhere from 0.49 to 2.7, with most evidence and larger studies indicating rates closer to less than one per 100,000.

In terms of hyperbilirubinemia and the link with ABE and CBE, there is no specific bilirubin level or threshold associated with acute or chronic bilirubin encephalopathy, although in general, higher levels are associated with higher occurrence of these two conditions. Most cases of chronic bilirubin encephalopathy have a TSB of greater than three. This was discussed with our experts. And they concurred with this.

Although many papers also discuss cases which occur below a TSB of 25. And, in fact, when you look at current and past guidelines for treatment, 25 is often where the curves plateau in terms of treatment levels. Although some neonates develop less severe signs, the large majority of studies indicate no long-term effects of this condition.

In terms of the screening key questions, what methods exist to screen newborns for neonatal hyperbilirubinemia? What are the validity, sensitivity, specificity and other properties? What tools help to interpret the risk of developing hyperbilirubinemia? What is the predictive validity? And finally, how do timing of screening after birth, the gestational age, threshold levels and other considerations affect the number of infants identified with or at significant risk for developing this condition?

In terms of screening, there are three current forms: a visual assessment -- we included some papers in our review about the sensitivity and other properties of visual assessment. And these studies show that TcB and TSB add to the ability and accuracy of risk assessment of a child or a newborn for developing hyperbilirubinemia. TcB appears to be a valid screening tool for developing significant hyperbilirubinemia, requiring confirmatory follow-up with TSB. Notable is that TcB is most accurate at lower levels of TSB.

And our specific nomogram, based on TSB values, allows

prediction of significant hyperbilirubinemia. And you can apply this risk nomogram also to TcB levels, trans-cutaneous.

In terms of treatment key questions, what methods exist to treat neonatal hyperbilirubinemia? And what is their effectiveness? What's the relationship between the outcomes and the timing of treatment? What proportion of cases of chronic bilirubin encephalopathy would earlier detection and treatment prevent? And what proportion of these cases of other neonatal hyperbilirubinemia manifestations would be preventable? And finally, what are the potential harms or risks associated with treatment?

In terms of evidence, our C.T. evidence shows that phototherapy effectively decreases risk -- decreases levels, excuse me, of bilirubin in the neonatal period. Indirect evidence suggests that screening and phototherapy decreases rates of CBE. Case series, which we've talked a little bit about in terms of their utility today, provide evidence that symptoms of ABE may resolve with treatment. Indirect evidence suggests that earlier treatment with phototherapy effectively lowers serum bilirubin levels and diminishes the need for treatment with EcT, which is notable because adverse events are relatively common with EcT. With mortality, approximately 0.53 per 100 patients in 0.3 per 100 procedures.

In terms of the economic key questions, these are the key

ones that we've started to consider. What are the costs associated with screening, the screening test itself, the failure to find at-risk newborns in the pre-symptomatic period and the treatment of hyperbilirubinemia itself as well as the treatment of ABE and CBE? What is the cost-effectiveness of newborn screening for hyperbilirubinemia?

In terms of the evidence, there is a limited quantity. We found five cities, four of which were based in the U.S., the other one of which we excluded, as well as the quality of the evidence due to the assumptions in these models as well as lack of information on actual costs versus charges and other factors. The estimated cost of TcB screen testing range from less than $1 to $7.80. Limited evidence per cost exists for readmission, phototherapy treatment and long-term outcomes.

Limited evidence for cost-effectiveness of strategies to prevent kernicterus exists. One study was noted. And the costs per case of kernicterus prevented ranged from $5.7 million for TSB to $9.1 for TcB with sensitivity analysis ranges noted as above.

In terms of harms and benefits for instituting a screening program pre-discharge, the harms of phototherapy include fluid loss, temper instability, skin rash, diarrhea, delayed of parenting and bonding, all of which are relatively minor risks, as well as the more significant risks of mortality from EcT and morbidity, which ranges from anywhere from 12

to 15 percent.

The benefits include identifying newborns who are most likely to develop a TSB of greater than 30, lowering bilirubin levels, reduces the risk of newborns developing both ABE and CBE and early identification and early treatment may prevent the need for EcT or readmission.

In terms of the boundaries of the benefits, with an estimated incidents of 4 million births in the U.S. per year and incidents of CBE from .5 to 2.74 per 100,000, an upper bound of 20 to 108 cases per year of CBE could be prevented, potentially, with early detection and treatment. With our reported incidents of TSB levels greater than 30 of 3 to 12 per 100,000, earlier detection and treatment could prevent maximum of 120 to 480 infants per year for developing these levels.

I don't expect you to read this decision tree in detail. I can barely read it with the screen right in front of me.

(Laughter.)

DR. CO: What I would note is that at the next Review Committee meeting, this model will be further developed with the notable health outcomes at the top left of ABE, kernicterus phototherapy cases as well as false-positive or negative cases. We'll talk more about this another time.

In terms of the gaps in the current evidence, there's a gap in terms of clear connection between specific bilirubin levels and development of CBE, also gaps in terms of if treating chronically significant hyperbilirubinemia would prevent CBE and associated with that, how many cases could be prevented with universal screening. Pre-discharge bilirubin newborn screening with gestation large-scale screening impacts -- so how would this be instituted and practically, how would the effectiveness of this program be assessed as well as cost-effectiveness of instituting a program such as this?

Thank you.

DR. HOWELL: Dr. Buckley is going to lead the discussion of this material.

DR. VOCKLEY: Can I ask a question first?

DR. HOWELL: By all means.

DR. VOCKLEY: Can you clarify, John, your slide on the number of potentially preventable cases that you had up there?

DR. CO: I could do it. Sorry.

DR. LLOYD-PURYEAR: I have a question, too, John. You were proposing to go forward with the decision tree analysis rather than presenting a final report. Is that correct?

DR. CO: Today? Correct.

DR. PERRIN: Which, if I could comment on that, Michele. This is Jim Perrin. I think that, based on the report Ned gave of the Evidence Review Group that met several weeks ago, when we discussed decision tree modeling and related things, it really led us to believe that we could provide more advice to the Advisory Committee using that methodology. But we did not (inaudible) in time for this meeting.

DR. BUCKLEY: I have a question also.

DR. HOWELL: Well, Jerry's still in the midst of -- he just found the slide.

DR. VOCKLEY: Yeah, these are the numbers. So when you say that 20 to 108 cases per year could be prevented with earlier detection and treatment, is that as compared to current practice, or is that simply based on the incidents numbers? Because certainly, kids who are at high risk are going to be picked up with other -- or they're going to have their bilirubin measured for other reasons. That is because of clinical practice as opposed to just saying it's all or nothing in terms of bilirubin measurements. So how does this number -- where does this number fit?

DR. CO: Right. So that range of the 20 to 108 is based on the range of incidents of CBE, which is based on several papers, which include papers that have different levels of screening. I don't think we know nationally what percent of nurseries or institutions have universal

screening.

DR. VOCKLEY: Yeah, I'm not trying to compare it to universal screening. I'm trying to compare it to clinical practice and clinical screening. So if someone walks in and says this baby needs a bilirubin level, some of those patients will overlap with this population.

DR. CO: Sure.

DR. VOCKLEY: And so, the number that you would identify purely by screening is not really the number that we need here. It's the number that we would increment by implementing screenings over general clinical practice.

DR. PERRIN: Jerry, if I could just comment on that briefly. These studies come from different periods of time and reflect different levels of screening. But they're not well-documented what those levels of screening are. So what we can say is there is some evidence that rates of kernicterus have gone down temporarily associated with increased rate of screening, but not that there's any direct relationship. So this number really represents the absolute maximum possible benefit.

Presumably, universal screening would not get to this level. But we can give you a clear estimate of what it would.

DR. CO: And we do know that in areas where they -- or institutions where they've done studies with more screening or universal

screening, the peaks of total serum bilirubin are lower and phototherapy rates are higher during birth hospitalization.

DR. HOWELL: Denise, and then Coleen had comments and question, Becky.

DR. DOUGHERTY: John, you had a slide -- and Jim.

Hi, Jim.

DR. PERRIN: Hey.

DR. DOUGHERTY: You had a slide that showed for the economic analysis that the quality and quantity of the studies was not ideal. Could you say something about the quality of the studies for the rest of the questions? And I guess what I'm thinking is one of the appealing things about a decision model is that you get a chance to incorporate into your estimates of uncertainty something about the quality of the evidence.

DR. CO: Sure.

DR. DOUGHERTY: Which is very hard to depict on slides like this, which may sound more definitive than the actual evidence leads you to believe.

DR. CO: Sure. So on page 32 -- I think it was the final draft -- page 32 of the report, there is a summary of the strength of evidence for several of the areas. And the ranges from fair evidence to moderate,

moderate being for sensitivity and specificity of risk assessment and screening prediction as well for effectiveness of intervention.

DR. HOWELL: Coleen?

DR. BOYLE: So just to summarize, it's fair, fair, poor and moderate?

DR. CO: Uh-huh.

DR. LLOYD-PURYEAR: I was just going to make the point on that slide we were just looking at with the range of problems estimates, was at the high end, which is really much higher than the other studies that are listed, table five, I think. That's a study based on ICU-9 codes. And we know that they have fairly poor validity, particularly in relationship to the study done in Denmark, I think. So, I mean, I guess I would like to see that reframed a bit.

DR. CO: Yeah, we probably should have said more, most and better evidence indicates rates of less than or around one per 100,000.

DR. LLOYD-PURYEAR: Yes.

DR. CO: Sorry.

DR. LLOYD-PURYEAR: But even at your range, then, of preventable cases.

DR. CO: Uh-huh.

DR. HOWELL: Becky?

DR. BUCKLEY: Yeah, was there anything published at all about how many cases we're missing by not doing a discharge bilirubin?

DR. CO: Yeah, I think some of the papers that really help with that are the papers related to visual assessment and the accuracy of that. And certainly, in several papers, they talked about the incremental benefit of adding a screening to visual assessment, whether it be TSB or TcB. Although I'm trying to remember if they estimated a number of cases that actually -- additional cases that they picked up. But in terms of those papers, those are on page 21 of the report.

DR. HOWELL: We're aware of the fact that many nurseries in this country are currently doing routine bilirubin screening. Do you have any data on the extent of that?

DR. CO: We don't, unfortunately. So it's hard -- in that way, it's harder to interpret current studies in terms of the incremental benefit of screenings, universal screenings.

DR. HOWELL: Yeah.

Carol?

FEMALE SPEAKER: Oh, and Mike.

DR. HOWELL: Carol and Mike?

DR. GREENE: Possibly, I'm just missing something simple.

But harms and benefit of pre-discharge screening program, that slide, under the harms, you have the risks of phototherapy and then the mortality of exchange, which is a harm of not screening. And what I'm not seeing on that slide is the harm of ending up -- the potential harm of ending up with neurologic disease.

And I understand that the gap in evidence has no correlation between specific levels and neurologic disease. But I think the notion that bilirubin has a role in neurologic disease is sort of like you don't jump out of a plane with a parachute-level of evidence. So I'm just curious about that slide, why you've got only one of two significant harms of not screening.

DR. CO: So you're asking about the overall societal costs?

DR. GREENE: No, no, no, no, no, not cost, just the other side. The title of the slide is harm -- it's slide number -- does anybody know what slide it is?

DR. CO: Oh, I'm sorry. Okay. The two columns.

DR. GREENE: Yeah, that one.

DR. CO: Okay, this one?

DR. GREENE: It just seems to me there's a big harm missing from that slide. I don't think it's missing from your analysis.

DR. CO: Sure.

DR. GREENE: It's just missing from that slide.

DR. CO: Okay.

DR. CALONGE: Could you add -- I'm sorry. This is Ned. Could you add -- you're adding a screening test. You usually don't talk about the harms of not screening (inaudible) from that standpoint. So that's --

DR. GREENE: Right, which is --

DR. CALONGE: -- benefit.

DR. GREENE: Which is why I was confused because on that slide, you've got, under the harms, a harm of not screening. So you've got one harm of not screening, but not another. So I was just confused by the slide.

DR. CALONGE: I see. I got it.

DR. HOWELL: And we have --

DR. CALONGE: I do want to take the opportunity, since I (inaudible), is just tell the committee that this is an exceptional job of really boiling down an enormous amount of literature to, I think, a really understandable presentation. And I really think it's important to recognize Joe in doing this, and Jim and his team, because bringing this together in what you see today was a Herculean effort that should not go unrecognized.

DR. HOWELL: Thank you for that comment.

We have Mike first and then Benny.

DR. WATSON: Yeah, it is a very nice review. There's an area where I, both here and in congenital heart disease, I had a problem in sorting through some of the data because some of the nursery-based screens aren't mutually exclusive of other things that are screened. So, you know, in congenital heart, we had SCID that's picking up some of the dagorge variants that's also picked up in congenital heart.

And in this, two states, the District and Pennsylvania, both screen for G6PD deficiency. So that's going to impact -- depending on how many states screen for something that's a significant part of the genetic etiologies at the end of it. It alters, certainly, the cost analysis. So I'm wondering if -- and a general question -- whether we should be looking at whether, when we look at a new condition, we acknowledge that it may overlap with other conditions for which we're already screening by other modalities. And then for this, G6PD was a pretty significant chunk of the end point diagnosis -- or etiologies, I think.

DR. CO: Or hemolytic, in general, risk.

DR. WATSON: Yeah.

DR. CO: Yep.

DR. HOWELL: Bennett?

DR. LAVENSTEIN: I just wanted to -- Carol had a segue into neurology here -- bring up the point that some years ago, you may remember there was an attempt to correlate bilirubin levels with abnormalities in the brain stem responses for the ABRs. And what was found was it was a sliding scale. There's a paper in the New England Journal about this some years ago. Maybe you saw that. As a helpful diagnostic tool since there isn't perfect correlation with level of kernicterus, but there is a pretty good correlation between the decline in the ABR as it relates to the ABR with rising bilirubin levels, which may be a reflection of potential (inaudible) damage or hearing loss. That particular tool may well have application.

I would say that in some (inaudible) this area close to 11,000 deliveries a year, every child that's born has an ABR. And they may have a bilirubin that's 18 or 20, but they could have an abnormal ABR, which would then put you in the category of looking into whether bilirubin is playing a role in their potential hearing loss. So kernicterus is really very important to help screen in that.

DR. HOWELL: (Inaudible) correct.

DR. WATSON: And that may be the tool that's not an expensive tool.

DR. VOCKLEY: Shall we move to the formal discussion?

We will have opportunities, I guess, as we go through to ask for additional -- for clarification on the evidence as we move through.

LLOYD-PURYEAR: I just, as a need to know, as the Executive Secretary, the Evidence Review Group has asked the committee can they move forward with the decision tree analysis. And I need to know if that's agreeable.

DR. VOCKLEY: Does that put off a decision on our part? Or is this now more an academic exercise to be applied to future decisions?

DR. LLOYD-PURYEAR: Does the answer to that question put off a formal vote? Is that what you're asking?

DR. VOCKLEY: Yeah. Do we want to wait for the decision tree? Or are we going to fight our way through at this time and let them use this as an example to develop the decision tree? But --

DR. LLOYD-PURYEAR: I want --

DR. BOYLE: I would propose that we wait. So I would --

DR. HOWELL: Yeah, I would --

DR. BOYLE: -- make a motion on the floor that we wait.

DR. HOWELL: Yeah, yeah.

MALE SPEAKER: It seems reasonable.

MALE SPEAKER: I'll second that.

DR. HOWELL: Yeah. The motion is seconded.

Those favoring that motion? We're going to wait, and so forth. But I think that it's fair to say that the discussion will come up soon.

Okay, Jerry, go ahead.

DR. VOCKLEY: So I'm off the hook?

(Laughter.)

MALE SPEAKER: A little bit, but not much.

DR. VOCKLEY: Do you want to go through the rest of this?

DR. HOWELL: Yeah, you should go through the -- I think, you'd like to, you can go through your --

DR. VOCKLEY: Okay. So perhaps the decision tree can take into account this discussion and see how it works. I will say that, spending a fair amount of time with this report and trying to distill it down to the things that I needed to make a decision, this has been, in many ways, one of the more vexing proposals that we've reviewed because I went into it thinking, yes, you know, high bilirubin causes kernicterus. Kernicterus is good to prevent. We should somehow or other help that out.

But it was just -- it seemed impossible, from the data that we had, from what's in the literature, to actually make that connection. And so, let's go through what we have in an informal review process. And

hopefully, if we get something more formal in terms of a decision tree, it will either improve or reflect this.

So this is the current decision matrix that we have. This is a little bit different than has been used in the past because we've been tweaking it. And this is the version that is in the report that will be going forward to Congress. And so, this is the one I've pulled up.

So we have category one, which is add the conditions. It's done. We agree with everything.

Number two -- this has moved up a little bit in the thing. And this is the yes, but category. That is we think that this is pretty good evidence, but there are a few gaps, and we can fill those and probably make our case.

Category three is the shoulder shrug. We really just can't tell, from the data we have at hand, if this is good or bad. And so, we can't accept it. But we're also not saying that it should be thrown out, which is what number four says, that we have enough data that we can just dismiss this. That is it either has no benefit, or, in fact, demonstrated harm.

To get to that -- and this goes back to the paper out of this committee authored by Ned. We have key questions that we have been trying to address. And they're listed here. I've called number one the

slam dunk question in the past. That is if we can say that there is direct evidence that this is beneficial, then all of the rest of the discussion is over and we go right to approval.

The other questions are designed to help us get to our decision when we don't have the slam dunk data. And that is question two. Is there a case definition that can be uniformly applied? And we'll come back to each of these in a separate slide. So I'm just going to buzz over them quickly.

Question three -- is there a valid screening test? Question four -- is it -- has it been validated in a -- and incorporated into an appropriate screening algorithm? What's the clinical utility of that algorithm -- and then a question regarding cost effectiveness. So this just puts that in the graphical form that was used in the Calonge paper.

And so, what I'd like to do is just go through these now question by question and focus the discussion on each of these in turn. So key question one, the slam dunk question, that is. Is there direct evidence that screening for the condition at birth leads to improved outcomes for the infant or child to be screened or for the child's family? And my read on it was that this is just too strong, that we're not there and that we need to work through the rest of the other questions. And if there are comments or disagreements, bring them up now, or, as they say,

forever hold your peace.

There's a question or a comment.

Carol?

DR. GREENE: I completely agree with what you said with respect to the conclusion based on the evidence. My question is actually about the question.

(Laughter.)

DR. GREENE: So this overarching question, is there direct evidence that screening for the condition at birth leads to improved outcomes for the infant or child to be screened or for the child's family. Now, I'm a geneticist, and I believe in that, wholeheartedly and passionately. I think that's a good thing. But I also think that's where we get into some interesting issues with, you know, we do things without consent because it's for the benefit of the child. If it's for the benefit of the family, that's a different discussion. And I'm not sure when that question evolved to include, "or for the family." I just thought I'd better ask.

DR. HOWELL: The committee has already made that decision. So we would have to go back and revisit, which I would suggest we not do this morning.

DR. VOCKLEY: At least not as part of this discussion.

DR. HOWELL: Right.

DR. VOCKLEY: But it is a point well-taken.

Okay, so then, as we worked through the other questions that are designed to let us make a decision when the answer to one isn't yes, is there a case definition that can be uniformly and reliably applied, what are the clinical history and spectrum of the disease of the condition, including impact of recognition and treatment. And I pulled out a couple of things here just to start the discussion. This is not meant to be the final answer, of course.

So under no to that, I highlighted the report conclusion that said that there were variable definitions of bilirubin level in the studies and that the evidence does not exist to link a specific bilirubin level to causing permanent neurotoxicity. Now, that, to me, was very, very surprising. But I'm pulling that -- that's a quote from the report. And in discussing that a little bit with some others involved in the report and, in particular, Jim, he did note that evidence from several case series indicates that treating high bilirubin in the unusual child with early neurologic symptoms prevents chronic bilirubin encephalopathy.

So it's kind of a fine line there between saying it's true in all cases versus if you've got a symptomatic child, you can predict toxicity in the child with acute bilirubin encephalopathy. So let's stop there and see if there are questions for the Review Group or additional comments.

DR. HOWELL: Question three?

DR. VOCKLEY: Question three -- is there a screening test or screening test algorithm for the condition with sufficient analytic validity? And I waffled a little bit, but I said probably. I think it's actually yes. The trans-cutaneous bilirubin appears to be a reliable screening tool for detecting significant hyperbilirubinemia requiring confirmatory follow-up with TSB. And these are all quotes from the report. This is not my language.

"Current practice and implementation of bilirubin newborn screening includes inter-hospital variability in bilirubin screening practice." So it's not perfect, but it seemed to me that this was a pretty reasonable -- this was an answer to the positive side.

Questions or comments? Is there another one? I'm sorry. I can't see.

Go ahead, Fred.

DR. LOREY: Yeah, I would just add to the second bullet. I guess this would fall under anecdotal. It's not in the report. But we collect RH reports. We're mandated to do so. And in the report is bilirubin level. And I would just confer that that's what we see.

DR. VOCKLEY: I think what we're seeing reflects Ned's comment that this is just an excellent report. And it's pretty hard to argue

with -- or we don't need much addition to some of those.

All right. Well, key question four -- I think four and five will be a little bit more contentious. Is the clinical validity of the screening test or screening algorithm, in combination with the diagnostic test or test algorithm, be determined? And is that validity adequate? And here, I pulled out some examples from the report that led me to conclude overall that I thought the answer was no.

The first bullet here that evidence did not comprehensively address the optimal protocol for newborn screening and follow-up for hyperbilirubinemia and that there are no population-based studies available yet. You're so much quieter than when we did SCID.

(Laughter.)

DR. VOCKLEY: Key question five has a number of components to it. So I broke them out. This is a yes or no. But you'll see the answers there. What's the clinical utility of the screening test or screening algorithm. And that is case -- so I pulled the following quotes out from the report. "Case series suggest," and this is from the previous slide as well, "that the unusual symptomatic child or the child with acute bilirubin encephalopathy is at risk to have subsequent kernicterus," and some numbers. You will need to treat at least 222 males and 339 females to prevent one infant from developing a bilirubin level of which the AAP

recommends the exchange transfusion. So this is not kernicterus, but this is getting to the level where you would do something much more aggressive.

What are the benefits associated with the use of the screening test? And this comes back to my earlier question. The maximum of 20 to 100 cases per year of chronic bilirubin encephalopathy could be prevented with earlier detection and treatment. And it's not clear to me that that's really the right number, that that's based purely on population statistics, that some of those infants were already have been picked up because of current clinical practice. And so, I still am not clear on how many infants are missed because we don't screen. And I find that to be a key point.

But the report did conclude that there is probably a reduction of morbidity and mortality of cases, of bilirubin encephalopathy. And I think that comes back to John's pointing out that, in nurseries and systems where either uniform screening has been instituted, that the overall levels of kernicterus are probably lower. But again, I think there -- at this point, it just seems like every time we make a statement, there's a modifier to it that implies some uncertainty.

What are the harms associated with screening, diagnosis and treatment? We've had a little bit on that already. Phototherapy is

minimal, and I don't think would stop any of us from treating it, even if we were going to over-treat a number of children. However, exchange transfusion certainly is much more invasive and would lead to considerable harm, if it were employed on the wrong children.

Chris?

DR. KUS: Yeah, a question for John. Any data or any evidence, as you can estimate, as what percent of term or pre-term infants get at least one bilirubin?

DR. CO: I don't recall a study that largely talked about that. There were some studies that talked about changes in numbers of tests based on screening practices. So --

MALE SPEAKER: Right. And we do not have evidence on the actual -- any kind of population bases of numbers of kids screening.

DR. VOCKLEY: Tracy?

DR. TROTTER: So that probably means this answer is going to be no, too. But the, sort of, obvious statistic that would be helpful, if we look at -- if we consider that phototherapy's relatively not harmful and that exchange transfusion is a difficult procedure, under any circumstance, and has harm to it and that the logic is that kids are being exchanged because their bilirubins are 25 plus and they are the group most likely to get chronic bilirubin encephalopathy. Is there any data to suggest that

screening decreases exchange transfusion rate?

MALE SPEAKER: Right. So there are at least one or two papers that talk about nurseries that have universal screening, rates of phototherapy actually go up, but EcT goes down.

DR. HOWELL: It seems to me that's an important observation because the morbidity and mortality is so very high with exchange transfusion that if your efforts reduce that, that would be significant, I would think.

MALE SPEAKER: So we're actually screening for the need to do EcT as opposed --

DR. HOWELL: Well --

MALE SPEAKER: -- to preventing kernicterus.

MALE SPEAKER: Well, it may be that you can screen for, that you can measure that. That question, of course, becomes the relationship of -- if we had the relationship of number, it would be simple. We don't have that. So now you're looking for an indirect relationship. And I suspect that represents the group. I don't know that.

DR. HOWELL: Becky has a comment.

DR. VOCKLEY: Becky?

DR. BUCKLEY: Yeah. You know, we've been talking about --

DR. HOWELL: Microphone. It's on.

DR. BUCKLEY: We've been talking about the different kinds of evidence to include. And one of the things that occurred to me -- the crucial bit of data that we're missing on this particular condition is how many are we missing. And is there a way to screen pediatric practices to find out how many babies they pick up at the first well baby visit? Maybe some of the pediatricians sitting around the table could comment.

If we could, you know, develop screening tools where we could send out a questionnaire or a survey asking how many did you pick up that were missed. I don't know whether there's any merit to that sort of thing.

MALE SPEAKER: Well, we ought to be able to get that by readmission rates as a formal tool, I would think.

DR. BUCKLEY: Uh-huh.

DR. HOWELL: And you have data on readmissions, do you not, John?

DR. CO: Yeah, I believe readmission rates were also decreased. But, you know, in-hospital phototherapy during birth hospitalization go up, but with universal screening.

MALE SPEAKER: Right.

MALE SPEAKER: Other questions or comments on any of

these?

DR. VOCKLEY: I'm still boggled by not knowing the final number that we're preventing here, whether it's exchange transfusion or kernicterus. You know, we just -- we don't have the end point, it seems to me, which is pretty critical when we're taking a step as large as adding this to the universal panel.

Okay. Question six comes back to the relative cost and benefit. So you saw that there were minimal data, though actually a little bit more than some of the other discussions we've had. We have an estimate of point of care screening at between $1 to slightly under $8 for tests. And the analysis that nobody really likes to discuss, right, is -- I mean, we have to do it -- and that we're spending $6 million, in one of the analyses, to prevent one case of kernicterus, and that it costs $1 million to care for a child with kernicterus over the course of their lifetime.

So we're clearly not going to make this argument on the basis of economic benefit to the system, which we have done in some of the other conditions. You know, we say we can save the system money by finding and preventing these disorders. That's not the work here, based on the data that we have. We're going to have to make the argument on other points, it seems, if we're to add this one to the universal --

DR. HOWELL: Do we know the date of the CDC estimate?

DR. BUCKLEY: That's what I was just going to say, that that information from the third bullet there, the $900,000, that's probably an underestimate, because that's all children with cerebral palsy. And obviously, children with kernicterus are much more impaired, so in the severe end of the spectrum. And on the third bullet, on costs, my economist tells me that's a definitely an underestimate, relative to the methodology that was used. It wasn't a standard methodology used. It was one study looking at costs. So just those two figures are a little --

DR. VOCKLEY: Okay. Okay. So the figures may not be accurate, but if anything, they're both going to nudge up and the ratio may be similar. It's hard to say.

Carol?

DR. GREENE: I was going to make the same comment about that $900,000. That's got to be a phenomenally low estimate because the majority of cerebral palsy, you know, might need splints for the ankles and doesn't need special ed. and a powered wheelchair and computers and somebody to care for them their whole life. That number is going to go up by five to ten times.

DR. VOCKLEY: What you're saying is you think that number is inaccurate, which also then implies that we just don't have the right

data. I think we have to be explicit about that again, because that comes back to our decision.

Any other comments?

So if we go to our framework here, actually, I realized that number three I said yes on. So we can change that with a yes. But there are a lot of nos there. And that, and the way the questions are framed, yes puts you closer to saying we want to screen. And no is an answer that pushes it towards the negative, in the overall decision process. And we have a preponderance of uncertain or negative answers, uncertain at best.

And so, in summary, I had pulled these key points out. And it seems to me that the screening methodologies is good. It seems robust. But we don't have any real population studies. The evidence that screening will, in general, prevent chronic bilirubin encephalopathy is missing, even though all of us want to believe that's true. And the cost/benefit ratio is very high. And the bottom line here is that as compared to many of the other discussions that we've had, you know, we don't just have small gaps in evidence here that we need to fill. It seems to me that we have significant gaps. And, as I said when I went into this, I was feeling like, you know, this is really something that where it shouldn't be too hard to make the case. But it is, or it was.

And so, I think this falls into category three, which is that we're not going to add it, not because we think there's no benefit or that there's harm, but because we just don't have the data that we need to support a conclusion of positive benefit. And this is, again, what I called previously in this meeting, the yes, but category, which is where we can identify, you know, very small, very specifically gaps in the data that we could point to to the various agencies and try to see if we can convince them to help us close those gaps and substantiate an otherwise yes decision.

I think this goes back -- this falls into the category where it goes out and the advocates of screening for this particular marker have to do a better job of now going back to this, identifying the gaps and trying to work on them, the same as anybody else who hasn't gone through this process is going to do.

DR. HOWELL: Any comments before I make comments?

DR. CALONGE: This is Ned. I just want to thank Jerry. I think that this is kind of where I end up as well. It's an interesting issue because you know that there's a precondition that we can screen for and find. You know there's -- but it's hard to determine exactly what the levels are that we're looking for that would prompt action. We know we have a treatment that treats the precondition that the risks, compared to the

potential adverse outcomes, are good. You know, so you minimize the risks, I guess.

And then, we know there's probably something we're preventing, but we don't know how much we're preventing. And we don't know how much universal screening would add. So it's an issue where we kind of understand what we're trying to do in that we can't fill in the evidence gaps sufficiently to make a universal recommendation. So I appreciate that summary, Jerry.

DR. HOWELL: Jeff?

MALE SPEAKER: But under the circumstances, are we really making a decision here? We have already said we're going to wait until next time around; right?

DR. HOWELL: Well --

DR. CALONGE: No, I agree with that. I --

DR. HOWELL: We're still, I think, in the discussion phase. Jeff had a comment.

DR. BOTKIN: Yeah, and I certainly agree that this was an outstanding report. I would say one of the things I didn't see reflected, to my mind, quite adequately within it was the heritable conditions. And I'm thinking of the G6PD, and I'm thinking of the glucuron transferase deficiency syndromes.

And my understanding -- and this has been informed by the Academic Society meetings this last week, where folks were looking at these kids with catastrophic hyperbilirubinemia and kernicterus and suggesting that many of these children are kids who have probably a combination of factors, G6PD plus glucuron transferase deficiency. And these are the kids who have rapid increases in bilirubin that may, in fact, be very difficult to treat, irrespective of the modality used.

And they're probably not responding to phototherapy alone, exchange transfusion, et cetera. So, you know, if, in fact, a lot of these kids who get into trouble have these heritable factors involved, it seems to me there's some potential implications for that. And one large implication might be that these are kids who are going to get into trouble, no matter what, and that we're then ending up doing a lot of phototherapy on kids who were never destined to have any problem anyhow. So we're, sort of, over-treating a lot of kids and then not adequately preventing kernicterus in that very small subset of kids who have a combination of high-risk factors.

The other thing is, you know, are there ways to think about a more targeted screening. If screening every baby for hyperbilirubinemia -- we don't have the evidence to make a clear distinction about that, ought we be thinking about other more targeted screening approaches? ABO

incompatibility was a huge problem in the past. And we didn't solve that by screening babies for bilirubin. Right? It was a different approach there. And are there ways to identify kids who are at risk prenatally rather than through the bilirubin?

So, you know, I just want to think about what role these heritable conditions play in this spectrum and whether that suggests there might be more targeted ways of addressing this problem, short of population bilirubin screening.

DR. VOCKLEY: I will say that the couple of neonatologists that I asked from our institution about this, just to get some practical views on it, said that their point was we should be screening high-risk kids. And they thought that that would be adequate to pick up the children who were likely to go on to have kernicterus. But again, this comes back to the evidence that's out there which doesn't let us make that conclusion. We can't tell, from what's been published, how many additional children we would identify through screening over and above the practical clinically-indicated approach to doing a bilirubin level.

DR. HOWELL: Carol, you had a comment?

DR. BOTKIN: I'm sorry, just one quick question I would have. Sort of, you know, are there ways we ought to be screening pregnant women to identify babies that are at high risk for these

outcomes? And how effective would that approach be?

DR. HOWELL: Carol had a comment.

DR. GREENE: It actually comes to that point. And that is that gets to some of the difference between identifying risk factors and identifying a condition that needs to be treated. And I think timing is an issue. Mike brought it up before. G6PD is big. We also, when we do the regular newborn screen and the methianine is high and its hyracine is high, that's usually a child with liver disease, even if it isn't tirisinemia. Well, if it isn't hyperal.

But I think timing is an issue because by the time you get the newborn screen back, you really need to have had that baby on -- you know, the hope being that whatever the combination of factors, that the lights will reduce your chances of needing an exchange transfusion. So I think that comes to timing. And that brings us back to a whole lot of point of care. And obviously, this does not need to be decided now, but I wonder if this is the time to say that -- I wonder if you could show the evidence for a physical exam and whether this is just not a newborn screening question, whether this should be kicked back to be a question of professional practice and hospital practice.

DR. HOWELL: Let me make a comment -- is that, like the other members of the committee, we have had this review for some time.

And I, like the rest of you, have read it with great care. And I was particularly interested to hear Ned's discussion of their recent committee meeting, and so forth. And what I would find extremely useful is our earlier discussion -- is to see this extraordinarily well-done report back with an evidence tree included that would help me reach conclusions because I had a real problem.

I mean, it's perfectly clear that kernicterus is related to high bilirubin. It's perfectly clear that babies that don't have high bilirubins don't get kernicterus, and so forth. So it would be very helpful to have an evidence tree that we could look at. And what I would suggest, if the committee is -- I'm sympathetic to the conclusions that Jerry has brought here. But I would think it'd be very helpful to see this back at our next meeting, et cetera.

The other thing I'd like to comment about is, kind of, a little off the record. I was not in Denver, but I was told there was some very important presentations in Denver on hyperbilirubinemia and some large studies presented. And I guess it's not too late to find out about those and try to see if they add any additional light to our subject.

Is the group comfortable with the idea of asking our distinguished colleagues to come back with a decision tree analysis so that we can then look again at this same excellent data and then, I think,

reach a conclusion at the next meeting? Or would you like to do something different?

DR. BOCCHINI: No, I would agree with that approach. I think that this discussion has brought out some of the key issues and some of the gaps that are missing in the data and some of the issues. I think the comment by Carol is really important -- is that, because of the complexity of this issue and the fact that people have worked very hard to try and develop an algorithm over the years, is this more of a clinical practice issue, especially with the fact that we don't have any real good information about how many babies are actually being missed with the current practice guideline. I think we need to look at the decision tree analysis, I think.

DR. HOWELL: That would be very helpful to me.

Is there any further comment, and so forth?

John, thank you very much. That was an excellent report.

But could I have a motion that we see this back at the next meeting with a decision tree embedded in the materials so that we can make that?

DR. VOCKLEY: So moved.

DR. HOWELL: Jerry makes that move.

A second?

Those favoring that?

You don't vote, Carol.

But those favoring that?

Any opposition?

Any abstentions?

Unanimous. We're going to see it back next time, hopefully, with a decision tree that will help us move along. And there might be something useful that we could add to it, and so forth.

And it would not be a bad thing if routine screening dramatically reduced exchange transfusions. I mean, most people in the room haven't done them, but I've done lots of them. And we don't -- you don't want to go there. That's not a good place to be.

So thank you very much. And that was an excellent report.

Jerry, thank you.

Let me announce what my goals are for the meeting today -- is that I think we have a good chance of finishing by lunch. And so, I'm still moving in that pattern.

One is that we're going to now move to the discussion of the SCID report by Amy Brower. And, as you remember, when this committee approved the addition of SCID to the core panel, the letter that I sent on behalf of the committee to Secretary Sebelius had the following three

bullets at the end.

And it said, "The addition of SCID to the uniform panel is done with the understanding that the following activities will take place in a timely manner. The National Institutes of Health will fund surveillance activities to determine health outcome of affected newborns. The Health Research and Services Administrations will fund development of appropriate education and training materials. And the CDC will develop and distribute activities suitable for underwriting this," and so forth.

And I think that it's just been amazing to me to see private groups such as the Immune Deficiency Foundation, the Jeffrey Modell foundation help funds these, along with the CDC, HRSA and NIH working together. And I think that Amy will be able to present outstanding efforts at this time. Where is Amy?

DR. BOYLE: Is Amy here?

DR. HOWELL: All we need now is Amy. Is she here? Who is hunting her?

FEMALE SPEAKER: Alaina is.

DR. HOWELL: Alaina is seeing if she can identify Amy at this point in time.

DR. DOUGHERTY: While we're waiting, could I ask a question?

DR. HOWELL: By all means.

DR. DOUGHERTY: Okay. So I've looked at the SCID report, which is very nice. But I'm wondering what the meaning of the first activity was. And that was to the NIH help fund surveillance activities to determine health outcomes. So so far we have -- the only result we really have is how many cases of SCID and other immune deficiencies have actually been identified through these pilot tests. But we don't have health outcomes.

DR. HOWELL: Well, Amy is going to discuss that, I'm sure, more extensively. But fundamentally, this is going to be a report of the Newborn Screening Translation Research Network, which is funded by the NIH. And the purpose of that is to gather information about patients who are in the -- who are collected from newborn screening and would be eligible for research, training efforts, and so forth.

But Amy is here somewhere.

DR. BOYLE: So she'll be here in a minute. Just to correct, this is actually a report of, not just the NIH Translational Research Network, but of CDC's and state and NIH and then very minor HRSA efforts in the implementation of SCID screening.

DR. HOWELL: It didn't occur to me that she would not be here.

FEMALE SPEAKER: She's here. She's just wrapping something up.

DR. HOWELL: While we're waiting on Amy to wrap up her business, I wonder if there's other committee business because that's the remaining idea, remaining thing on our agenda. Is there committee business that the group would like to bring up at this point? Anything as far as for the next meeting? Our next meeting will be -- the next 25th meeting, for Heaven's sakes, will be in September. And are there suggestions? We will obviously hear, as we have heard today, from the Evidence Review Group here concerning hyperbilirubinemia. Any other business?

FEMALE SPEAKER: Jeff, you had a suggestion for a session in September. Can you speak to that?

DR. BOTKIN: This, sort of, picks up on, I think, Ned's comments a little bit earlier. And we had a meeting of the Translational Network by what I think was the Legal Committee a couple weeks ago. And I think that there's a need to try to address the ethical and regulatory issues with pilot newborn screening programs.

And I think if we're successful here in fostering such pilots, states and academic IRBs are going to be faced with models for that research. And I think the standard informed consent approach to those is

a serious challenge to get effective recruitment for those studies. So I think there needs to be additional discussion about the ethical and regulatory issues with pilot newborn screening programs and that IRBs would benefit from some commentary at the national level about what's appropriate and what isn't for the conduct of these studies.

So I'm involved with the SMA pilot study. And so, we're going to be dealing with these issues in that particular context. But they're relevant to a whole host of studies that are important to this committee. So I guess I'd like to foster some additional analysis and perhaps discussion about those issues. And if we can get support for certain models of approaching this at the national level, that will greatly help local IRBs in reviewing these protocols.

DR. HOWELL: So what would be the title of the session, as you're envisioning, Jeff?

DR. BOTKIN: Ethical and regulatory issues in pilot newborn screening research.

DR. HOWELL: And within that, you would like to focus on informed consent? Or what other areas would you like to have as core?

DR. BOTKIN: Well, I think the informed consent would probably be a sufficient issue right now.

DR. HOWELL: Okay.

DR. BOTKIN: Because I think that'll be the core issue. I think a number of these protocols might well entail use of residual newborn screening samples. But I think that is not a necessary focus at this point.

DR. BAILEY: If we do do that, I'd like to volunteer to work with you on that, Jeff. With our fresh elects pilot study, the IRB ruled that it was of no potential benefit to the infant and greater than minimal risk. And so, it required mother and father consent to participate in the study. So it really ramped up the consent burden, but also opened up some interesting possibilities for some studies. But I'd love to be a part of that.

DR. BOTKIN: Great, thank you. And I think part of the problem with that sort of determination is that you then end up modeling a screening program that's not an accurate reflection of what a population screening program would look like.

DR. BAILEY: Right. Right.

DR. HOWELL: Is there any other committee business?

Let me welcome Amy. She was the last to know that we were an hour and-a-half ahead of schedule.

(Laughter.)

DR. HOWELL: But, Amy, welcome. And we are looking forward to hearing about your wonderful efforts relating to SCID.

DR. BROWER: Great. Good morning.

Thank you, everybody, for the opportunity to present today. In your binders, you have a draft report, a committee report titled, "Newborn Screening for Severe Combined Immune Deficiency." The purpose of this report is to summarize the current status of screening for SCID in state-based programs.

This report was requested by the Secretary in May of 2010. This presentation that I'm going to give to you today provides an overview of the report. And we hope that it's helpful as the committee continues its work.

Thank you to the many individuals and agencies that contributed to this report, especially Dr. Tina Er and Dr. Robert Boyd.

The three of us were tasked with putting this together for the committee to consider as of the meeting last January. Let's get started.

FEMALE SPEAKER: I think they're just loading it now.

DR. BROWER: Okay. I did not just finish this.

(Laughter.)

DR. BROWER: Contrary to popular rumors.

(Laughter.)

DR. HOWELL: Amy was meeting with the president, and she was a little bit late getting back from that meeting.

DR. BROWER: Yeah.

(Laughter.)

DR. BROWER: I'll tell you what really happened in that situation.

DR. HOWELL: Here you are. Okay, great.

DR. BROWER: All right. Okay. So we begin today with a brief reminder of the clinical features of SCID and review the significant efforts of this committee on newborn screening for SCID and related T-cell lymphocyte deficiencies. We will then review the report to the Secretary with the focus on the efforts and the findings from the initial SCID pilot and the expansion of the SCID pilots that began after the committee's recommendation last January. We will present emerging findings from the pilots, discuss lessons learned and propose next steps.

We have the principle investigators for the pilots in the audience and at this table: Dr. Fred Lorey, Dr. Mei Baker, Dr. Ann Comeau and Dr. Michele Caggane. Dr. Puck, who is head of the pilot for the Navajo Nation, couldn't join us today. But Dr. Lorey is familiar with that project and is involved in it, if you have any particular questions about that effort. So along with them and our colleagues at CDC, NIH, NICHD, HRSA, NLM, NSGRC, APHL, ACMG and HHS, we look forward to the committee's discussion.

SCID and related T lymphocyte deficiencies are a group of disorders and are characterized by a lack of a functioning immune system. Babies born with SCID appear healthy, but are extremely vulnerable to infection. Exposure to common infections and live vaccinations is life-threatening. SCID leads to death in infancy unless treatment, usually stem cell transplantation, is provided. Variations or misspellings in the DNA sequence of more than 13 genes can cause SCID or a form of combined immune deficiency. And in most cases, the misspelling occurs in a newborn with no family history of SCID.

Since SCID is not apparent at birth and early recognition is essential for life-saving treatment, SCID has been recognized for many years as a candidate for newborn blood spot screening. SCID actually was part of the ACMG review of conditions suitable for the recommended panel. But at that time in 2005, there was no test for newborn screening. And, in fact, early work on that test was just beginning and being reported from NIH.

Because this committee has the responsibility of making evidence-based recommendations at the national level regarding important health conditions for which newborns and children should be screened, this committee has established a process to nominate and review conditions for the recommended uniform screening panel.

Committee recommendations are based on a standardized process it has developed for evaluating disorders and gathers input from key stakeholders. Several conditions, including SCID, have been submitted for nomination and review.

In September 2007, SCID was nominated to the committee for addition to the recommended uniform screening panel. An evidence review was undertaken, and the evidence report was discussed by the committee in February 2009. At that time, the committee voted to not add SCID to the panel, noting specific gaps in evidence that should be addressed before SCID could be added to uniform screening.

In particular, these were prospective identification of at least one confirmed case of classic SCID through population-based newborn screening; two, the demonstrated willingness and capacity of additional states to implement newborn screening; three, the continued reproducibility of a screening test and the continuance of a false-positive rate that is specifically low, less than .1 percent and the creation of a laboratory proficiency testing program through CDC's National Quality Assurance Program.

In January 2010, the nomination of SCID to the uniform panel was again brought before the committee. The committee reviewed the activities undertaken to address the evidence gaps previously

identified. And the committee voted to recommend to the Secretary of Health and Human Services the addition of SCID to the uniform panel with the following activities -- with the understanding that the following activities would take place in a timely manner.

And this just reminds us of what, in 2009, the gaps were and the significant efforts by CDC and their colleagues in the state programs to address these gaps. And all of this is spelled out in the report, if you would like to review that in more detail.

But important in this is the reminder the identified cap of identifying at least one SCID confirmed case was our reminder that this is not only about classic SCID. It's also about related T-cell lymphocyte deficiencies. And many of those cases had been identified through the pilots and continue to be identified, as you'll see in the upcoming slides.

Based on the committee's recommendation and other efforts, we did expand the pilots from Wisconsin to Massachusetts and in a high-risk population in the Navajo reservations in New Mexico and Arizona. We saw continued reproducibility of a low false-positive rate with the TREC screening. And the CDC generated, with their partners in Massachusetts and Wisconsin, a Q.C. program that's now being implemented. And we'll talk a little bit about that coming up.

After consideration of the activities undertaken to address

these evidence gaps, as highlighted in the previous slide, the committee voted to recommend to the Secretary to add SCID and related T lymphocyte deficiencies to the uniform panel with the understanding that these activities would take place in a timely manner. Specifically, that NIH shall fund surveillance activities to determine health outcomes of affected newborns with any T-cell lymphocyte deficiency receiving treatment as a result of prospective newborn screening; that HRSA shall fund the development of appropriate education and training materials for families and public health and health care professionals related to the screening and treatment of SCID; that CDC shall develop and distribute to performing laboratories suitable dried blood spot specimens for quality control and quality assurance purposes.

In May 2010, based on the committee's report, the Secretary adopted the recommendation to add SCID as a core condition to the uniform panel and related T lymphocyte deficiencies to the list of secondary target and requested that this committee submit a report in May of 2011 on the status of state implementation of the recommendation, including the surveillance activities conducted through the NICHD Newborn Screening Translational Research Network.

So today we'll go through a little bit of the background related to SCID. We'll go through the initial SCID newborn screening

pilots. We'll talk in great detail about the NIH-funded expansion of newborn screening pilots, present some interim pilot study results from all of these pilots, talk about efforts in the non-pilot states, highlight the educational activities that have taken place over the last several months and discuss lessons learned and propose some next steps.

As we said, SCID is not apparent at birth. And early recognition is essential for life-saving treatment. So SCID has been identified as a candidate for newborn screening for many years. However, as we said before, there was no laboratory test to detect SCID until it was developed and validated in population-based screening by Dr. Chen and Puck at NIH in 2005.

This screening test detects the presence of a byproduct obtained during the development of an important part of the functioning immune system, the T-cell. Patients with SCID have few or no T-cells, and the absence of this byproduct, the so-called T-cell reception excision circles, or TRECs, identifies SCIDs, regardless of the underlying genetic defect.

The TREC assay utilized molecular methods to count the number of TRECs present in DNA isolated from dried blood spots. In 2005, the TREC test was brought to the attention of this committee at its inaugural meeting. And the committee has monitored its development

over the last several years.

In 2007, scientists in Wisconsin and the New England Newborn Screening Program both developed high-throughput TREC assays based on the early work at NIH. Massachusetts developed a 384 well plate format with automation representing one of the first developments of such high-through capacity for the newborn screening laboratories. So throughout the development of the TREC screening test for SCID we've learned a lot in the newborn screening laboratories about how to input molecular methods and how to do this in a high-throughput method. And your report contains all of the references that were produced in publications produced by this work at Wisconsin and Massachusetts.

In 2008, a partnership among the Wisconsin Laboratory of Hygiene, Children's Hospital of Wisconsin and the Jeffrey Modell Foundation led to the first pilot study screening all births in state. Federal funding from CDC was then made available to continue the pilot study in Wisconsin and to initiate a second state-wide pilot in Massachusetts. These two CDC-funded pilots are scheduled to conclude in 2011. A third pilot study began at the University of California, San Francisco and targeted a high-risk population, the Navajo Nation, in two hospitals in Arizona and New Mexico.

The pilot studies in Wisconsin, Massachusetts and at the

University of California, San Francisco generated screening and follow-up algorithms. They created educational materials for families and health care providers. They hosted multiple state programs for training in the assay. And they partnered with CDC in the development of proficiency materials that are now available to all newborn screening programs. Investigators from these three pilots presented their finding to the committee in January 2010 and at that time, had successfully screened over 200,000 infants.

Although no cases of classic SCID, or total failure of the immune system, were found, they did identify patients, or infants, with immunodeficiency disorders called SCID variant where a partial failure of the immune system that did require medical intervention. These programs and pilots documented the feasibility of screening for SCID and provided valuable information to the committee and paved the way for larger efforts.

To increase the likelihood of detecting classic SCID cases by increasing the sample size, NIH initiated the pilot project in 2010 through the Health Research, Incorporated, a non-for-profit corporation affiliated with the New York State Department of Health. The NIH-funded project enabled HRI and their collaboratees to provide evidence and feasibility of screening technologies and to expand SCID newborn screening to four additional states and territories: New York, California, Louisiana and

Puerto Rico.

This NIH initiative enabled screening to begin in two large states, New York and California, and expanded the ongoing efforts in Wisconsin and Massachusetts. Wisconsin actually did the analytical screening for Louisiana. And Massachusetts did the analytical screening for Puerto Rico. The efforts in New York and California were also supported with funds from the Jeffrey Modell Foundation in New York and California and from Perkin Elmer in California.

Piloting SCID screening in states with a large number of births provided evidence that TREC screening is compatible with high-throughput, automated environment. Sending the samples from Louisiana to Wisconsin and from Puerto Rico to Massachusetts established feasibility for a regional approach to SCID screening while the ongoing screening in Wisconsin and Massachusetts provided additional information about screening over multiple years.

There were several key features that we wanted to highlight about this project, including the CDC quality assurance program that was developed in the earlier pilot that then carried through in this pilot so that we could make sure that the assays, each assay, was independently developed and validated in the laboratories, that as we looked collectively at each assay, that they were performing correctly. We also created a

SCID data portal. And we fostered monthly conference calls to share expertise.

So with the SCID portal in mind, our goal is to collect, aggregate and analyze the de-identified screening data generated during the pilot. NIH provided a subcontract to the laboratory performance program to develop this SCID data portal. The subcontract was administered through the NIH Eunice Kennedy Shriver National Institute of Health and Child and Human Development's Newborn Screening Translational Research Network, which was established to provide infrastructure resources for research in newborn screening.

Access to the SCID data portal is widely available to any newborn screening program, clinician or researcher around the world interested in learning about or contributing to the understanding of the performance of SCID newborn screening assays. This aggregation of laboratory performance data in real time during a pilot represents a useful model of translating novel genomic technologies to a high-throughput public health setting while utilizing the latest in language standardization and electronic information exchange.

So we want to now turn to some of the findings that are emerging from these pilots collectively. And I want to spend a little bit of time on the disease categories. And this is a work in progress. We're

working with experts in the field to really come up with these categories and begin to call out the cases that are identified through the screen.

So a classic SCID presentation is caused by a complete lack of an immune system. Often, these are caused by deleterious mutations in one of several genes. These infants have a significant problem with immune function.

There's another category that we highlighted SCID variants. These are where there's a variation in the DNA of one of several genes. These infants have partial failure of a normal functioning immune system. These are so-called leaky SCID combined immunodeficiency, or Omenn Syndrome.

And then we have the category of non-SCID, which represents a loss or gain of a large section of DNA in one or several genes. These conditions involve multiple systems and syndromes, and although these children do have a significant impairment in immune function. I want to point out that even though we have these there categories, all of these infants would be missed if it was not for newborn screening. And each one of these cases requires significant follow-up by the health care teams and treatment.

As of the end of March 2001, SCID newborn screening has been piloted in six states and territories and one Navajo Nation. Over

914,000 newborns have been screened. And 12 cases of classic SCID, seven cases of SCID variant and 55 cases of non-SCID have been identified, diagnosed and treated. Throughout the pilot, the newborn screening programs heard of no child that had been missed by the screening and no child that had not received the adequate treatment.

Taken as a whole, these pilots represent over 119 months of continuous newborn screening for SCID across the United States. If we begin to look at the incidences of SCID as a whole, for this population, with SCID, we look at 1 in about 76,000; SCID variant, 1 in a 130,000; and non-SCID, 1 in 126,000. But as we look -- and this is another way to look at the cumulative work across these pilots.

So this graph represents the states in colors starting in 2008, when newborn screening began in Wisconsin through the end of March. And then, the little figures -- I guess they should be babies --

(Laughter.)

DR. BROWER: I would hope they're all healthy adults. Right? They belong to each individual state. And this is the cumulative percentages and totals for classic SCID. Just give you a minute to look at that.

And then, if we add in the variant SCID to this -- and these little guys are multiplied over the last few days. So that's why --

(Laughter.)

DR. BROWER: -- I was late to coming. Because one of the things that we're finding in the pilot is that we can get an early screen that a child has low or no TRECs. But it may take several months to figure out the molecular etiology and be able to place the children in these SCID, SCID variant and non-SCID categories.

If we begin to look at some of the emerging findings, generally what we're seeing is that the incidents is generally higher than previously reported. In the evidence-based review, remember that we were looking at 1 in about 100,000 for SCID. As we look across the different diagnostic categories and across the different states, we begin to see some differences in the incidents rates across the different populations.

You can see that in this table, Louisiana and Puerto Rico are not included because they have not yet identified a case. And Wisconsin had a late-breaking case that we wanted to include because they felt that it accurately represented their incidents rates in Wisconsin.

Another way to look at this data was provided by California. And this was based on their first six months of screening. And Dr. Lorey and Dr. Puck and their colleagues began to see differences in the incidence rates between different ethnic groups and racial groups. So in

the classic SCID, looking at California, 1 in 33,000 we've seen in the first 6 months. It's important to point out that our confidence intervals are quite wide. And that's because it's early days of screening. So we want to make sure we highlight that.

But what they're seeing is that the Hispanic cases have a higher incidence of SCID. And all related T-cell lymphocyte deficiencies have an increased rate as well. We are still working through understanding the racial and ethnic groups in the other states as well as the molecular etiology of the SCID cases.

Other emerging findings are that 0 TREC with normal copy number for the genomic PCR control consistently means that the infant is at risk for profound T lymphocyte deficiencies. So all of the laboratory-developed tests so far have displayed analytical and clinical validity that is outstanding. And so, the majority of classic SCID cases actually have 0 TREC. We're working to understand the molecular etiology of the low TREC cases, and we're finding that it's widely varied. We're also seeing a relatively low number of excellent SCID in California. But these are early days, remember.

So a few caveats on the incidences. Definitions are still being defined by experts. And I probably got a few messages as I'm presenting. There's large phenotypic variability, both within the SCID and

the SCID variant cases. And many cases, as I said before, are sometimes not finally diagnosed for several months. And the pilots are still in progress.

So let's take a minute to look a little bit at the tools and resources that were developed through this pilot, beginning with the Q.A. program. To support the quality assurance measures required by CLIA, CDC provided dried blood spots reference materials for within laboratory and between laboratory proficiency testing.

As of April 2011, results obtained from 11 newborn screening laboratories, including all of the pilot labs, showed excellent analytic validity or how well the test predicts the presence or absence of TRECs of 100 percent. And 100 percent, or 99 percent, specificity, or how often the test is negative when TRECs are not present. So these tests are performing very well across all the different laboratories.

We highlighted the data portal earlier. That's providing us with real-time clinical validation, which was one of the major weaknesses pointed out in the first evidence review. It's available to any interested stakeholder. And we're working on novel disease categories that we think will improve the field and help inform immunologists as we go forward.

These efforts has also led to laboratory protocols being widely available to any laboratory interested in adopting SCID newborn

screening. We have now four independently validated laboratory-developed tests. And these laboratories are available to train and to assist others as they implement SCID.

Results have also, through this pilot, done a monthly conference call that has really been interesting to be part of. We share expertise. We talk about challenges and opportunities of implementing SCID. We do a lot of troubleshooting. We find resources for states that are beginning to think about how to implement SCID. We help with materials to present to their advisory boards. And we really benefit from the expertise of these four laboratories, including Dr. Puck's laboratory with the Navajo Nation being on the phone once a month nationwide to really help out with the implementation. We've also been joined on those calls by clinicians and foundations that can help us in our efforts as well.

So we promised to talk a little bit about what's going on in the other states. So while these six pilots cover approximately 25 percent of the births in the United States, consideration of SCID newborn screening by the other states not involved has been extensive. The Immune Deficiency Foundation and the MBSTRN did a survey and found that all state programs have actively considered implementing SCID with newborn screening, based on this committee's recommendation in January 2010.

Two states, colored here in -- or one state, colored here -- the pilot states, sorry, are in blue. We have partial screening in Pennsylvania. That's blue polka dots. And then we have a few states that are involved in targeted populations screening. This is Texas, New Mexico and Arizona.

And a number of additional states, the greens, have actually presented SCID screening to their newborn screening advisory panels and have approval to implement screening as soon as logistically possible. Once these states are actively screening, over 45 percent of the babies born in the United States will be screened. All of the other states are at various stages of assessment of analytical platforms, cost analysis, development of referral and treatment services and infrastructure and recruitment of necessary personnel. And these are highlighted by the states that are in white.

The states in yellow are regional partners of one of those states in white. And so, they will implement -- they're doing their own fact-finding. But they will implement actual analytical screening once their regional partner adopts the screening.

We have found, through our survey, no instances of state advisory boards choosing not to implement SCID screening, to date. We have heard, however, that several states do require an FDA-cleared or

approved kit to begin screening.

So some key points that we took away from the survey and our work with the states is that all of the states have actively considered SCID. Twenty states have presented the SCID screening to their state advisory committees. And all have recommended implementation. About a little over a third of the states participate in a monthly call to share expertise and information. And we'll continue to have those calls even after the pilot has ended.

The pilot states have played a key role in educating interested stakeholders and states. And this can't be emphasized enough, the countless hours that the state programs have put into this and really disseminating the information and the lessons learned from their early experiences. We know, as I highlighted earlier, that nine states rely on a regional partner, and three states report that requirement for an FDA-cleared or approved kit, which, based on yesterday, sounds like a snap.

(Laughter.)

DR. BROWER: No problem.

(Laughter.)

DR. BROWER: So many activities to educate and support key stakeholders have been evident throughout the pilot. The six pilot state newborn screening programs have created and distributed

educational materials for parents of newborns with a positive screen and/or with a confirmed diagnosis. And I'm sure that they will be willing to share these documents with you, the committee, if you'd like to review them, or with any interested stakeholder.

The second, sort of, rectangle highlights an October 2010 meeting sponsored by CDC, the Association of Public Health Laboratories and the National Newborn Screening and Genetics Resource Center, with HRSA funding. They hosted a meeting devoted to SCID newborn screening.

The meeting was attended by 192 laboratorians, follow-up professionals and immunologists from 48 states and 3 countries. They also had a supplementary laboratory workshop that was attended by scientists from 28 U.S. newborn screening programs.

The third rectangle is HRSA and ACMG's effort to support primary care providers and to facilitate timely diagnosis and treatment. HRSA funded the development of SCID clinical decision support materials or action sheets, known as ACT sheets, through its National Coordinating Center for the Regional Genetic and Newborn Screening Collaboratives.

The fourth rectangle represents efforts by the Immune Deficiency Foundation to support families and to encourage the adoption of SCID newborn screening. IDF launched several efforts, including a

Web page for parents, a SCID newborn screening advocate toolkit for use by families to educate their policy makers and a brochure to warn providers about the danger of administering live rotavirus vaccine to infants with SCID.

And the fifth and final rectangle highlights the CDC, APHL and Jeffrey Modell Foundation's two-year fellowship for post-doctoral candidates, where these candidates can focus on newborn screening research, including research into immune deficiencies.

So after 17 months after this committee recommended screening for all newborns in the United States for SCID and related T-cell lymphocyte deficiencies, one-fourth of the births are being screened through pilots funded by multiple federal and state agencies and private foundations. What we found is that what this committee does matters.

So the committee recommendation triggered all of the state newborn screening programs to do something, whether it was to get involved in a pilot, to write a research grant, to begin to talk to their advisory committees, to begin to engage stakeholders. Every one of them acted on your recommendation to add SCID to the universal newborn screening program.

We also discovered that the biomarker that was previously discovered begins to identify two clinically distinct populations. One is the

infants with no TRECs. And the other is the population with low TRECs. And, as we said, we're still looking through the data to understand the molecular etiology and the health outcomes of those cases.

Through this effort, we've been able to develop and validate and pilot novel screening technologies. And these are molecular methods that were able to be developed in four diverse newborn screening laboratories. And no known missed cases of SCID assay that we're aware of.

This also taught us that the initiation of newborn screening for a new disorder does contribute to the clinical and scientific understanding and facilitates new research questions. We have many avenues to explore this emerging evidence. And we have many, many grants that, hopefully, will be written and funded over the next several months as we work to understand these early results from the pilot.

In January of 2011, the -- or January 2010, sorry, last year -- no, this year, just a few months ago, IDF reported to this committee several issues that may be delaying the implementation of SCID screening. And we thought we should highlight that.

What they found was that there is a lack of cost/benefit information. So we're working in the pilots to make sure we can fill that gap. The states report a lack of financial resources, a lack of personnel

and expertise, a prior commitment of state resources to implement a legislative mandate to screen for other disorders, and in a few states, as we highlighted before, the lack of an approved or cleared kit, in some states.

So next steps -- ongoing efforts by NIH and CDC and HRSA will continue to support the adoption of SCID newborn screening, as these pilots conclude in June and this October, will continue to work to support the projects through their public dissemination of the pilot findings and of the screening and follow-up protocols as well as the educational materials that have already been developed.

We will continue to have monthly calls and invite all the states and interested stakeholders to participate. And the R4S SCID data portal will continue to be admitting cases and analyzing the results.

We have some new efforts that we're working on where we're beginning to create long-term follow-up data sets for the SCID, SCID variant and non-SCID cases. We're working to convene an expert workgroup to continue to refine the screening, diagnosis and treatment protocols. And CDC has a new funding opportunity for up to two new newborn screening programs. They're programs that hadn't yet been screened by January 2010. And that application -- I think those applications are due early this summer.

We also wanted to highlight an NIH-funded effort through the Primary Immune Deficiency Treatment Consortium. This consortium is working to identify factors, including whether or not early identification through newborn screening impacts health outcomes in children with SCID. So we're beginning to work with the PIDTC, look at how they identify the SCID cases and compare our definitions of SCID and begin to work together in the prospective and retrospective analysis of these SCID cases.

The activities recommended by this committee fostered collaboration among health and human services agencies and enabled each agency to focus on their areas of expertise while sharing tools and infrastructure resources with stakeholders and public health and clinical health care teams. Highlights from this team work are listed in this table.

CDC -- the initial pilots, quality control and improvement materials to ensure tests are accurate were distributed by the CDC to the pilot states. HRSA funded clinical decision support tools, or ACT sheets, to guide infants' health care providers. NIH, NICHD expanded the pilots and provided infrastructure for databases to enable the diagnosis, treatment and long-term follow-up of SCID cases.

This update affirms this committee's system of evidence-based review of conditions nominated for addition to the uniform panel

and subsequent recommendations to begin newborn screening for nominated conditions and, we feel, lays the foundation, an effective foundation, for future efforts to improve the health of newborns.

This is a draft for the report. I'm going to start showing the acknowledgement slides because they are many people to acknowledge. This committee thinks that its recommendation to begin screening for SCID, along with the suggested activities, has saved lives, improved scientific understanding of immune deficiencies, including the molecular etiology and the racial and ethnic distributions of molecular sub-types, expanded clinical knowledge of the care and treatment of SCID and emphasize the relevance of early diagnosis and intervention.

This recommendation has also been a triggering event for the majority of state screening programs. And screening for SCID represents the largest expansion of newborn screening since the advent of tandem mass spectrometry a decade ago and the recommended uniform panel five years ago. We know that SCID screening is a DNA-based molecular test. And the state newborn screening programs will be appropriately challenged to develop the expertise and molecular methods or share existing regional expertise to implement SCID screening.

And we know that we have experts in these states. California, principle investigators, Fred Lorey; Louisiana; Massachusetts,

Dr. Ann Comeau and colleagues; New York, Dr. Michelle Caggane; and Puerto Rico and Wisconsin, Dr. Mei Baker and colleagues; and then, at the Navajo Nation, Dr. Jennifer Puck, principle investigator; and our colleagues at Mayo Clinic. Roshini Abraham actually helped us define the cases of SCID. Her and Dr. Fred Lorey were the co-curators of the SCID data portal -- and then, Dr. Rinaldo and his colleagues, who actually developed the SCID data portal. And then, another list of agencies who have been very helpful -- it takes a village to write my report. Okay.

(Laughter.)

DR. BROWER: So many of these agencies have played a key role in both the early work in SCID and the work going forward. So we thank everybody.

And thank the committee for your time and look forward to the discussion.

DR. HOWELL: Amy, thank you very much.

(Applause.)

DR. HOWELL: -- your willingness to come and present early. I wonder if there are comments about the report that you have before us.

Becky?

DR. BUCKLEY: Well, first of all, Amy, I'd like to congratulate

you on your report. I think it's very good and comprehensive.

DR. HOWELL: Yeah.

DR. BUCKLEY: And I was very excited yesterday when I came in to learn about two new cases of SCID that had just been discovered, one in New York and one in Wisconsin. I don't know whether they were in your figures or not. But I think that we're going to find more and more as we go along.

Denise asked a question earlier about whether or not your report would cover the outcome of discovery of these patients and what's happened to them.

And Amy mentioned in her slides the Primary Immune Deficiency Treatment Consortium, or the PIDTC. I was at the meeting that was held in April in San Francisco where people talked about how they had treated the patients who'd been discovered by newborn screening.

And I can assure you, Denise, that they're all receiving appropriate treatment. And I have not heard of any deaths that have occurred in any of the patients who have been treated. I think they've been mainly bone marrow transplanted, but some of them have also been treated with enzyme replacement therapy for adrenosine diaminase deficiency, called Peg ADA in anticipation, hopefully, of getting gene therapy because there's several gene therapy protocols for ADA

deficiency that are operating right now.

But I think that your report is really wonderful. And I hope the Secretary will be as impressed as, I think, we all are. Thank you.

DR. HOWELL: Alan? Alan? And then, Denise.

DR. FLEISCHMAN: This is just spectacular. And I'm proud to sit near the committee that made this recommendation.

(Laughter.)

DR. FLEISCHMAN: And I wonder if we might consider the chair's letter that will go along with this report because it does seem that geography, again, is destiny in the U.S. at the moment. And are there things that we could recommend, in the cover letter, that the Secretary do, through her good offices, that might speed up the implementation? Now, I see that the CDC has, in their good wisdom, two grants. But, you know, are there things that we might brainstorm about that the Secretary and her office could do that might facilitate the universal activity?

DR. HOWELL: Did you have specific suggestions?

DR. FLEISCHMAN: Well, I don't have the wisdom to understand the power that she might have. And maybe others around the table might. I mean, there are dollars here that could be helpful, certainly, if the CDC program could fund 10 rather than two. There are regional efforts. If we could enhance those who have already gone up and are

running, that they could, in the interval, do additional testing. I mean, you know, I'm just doing this off the top of my head.

But we've also heard from some states that, although their advisory committees have looked at this, there are some serious funding questions about whether they're going to be able to implement this, in light of all of the state problems that are going on. So I'm a little worried that our real happiness about this first year might actually not result in our being universally happy at the end of the next year.

DR. HOWELL: Denise, you had a comment.

DR. DOUGHERTY: Yes. It wasn't about this with any recommendations. But I guess I have one minor question and one suggestion because I do think this is a fabulous report and a fabulous effort. And I agree with the concluding statement in the report that this is a model for future activities of the Advisory Committee. However, as we saw when we tried to make it a model in CCCHD, it's not quite a model for what the committee does yet.

So my proposal -- this is not the minor question. My proposal for the next committee meeting is we actually review that framework for making recommendations that we have and see if we might want to address how to have recommendations that actually do include future research. Because there's always uncertainty in these

recommendations. And additional research on screening and on outcomes, I believe, would be helpful in many cases, not just in this one or in CCCHD.

DR. HOWELL: Becky?

DR. BUCKLEY: Can I just add one thing? You know, there is a law now that says that all newly-diagnosed SCID patients have to be reported to the International Bone Marrow Transplant Registry. So each of these babies, as they're being discovered, is being reported to the registry.

And that means that they're getting long-term follow-up through the CIBMTR. But also, the PIDTC, the Primary Immune Deficiency Research Treatment Consortium, has a five-year grant to do the long-term follow-up of these babies that are being treated.

DR. HOWELL: Jeff?

DR. DOUGHERTY: I didn't ask my minor question, if I could, which is do you have any idea why there appears to be considerable variation by state in the rate, the incidence rate. For example, Massachusetts and Wisconsin have 1 in over almost 200,000, and others have 1 in 30,000 identified. Do you know what the reason for that might be? Fred has -- thank you.

DR. LOREY: This is just a guess. But, based on our results,

I think it's the minorities, based on our increased rate in Hispanics, which are 50 percent of our births. And if you look at the other states, New York is finding the higher rate, like we are, also a multi-ethnic state. So it's a guess at this point. But --

DR. HOWELL: And the newly-diagnosed patient that we heard about today in Wisconsin change their numbers to be very similar to the other states. Massachusetts is still less common.

Yes? Melissa?

DR. PARISI: Amy, thank you for a really nice report. My question is about those states that currently have what you called targeted screening. Could you clarify what exactly they're doing?

DR. BROWER: Sure. Texas is actually doing a pilot with Massachusetts to try it out in a few hospitals. And New Mexico and Arizona are part of that Navajo Nation. So they're only screening at particular hospitals.

DR. PARISI: Noting that those states also have a very relatively high Hispanic population, I thought it might include --

DR. BROWER: Right. And Navajos, as reported, have one in 2,000 incidents. So that's why Dr. Puck is targeting that. They're now at about 1,200 babies, but have yet to find a SCID case. So that pilot, hopefully, will continue.

DR. PARISI: Thank you.

DR. HOWELL: Jerry, you had a comment?

Jeff, you had a comment?

DR. BOTKIN: Yes, I did.

DR. HOWELL: Okay. All right.

FEMALE SPEAKER: Jerry doesn't.

DR. HOWELL: Jerry doesn't. He's --

DR. BOTKIN: Oh, he does not? A couple things.

(Laughter.)

DR. BOTKIN: All right, thanks.

DR. HOWELL: Let me make one. To pick up on Denise's comment -- is that the reason I read the letter that we sent originally to the Secretary that had these three specific things at the end of the letter -- and the program that you have reported on answered those so crisply. And I did not point out those three recommendations were virtually identical to those that went forward on the congenital heart disease thing, as you also pointed out. So I think the idea of talking about the way we format things is a worthwhile thing to do. And I think we should do that at the next meeting, and so forth.

There are a couple things that -- this Secretary requires that we send this report this month. And I think that I would like -- we will need

to vote on this, and the vote will be a recommendation that we send this forward to the Secretary. And there are a little more recent data. And so, the things that will change in this report are the numbers, which will be brought up to date. But we need a motion to send this forward with the modifications of the data up to date. Can we have such a motion?

DR. BOTKIN: Wait. I have some more -- I've had comments waiting here. Can I offer that first?

DR. HOWELL: Yeah.

DR. BOTKIN: Okay. So a couple of things. I also agree it's an excellent report, both because it's well-done and because it's got a lot of good news in it. But I'm uncertain why there's not any outcome data for the kids in the report. That seems to me to be a huge hole because that's what the whole effort's about. Why don't we have some information verifying that these kids are, in fact, getting appropriate treatment and are benefiting from that treatment? So is there an explanation for that?

And then, two other quick things. I think the report would benefit from a little bit more information about cost. And I know our state is struggling with some of the cost issues. And that's, sort of, part of a suggestion about the lessons learned piece and what the report has and your slides demonstrate is, sort of, a list of challenges that people have identified. But I don't see any particular strategies commenting on those

challenges that have been identified. Is it possible to expand this a little bit so that folks have an understanding of what strategies are being adopted to overcome the challenges you've identified?

DR. HOWELL: Can you add some of that? I think that some of those data will probably need to come as the program continues. But could you add some outcome data specifically from the report that Becky mentioned?

DR. BROWER: Sure. The first infant was actually diagnosed in April 2010.

DR. HOWELL: Okay.

DR. BROWER: So it's about a year now. And so, we could report on some of those.

DR. HOWELL: I think it would be nice to have as much outcome data as could be. And again, it'll be interesting and also fun to see the data on the economics because the missed infants, not only die, before they die, they run up enormous costs. And the cost of doing the treatment is a bargain at any place. And so, that those data will really be fun to see. And I think that they can come in detail later.

DR. BROWER: And right now, there's no national resource to follow those kids who weren't part of the newborn screening program, since the pilot started, but did get a transplant. And so, the PIDTC will be

-- they're also doing, in addition to their prospective, a retrospective look.

DR. HOWELL: Yeah.

DR. BROWER: So we'll be working with them to get those cases and begin to compare the cost/benefit.

DR. HOWELL: So can we now have -- and she will add a bit of that data. Can I have a motion to send the report forward?

FEMALE SPEAKER: I move that we send the report forward with modifications as (inaudible).

DR. HOWELL: Second?

Those in favor?

MALE SPEAKER: Aye.

DR. HOWELL: Aye. We see all hands raised.

Anybody opposed?

And no abstentions, and so forth?

So we will send that report forward.

Thank you very much, Amy.

Ann, do you have an extremely brief comment?

DR. COMEAU: Extremely brief. I just wanted to address the variability in rates. Not only do we know that no one has found any false-negatives, but in Massachusetts, much to -- and in any other states, we have had specimens sent to us that we did not know were SCID. We've

had about 30 of these sent to us. And all of them have been identified. So in addition, between that and the CDC proficiency testing, I think that we can be confident that all of the different tests are working very, very well to identify all SCID infants.

DR. HOWELL: Thank you. It would appear that the labs have really been doing very well.

Mei?

DR. BAKER: Quick -- (inaudible) the first SCID in our state, and I just want to quick comment. And obviously, the baby had a bone marrow transplant. And I'm very happy to say the first -- after five, six months and asking them to spot -- the dried blood spots come back and TREC is normal. So I wanted to mention that.

And secondly, is that I think that population variability -- I think we need to start thinking about ethnic group. And I understand in California eight cases -- six is Hispanic. So this will maybe come the different. So, you know, we learn going forward (inaudible).

And the third point I was going to mention is newborn screening for SCID is not just happening in U.S. I think internationally, especially Europe, is a lot of activities. I mean, my personal experience -- I have several countries come to the laboratory to learn the assays. So I just wanted --

DR. HOWELL: Excellent, excellent. Thank you very much.

Amy, thank you very much for an outstanding report.

After we've discussed committee business -- and I think, unless someone has some burning issue -- after the meeting today, you're going to get an e-mail. The members of the committee will get an e-mail from Altarum asking you to evaluate the logistics of the meeting. And it's a Web survey. Please fill that out and so that they will be able to more effectively plan for the meeting.

Our next meeting will be September the 22nd and 23rd. And we have a few suggestions already for the meeting. And Michele's --

FEMALE SPEAKER: Alaina has --

DR. HOWELL: Alaina seems to have some issues.

(Laughter.)

MS. HARRIS: Right. Well, this one's going to affect you all more. It's come to our attention that everybody who had booked a hotel room through the Altarum Web site this morning -- it looked like that had all -- the price of your hotel had been covered. It's not. So they have fixed that, and now all your credit cards have been charged. So I just wanted to let you know. And if you need a copy of your bill, please go by the front desk.

DR. HOWELL: I'm also aware of the fact that, at least some

people who came by air, also got charged for parking.

(Laughter.)

DR. HOWELL: And the parking is essentially the same as the room rate.

(Laughter.)

DR. HOWELL: So after you pay for parking, you'll have to sleep in your car.

Are there any other things to come before the committee? Thank the committee very much. I think it's been an extremely productive meeting, as usual, with this group. And so, we'll look forward to seeing everybody in September. Thanks very much.

We need to have a motion to adjourn, for Heaven's sake.

MALE SPEAKER: (Inaudible).

DR. HOWELL: Second?

MALE SPEAKER: (Inaudible).

DR. HOWELL: In favor of adjourning?

MALE SPEAKER: Aye.

DR. HOWELL: Aye. It looks like it's an overwhelming vote.

FEMALE SPEAKER: There is lunch for the committee members and representatives and speakers.

(Whereupon, at 12:00 p.m., the meeting adjourned.)