HEALTH RESOURCES AND SERVICES ADMINISTRATION
(HRSA)

WEBCAST:
16TH Meeting of the Secretary's
Advisory Committee on Heritable Disorders
in Newborns and Children (ACHDNC)

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Monday,
November 24, 2008

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PARTICIPANTS:

Committee Members

R. Rodney Howell, M.D., Chairman
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Leonard M. Miller School of Medicine
University of Miami

Rebecca H. Buckley, M.D.
J. Buren Sidbury Professor of Pediatrics
Professor of Immunology
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Jana Monaco
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PARTICIPANTS (continued):

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Presenters

Bruce Nedrow Calonge, M.D., M.P.H.
Chief Medical Officer
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C O N T E N T S

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 P R O C E D I N G S
[Roll call.]
CHAIRMAN HOWELL: We have a quorum. Thank you very much. As Michele pointed out, we were very sorry to have an Email from Piero. His father, who has been quite ill in Italy, had died. He is probably en route to Italy, and so not on the call. We have extended our condolences to Piero.
The first item of business today is the approval of the October 1st and 2nd meeting minutes. Can we have comments about the minutes? Are there comments or changes to the minutes from that meeting?
[No response.]
CHAIRMAN HOWELL: Hearing no comments, can we have a motion to accept the minutes?
DR. TROTTER: I so move. This is Tracy.
[Motion so moved.]
CHAIRMAN HOWELL: And a second?
PARTICIPANT: So moved.
[Motion seconded.]
CHAIRMAN HOWELL: Thank you very much. All in favor say "aye."
[Chorus of ayes.]
CHAIRMAN HOWELL: Any opposition?
[No response.]
CHAIRMAN HOWELL: Anyone abstaining?
[No response.]
CHAIRMAN HOWELL: Since we see no hands and hear no voices, we will move ahead. Thank you very much.
[Approval of minutes.]
CHAIRMAN HOWELL: I would like now to welcome Dr. Dennis Williams, who is the deputy administrator of HRSA, for his comments. Dr. Williams?
Remarks by the Deputy Administrator
Dennis Williams, Ph.D.
DR. WILLIAMS: Thank you, Dr. Howell. I want to thank you all for convening today and continuing to refine the issues surrounding newborn screening for heritable disorders. In the Committee's materials for today's meeting is Dr. Duke's letter of October 21st on behalf of Secretary Leavitt to Dr. Howell in response to the Committee's

recommendations in its three prior letters. As I'm sure most of you have already seen the letter, I'm going to keep my comments today brief.
As Dr. Duke noted, the Secretary is considering adopting the conditions recommended in the American College of Medical Genetics Report as a national standard for newborn screening programs, but he feels that we need to have input from the President's Council on Bioethics and other sources beforehand.
I note the Secretary was hoping to receive the Council's report very soon, perhaps as early as this month.
In the meantime, I would like to commend Chairman Howell and the Committee on the progress that it has made toward refining the process for evaluating conditions for newborn screening and for ensuring that the process is systematic, thoughtful, and transparent. There are advocates on all sides of these questions, and it is vitally important that we have a process that inspires confidence and a sense that all points of view have been fairly and fully heard.
As technology improves and diagnostic tools are refined, other conditions are bound to be nominated for newborn screening, as severe combined immune deficiency is today.
As for continuing this work, the transition process began this week at HRSA. We expect that there will be changes with the incoming administration. But the continuing budget resolution runs through March 6th, so there is actually no reason for concern by the Committee or the interested public about its continuing functions or priorities.
At a time when certain issues in healthcare delivery were barely on the horizon, you already were talking about them in the area of heritable disorders, and this speaks well for the Committee.
A good example is health information technology. To make long-term follow-up feasible and seamless, individual health records must become truly portable over a patient's lifetime and able to be shared within interdisciplinary teams. In endorsing the personalized healthcare use case, the Committee is supporting a process for setting uniform standards for future IT contracts and infrastructure investment.
In the area of health professions and current education, we appreciate your advice and endorsement of the Newborn Screening Action Sheet and algorithms as clinical resources for health professionals, and the newborn screening informational brochures for parents, and your continual assistance in helping us to further define newborn screening educational needs.
To the central ACHD website, we now place lifesaving diagnostic information for these rare conditions at the fingertips of physicians across the country. This kind of steady incremental progress adds up over time.
Once again, thank you for your leadership, your foresight, and the great depth of seriousness and insight that you have brought to this sensitive and critically important area of medicine. I wish you well as you work through your agenda today. Thank you.
CHAIRMAN HOWELL: Thank you very much, Dr. Williams. Are there any comments from the Committee about the letter that was sent to me and copies of which each of you has in your booklet from Dr. Duke about the work of the Committee and the future of the Committee? Any comments?
[No response.]
CHAIRMAN HOWELL: I can comment just briefly. I think that many of you, as Dr. Duke has commented, are aware of the fact that the President's Commission on Bioethics has

recently developed an interest in newborn screening and is having discussions on the subject. We will be very interested in seeing how their deliberations and comments proceed in the future.
Again, thank you, Dr. Williams. If there are no comments about that, let me make one other comment. In your books there is a letter also addressed to the Committee from Angela Trepanier from the National Body of Genetic Counselors, NSGC, about their interest in becoming an organizational representative on the Committee.
I think each of you know at the current time that the operating situation at the Committee is that there are no further slots available at the current time for organizational representatives. I think that is something that we can consider in the future.
Would anyone like to make a comment about that? That is an informational matter. It is in your book. Obviously, their interest in the Committee, as well as others', will continue.
If there are no further comments, I would like to call on Dr. Rebecca Buckley, who has been kind enough at the last moment to review the material from the internal working group on spinal muscular atrophy. Piero was to do this, and I have already mentioned that he has been called away because of his father's death.
Dr. Buckley, can you comment about this document?
DR. BUCKLEY: Yes. Can you hear me?
CHAIRMAN HOWELL: Very well. Thank you.
Internal Review Workgroup: Report on the Candidate
Nomination: (Spinal Muscular Atrophy)
Dr. Rebecca Buckley, M.D.
DR. BUCKLEY: I will first read the summary, which is a summary of the comments of all the Committee members. Then, if there are any questions, I also could give some comments from my own report.
The summary information is derived primarily from the nomination form and also from submitted references and other publicly available materials.
The nominated condition is spinal muscular atrophy. The date of the review was October the 20th. The first point is, is the condition medically serious? Spinal muscular atrophy (SMA), also known as Werdnig Hoffmann disease, which is the most severe form of this, is a very frequent condition. It is one in 10,000 births or less. It is characterized by progressive degenerative motor-neuron disease. It is manifested by weakness and respiratory and feeding difficulties before one year of age. The expected lifespan is less than three years.
The onset could be as early as birth and usually within two to three months of life. Even the more moderately affected cases of SMA-2, which comprise 10- to 20 percent of the patients, experience severe symptoms by 18 months of life.
The second question is, have there been any prospective studies? There is a study that has been done at the Ohio State University in the Molecular Pathology Laboratory. In this lab they did population screening using a PCR Luminex Array system. This was facilitated by the fact that the SMA gene is mutated in these patients. Most of them carry a homozygous deletion at SMN-1-Exon-7.
So they pursued analytical and clinical validation in 40,130 blood spots in a single laboratory. As I said, this was the molecular path lab at Ohio State. It remains to be seen how effectively the method could be implemented in public health laboratories. As

you will see, this is probably one of the main concerns we had. The study did demonstrate that screening for SMA can be technically accomplished on a large-scale basis.
The third question is, is the spectrum of the disorder well described? Does it help predict the phenotype of the child who is affected? The answer to that is, the SMA-1, SMA-2, and SMA-3 phenotypes can be discerned by PCR-based sequencing copy number analysis of the SMA-T and SCMA-C gene. The different genotypes largely correlate, although not perfectly, with SMA-1, -2, and -3. This is a publication from Pryor and Swoboda.
The next question was, are the characteristics of the screening tests reasonable for newborn screening? Among other aspects, is there a low false negative rate? The comment that we had is that the proposed method is one of the first examples of a primary screening test based on genotyping. Accordingly, the sensitivity and specificity are expected to be high. The nomination form mentions a potentially imminent pilot study.
The next question is, if the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky. It is feasible to predict by genotyping the patients most likely to benefit from treatment. The screening assay can be performed from a dry blood spot by real-time PCR, perhaps with first-tier screening by Luminex.
The false positive rate of population-based analysis is not reported, even from the above-cited Ohio pilot study, although Dr. Pryor reports 95 percent sensitivity and 99 percent specificity for the PCR Luminex assay.
Also, the screening test can be adapted to avoid identifying carriers.
The next question was, define treatment protocols, SCA-approved drugs, and other treatments if they are available. The answer to this is that those that can benefit from treatment are easily identifiable. However, nutritional support and respiratory care are the only available options at this time. There are unproven drug treatments that are under evaluation. Notably, their effectiveness in mice depends on timing of administration before onset of symptoms.
Overall recommendations to the Advisory Committee. The nomination of SMA might be premature for evaluation at this time as judged by the evidence I just presented. There are critical elements missing from both the test characteristics, such as reproducibility outside of an academic lab, and treatment efficacy beyond the relatively limited benefits of palliative measures.
The Internal Nomination Prioritization Workgroup recommends no evidence review at this time and further recommends a nominator to conduct prospective pilot studies in one or more traditional public health laboratories in order to show reproducibility of the preliminary findings in Dr. Pryor's laboratory.
The time frame required to collect the analytical evidence mentioned above could also lead to a better assessment of the efficacy of novel treatment modalities under investigation.
That is the end of the summary.
Discussion
CHAIRMAN HOWELL: Thank you very much, Dr. Buckley. Dr. Rinaldo had been responsible for drafting this report. I wonder if Dr. Frempong or Dr. Skeels has any

additional comments.
DR. FREMPONG: This is Dr. Frempong. I don't have anything new to add. I agree with the sentiment of the summary.
DR. SKEELS: Rod, this is Mike Skeels. For me, I think it is well written and reflects the consensus of our group.
CHAIRMAN HOWELL: I had an opportunity to sit with that group. I think that the sense was that this is an extraordinarily important condition and the evidence is fairly overwhelming that for the early infantile onset of this disease, early identification and therapy is going to be critical. I think that the issues that remain, as far as moving this ahead at the current time, have been quite clearly outlined.
It is tremendously encouraging that folks involved in this area are conducting pilot studies using the state laboratory, so that one can see how this works in that real-life setting. Obviously, we will be very excited to hear results of the clinical trials that are currently ongoing as far as any potential therapies for this disastrous group of conditions.
Are there any other comments from the Committee?
DR. VOCKLEY: Rod, Jerry Vockley. I just think it is important to emphasize that if we are going to look at conditions where the therapy is either purely supportive or not much more than supportive that we really have to have a pretty strong rationale to consider newborn screening. I know that we had a lot of talk about the idea of being able to diagnose early and family planning and other non-therapeutic issues, but for the most part those are for disorders that we get without having to add an additional test to the screen. In other words, they are second-tier disorders that come in on that screen. Here we are talking about adding one test for one disorder. To implement that, I think we have to have some pretty strong clinical rationale.
CHAIRMAN HOWELL: Thank you very much, Jerry. I wonder if there are additional comments about this report from the internal working group of the Committee. Again, the critical issue, and I think the summary states it very well, is that this is a very important condition that has great strength as far as adding it in the future, but it was felt by the internal group that evidence review would not be appropriate at this time. The group encouraged the nominators to proceed with the recommended content of that report.
We will need to vote on this. If this is the sense of the Committee, what we will do is write a letter back to the nominators with those recommendations and so forth.
Can I have a vote concerning this particular report?
DR. CALONGE: Dr. Howell?
CHAIRMAN HOWELL: Yes.
DR. CALONGE: This is Ned Calonge. I move that we adopt the recommendations of the advisory committee as written.
[Motion so moved.]
CHAIRMAN HOWELL: Thank you very much, Dr. Calonge. Second?
DR. TROTTER: Second. Tracy.
[Motion seconded.]
CHAIRMAN HOWELL: Can we hear those favoring this nomination?
[Chorus of ayes.]
CHAIRMAN HOWELL: Is there any opposition?

[No response.]
CHAIRMAN HOWELL: Did any member on the phone call abstain?
[No response.]
CHAIRMAN HOWELL: Thank you very much.
[Motion carried.]
CHAIRMAN HOWELL: And thank you very much, Dr. Buckley, for stepping in at the last minute for Dr. Rinaldo's commentary and so forth.
The group is doing famously this afternoon. One thing I forgot to mention is, at the beginning of the call we had had considerable commentary about the need for having a break during this three-hour meeting. It will be my intention for us, after Dr. Calonge's report, to have a brief 10-minute break, if that is the sense of the Committee.
I wonder if we can go ahead now and move to Ned Calonge, who has been doing a great job overseeing the Decision Criteria and Process Workgroup. Ned?
Decision Criteria and Process Workgroup
Bruce Nedrow (Ned) Calonge, M.D., M.P.H.
DR. CALONGE: I just have to start by sharing that great job with my colleague, Michele, who does such a great job of herding this particular group of cats, and Nancy Green, who has also taken on a lot of responsibility for the edits. I appreciate those issues.
I don't know if it is possible to actually get the Version 14 that was sent out on the screen?
PARTICIPANT: No. Unfortunately, we won't be able to pull that up at this moment.
DR. CALONGE: Not a problem. I'm sure that is my fault. Hopefully, you have had access to the document through Email and you may actually be able to bring the document up in the PDF in front of you.
What I would like to do is talk about some key leftover issues and tell you that I think we are actually pretty close to being able to say we would like the Committee to vote on this document and this process and adopt it as an approach that we will take in taking the evidence reports to a recommendation.
There has been a review by Denise Dougherty. Denise, are you on the line?
DR. DOUGHERTY: Yes, I am.
DR. CALONGE: Denise, I don't actually understand all of your issues.
DR. DOUGHERTY: I guess I'm trying to get some different things synched and to have checklists, which have been important for airline safety and patient safety, to make it easier. It seems like a long document for guidance for the Advisory Committee itself as a whole.
DR. CALONGE: I appreciate that comment. I think, given the challenge to make it more concise and at the same time, hopefully, clearer, that is something that Nancy and I will take on for the February meeting so that this is ready to say, yes, we are all okay with this.
DR. DOUGHERTY: I think that is my main concern. It is very easy to lose track. There should be a one-pager that the Advisory Committee can go through. I realize all of this is important and your text is important as we all learn how to do this together. But as a document that can live on, some things could be appendicized, for example.
I also found in one of my piles here something that Jim Perrin had put together about how the Evidence Review Group is working on the parts of documents that they will be presenting. It seems to me working to make this document and that document parallel

would be helpful to the Committee.
DR. CALONGE: Actually, Michele has gone a long way, coming from the last version to this version, in making sure that the two documents point to each other in a more rigorous way. We understand that issue as well. Again, I think that is one that we are closer to now than we were at the last call. I think we will have that wrapped up by the time we ask you to vote on a final version.
DR. DOUGHERTY: Fabulous. That sounds great.
DR. CALONGE: There are a few issues.
First of all, let me tell you I appreciate everyone who reviewed the document and provided comments. We will continue to try to engage the rest of the Committee members as it goes on. I understand it is long. Hopefully, as it gets shorter we will just point to what is different and can move on in a more timely way.
If there are additional comments that people have based on the draft that we sent out last week, I hope you will bring those forward.
Coleen actually brought together a nice set of discussion questions. If it is okay, Dr. Howell, I thought I might take that approach to going through Coleen and Michael Skeels' questions specifically as a way of just engendering some discussion around the documents. Then we can be done with it for today.
CHAIRMAN HOWELL: I would think that is sensible. The Committee members have both Mike and Coleen's as well as Denise's comments. I think that would be great.
DR. BOYLE: Did anybody get mine? Obviously, I have mine, but I didn't see it come out today.
PARTICIPANT: I don't have Coleen's.
DR. CALONGE: I think I can actually talk you through those because I have them right in front of me. Fair enough?
DR. BOYLE: Sure.
CHAIRMAN HOWELL: It seems that you have had a selective distribution, Coleen.
DR. BOYLE: I didn't reply to all. I just replied to our subcommittee.
DR. CALONGE: Coleen, I am assuming you have your comments too and you can help.
DR. BOYLE: I'm looking for them as we speak.
DR. CALONGE: The first section of comments was the Body of Evidence section. I think if I was going to characterize Denise's comments, [she focused] on the context here that we tried to bring in from other evidence groups and newborn screening that were explanatory. I think she actually -- a lot of those out. I think we will need to figure out how much we need to have those.
Coleen's specific question had to do with the final paragraph, which is actually on page 2, if you have the document paginated. It says, "While I agree, the evidence base for rare disorders will be different," and that is different from other things we look at in preventive services, "I also think that the balance of evidence for the key question will be to understand more as opposed to understanding less, and that this paragraph leaves too much room for interpretation."
I think later in the document we talk about adequate evidence. I think, Coleen, you were proposing that we either mention that here or at least point to the adequacy of evidence section in this paragraph.
DR. BOYLE: Yes, definitely.
DR. CALONGE: Do people have other comments on the Body of Evidence section?

DR. DOUGHERTY: This is Denise Dougherty again. I didn't think it was a necessary section at all. It actually could be harmful and not get us on the track of being really rigorous. We seem to be on that track, so I was wondering, why have this preface that says we are really not going to be able to be rigorous at all, which is how I read it.
DR. CALONGE: I think part of the paragraph actually outlines the chain of evidence approach that the Clinical Guide and the EGAPP both use. I think outlining the chain of evidence approach, or body of evidence approach, in our specific document still will be important for future committee members to try to understand how the analytic framework works and how this chain of evidence was put together.
Again, the original name of this section was "Chain of Evidence." I think Michele felt that "Body of Evidence" resonated better with this particular group.
DR. DOUGHERTY: I'm sorry. I'm not looking at the document, actually. It's just the first paragraph that I objected to.
DR. CALONGE: I think probably what we should do is make sure that we are not going to be turning evidence into recommendations. I think what is reflected in here, Denise, is the trouble I have been having trying to think of how to address rare disorders in some different way given that I can actually identify, at least in the adult world, disorders that will never have a good evidence body.
DR. VOCKLEY: Jerry Vockley. I think that is the key point here. We have had a lot of discussion about this. We won't have the opportunity to have the kind of placebo/double-blind control studies that we need to evaluate the efficacy of treatments. I think it is important to frame that up front.
I think you have done a good job. Denise, I would argue that it is important to keep that in some shape there. What will happen is we will all rotate off the Committee and people will look at it and say, why are they going after this disease? We don't have the kind of evidence that we would like to see. I do think it is an historical imprint on the process.
DR. LLOYD-PURYEAR: Denise, this is Michele. You did cut out the whole section that Ned is talking about that was labeled "Body of Evidence" and then previously labeled "Chain of Evidence." You just deleted that whole thing.
DR. DOUGHERTY: I'm sorry. I'm trying to get it in front of me here.
DR. LLOYD-PURYEAR: You rewrote part of the preface, but you deleted that whole section.
DR. DOUGHERTY: Maybe Coleen's edit will make that section a little more balanced.
DR. CALONGE: The way I look at it, Denise, is that we still need to maintain a high bar of certainty when we make a recommendation. That is really saying how adequate is the evidence in supporting a decision and how certain are we that we are not wrong. Those are the two issues that we will wrestle with and spend discussion time on with every evidence review. Do we think the evidence is adequate and how certain are we that we are not wrong and that [screening for] this condition will lead to a net health benefit for the screened population.
DR. TROTTER: This is Tracy. I have a comment. This consideration of rare diseases is in fact unique and has not been really done before. I think it remains important that our process and the stumbling blocks that we perceive are transparent to everybody who reviews what we review over time.
Without letting people know what the specific problems are and how we are going to try to approach that, I think it makes it much less clear at the other end when we come up

with a recommendation. I think we have been very vigorous and rigorous about this.
I think this Body of Evidence piece really does need to be here. It makes it more understandable, certainly to me and my colleagues.
DR. CALONGE: The only group I know that has looked a little bit at rare and uniformly fatal diseases has been GRADE. I'm not certain that I like their approach. I actually think that they ended up being a little less rigorous around this issue and that hopefully we will find the right balance.
DR. WATSON: This is Mike Watson. The only way out of the box is what other regulatory agencies end up doing, which is to recognize that it is rare -- and I think we do have to state that a lot of the conditions are rare -- and then essentially defer to Phase 4 surveillance at FDA, which means you keep watching to make sure that as evidence accrues after you have made your decision that everything is holding up. I don't know that we can necessarily link that kind of a process into this.
DR. CALONGE: Again, I think it is important to recognize that we want to do the best job we can to start with. Put that stake in the sand and say this is where we are starting from, recognizing that it is sand. My hope is that as we experience wrestling with the decision process with real evidence reports that the Committee is open to saying we can refine this and we can change this to make it better going forward. You really don't know how the process works until you actually wrestle with it with a real example.
DR. FREMPONG: This is Frempong. I have a question. Just applying these discussions to the diseases for which screening has been available for some time, are there disorder where we have uncertainty of the usefulness of newborn screening? It seems to me it is harder to look forward not knowing what developments there will be. But if you were to look back at what has been done before to see if we had very strong evidence, or lack of it, then certain disorders would not have been included in the screening with the experience that has been gathered.
DR. CALONGE: I'm not certain that we have taken on looking at the 29 reviews of existing core set. I think that is an important thing to think about the future. I think your question is an excellent one. You might get different opinions from different people on the call.
My feeling in looking at those is that in the ones that have already been approved there is a mixed level of certainty, although I think that the people who crafted that original core set of conditions would feel differently.
The one I might pick on would be Cooley's anemia, for which I understand we are working feverishly on a better discriminatory test that might otherwise meet our criteria. On the other end of the spectrum, I think that if we looked at the body of evidence around MCAD screening, we would conclude that the evidence is strong and that the health benefit is one that is unarguable. You live, and you live in high quality without any discounts for a decrease in quality-adjusted life-years.
So I look at the core set as a mixture that we can learn in both directions from. That is just one opinion, though. I just have to point that out.
DR. FREMPONG: Thanks.
DR. CALONGE: If we could move forward, again we start out with the key question. I think there were some recommendations by Denise for Key Question No. 1. We can work through those.
There is a request that we add a little bit more explanation around the figure about the

analytic framework. I agree. This is something that is just so second-nature to the other groups that I even forget it needs some explanation.
Key Question No. 1 there wasn't a lot of debate about.
For Key Question No. 2, Denise pointed out this issue about natural versus unnatural history. The problem is, it is actually hard to describe natural history today because we tend to muck around in things once we find them. I actually heard a couple of experts give a talk on natural versus unnatural history. We are stuck with the fact that we don't always know what the natural history is because we intervene once we find the disease. It is always this mixture of what would happen if we weren't around at all versus what happens because we are around and we detect these conditions. I don't know if there needs to be better explanation in this section, but I think that the clinicians in the room will resonate with that.
DR. WATSON: If we just call it clinical history, though, we capture the problem.
DR. VOCKLEY: Clinical history and spectrum disorder, I think those would cover it. Natural history is nice if you have it, but I think you are right, Ned. I don't think there are many disorders we are now going to have natural history on, except, I suppose, retrospectives.
PARTICIPANT: Right. Even then, since we weren't doing 100 percent ascertainment, I would state that we don't have a very good picture of natural history.
DR. CALONGE: Just so you know, this is a sticking point for all preventive services. It is hard to describe what would happen if we did nothing.
CHAIRMAN HOWELL: Again, let me interject. One thing that Mike has mentioned is the studies that are recommended by the FDA. I think one of the research agendas of the NIH of course is to set up a translational network so that all of the children who are identified in these areas will be followed and the definition of the condition will be clearer.
Again, Ned's point is very well made, and that is that the clinical story we know behind certain conditions is the tip of the iceberg because they are the only ones who present sick at the hospital. You really won't know the spectrum until you do newborn screening. I think the phase four, shall we say, follow-up is going to be critical, and that will evolve.
DR. CALONGE: What Nancy and I will do is try to rewrite this paragraph to better reflect this discussion.
DR. WATSON: Is there an obligation to use the words "natural history"?
DR. CALONGE: No. It is interesting; it is the word used in Key Question No. 2 for the Preventive Services Taskforce. There is nothing magic about that. Even there we recognize it is not really the natural history.
PARTICIPANT: Can you use the words "clinical course of a disease in the absence of treatment"?
DR. CALONGE: I think we would probably say "in the presence of absence of treatment." I think capturing what I heard, the clinical history and the spectrum of disease, what is known and what is unmeasured, is probably the best we can do.
Let's move on to Key Question No. 3. Coleen, your comment was that you think analytic validity would be critical for standardizing the screening approach from lab to lab. It was really interesting. When I asked other taskforce members to review the document, they didn't get this part. In the preventive services taskforce world, we make an assumption that there is lab analytical and clinical validity. Actually, until I came to the EGAPP, I

didn't get this, either.
But this is a core part of newborn screening because there is lab testing variability from lab to lab. The lab directors are all working hard to standardize this approach across states, platforms, software, and the different experts. So I agree, but was this mainly a comment, Coleen?
DR. BOYLE: Yes. It was in reference to the last paragraph, so we are jumping ahead here on Key Question No. 3. I did have some other thoughts on this whole piece, but I will wait until other people speak up.
DR. CALONGE: The other key issue was the use of the words "false positive rate." There is an active, and respectful, disagreement between our laboratorian, Piero, who said this is how it works in the clinical world, and Michael Skeels, who is actually being an epidemiologist and saying this isn't the usual definition of false positives.
DR. SKEELS: Actually, that is not correct, Ned. What I said was there are two legitimate but different usages of the phrase "false positive rate." We just need to say which one we mean.
DR. CALONGE: I apologize. You are right, Michael.
DR. SKEELS: Let me finish, please. I never said that Piero's usage was incorrect. In one case you are talking about the percentage of false positives among all samples tested. In the other you are talking about the percentage of all positive results that are false. It doesn't really matter which one you use, although for the 90-plus percent of people working in newborn screening who are in laboratories, it is very helpful for them to think in terms of the latter definition.
So we can do either, but I think it would just be helpful to the reader if we were clear.
DR. CALONGE: Michael, first of all, let me apologize for mischaracterizing your comment. I apologize for that. I actually looked at this as an epidemiologist and was understanding that there was another way of looking at it. Putting in a recall for an inadequate specimen is different to me.
Our solution for this issue was to clarify via footnote what definition we are using.
DR. SKEELS: That would be great.
DR. WATSON: Ned, this is Mike Watson. I had one question on the term "screening test," or "test," as we call it in the very first sentence after Key Question No. 3. That is the problem of all the test algorithms. It is only alluded to at the end of one of the paragraphs further below where it talks about a second-tier test, but it is not uncommon that there is more than one test involved in an algorithm. Like, in CF where it can be IRT and then another IRT, or IRT to DNA, or IRT to IRT and then to DNA.
So we might want to reflect that integrated aspect of test algorithms.
DR. CALONGE: Thanks, Mike. I think you actually said that in a comment, and we are going to incorporate that.
DR. BOYLE: This is Coleen. I also felt this particular question was getting into a level of detail. I don't know whether it belongs in an appendix or this is under the purview of the external review group, but I felt like this question in particular had a level of detail that was much more specific than any of the other key questions. I guess, as an advisory group, I didn't think we would be getting into the weeds here, but maybe I'm viewing what you are trying to get in these key questions a little bit differently than how other people are viewing it.
DR. CALONGE: Coleen, I would take that as a friendly suggestion. Piero is not here. He

wrote a lot of the detailed part of this.
DR. BOYLE: Right. In the last draft you actually had this as an appendix.
DR. CALONGE: I'm happy to move it back to an appendix. I would just like to make sure that Piero can weigh in on that before we do that. I agree. The main thing that I thought we needed with this section was for people to understand why these two concepts, the analytic utility and the analytic validity, were important given that outside the newborn screening world they are just assumed as a given.
DR. BOYLE: Right. The evidence-based review group would be looking specifically at some of these attributes and determining the analytic utility and validity. But that is how I view this process.
DR. CALONGE: Can I get a feeling from the rest of the Committee whether or not we can relegate some of the details back to an appendix?
DR. van DYCK: This is Peter. I think an appendix is fine for some of this detail.
DR. CHEN: This is Freddy Chen. I would agree, especially given the situation with the laboratories and the testing. It sounds like it is going to be changing quite dynamically in the coming years. So this feels like it is something that might date the document.
DR. VOCKLEY: This is Jerry, Ned. I think, though, it is important to ask question, is there a test? All of the details may be relegated, but as an advisory committee I think we have to ask, is there a test and is it a good test, for lack of taking out anybody's language and just putting it in as common sense, for lack of a better term.
DR. ALEXANDER: This is Duane Alexander. I would agree with putting the detail material in an appendix just to keep the volume down of the main text.
DR. FREMPONG: Hi. This is Frempong. I just wanted to mention that the discussion seemed to be concentrated on analytical validity. You mention utility. That is not elaborated on. So it doesn't matter where it is put; I think you need to elaborate on what you mean by utility. It may be applicability of the test in laboratories. Somewhere it should be mentioned, not just the existence of the test, which could be so specialized that it could only be done in a few places.
DR. CALONGE: I appreciate that comment. "Analytic utility" is a phrase that Piero has coined. I kept editing it out and he kept putting it back in.
[Laughter.]
DR. CALONGE: His explanation is, I think, right along the lines you are talking about. It has to do with the platform available for the testing. So I will challenge him to phrase it to us in such a way that we are all comfortable with it.
DR. TROTTER: Ned, this is Tracy. I think speaking to Denise's initial comments, making this a less bulky document in terms of somebody reading it through the first time is important, but losing that information would not be a good idea. I will weigh in on the side of an appendix-type thing so we know the question is on the board and if somebody wants to look at more information, they can. But they can still walk through this a little more quickly and a little less cumbersomely.
DR. CALONGE: Good. I'm happy to make that happen. Anything else on Key Question No. 3?
DR. TROTTER: I hate to use the word "home-brewed" just when I learned something, but I think it is a laboratory-developed test now, according to Mike.
DR. CALONGE: It sounds better, doesn't it?
DR. TROTTER: Well, I don't know about that.

[Laughter.]
DR. CALONGE: The other is so descriptive. But I'm worried that it is pejorative. We certainly wouldn't want it to be that.
DR. WATSON: I think that is why FDA changed it.
DR. CALONGE: Are we okay with Question No. 3?
PARTICIPANT: We are.
DR. CALONGE: Moving on to Question No. 4, Coleen's comment was we need to have a better definition of clinical validity, and so we will put that in so that it specifically talks about the ability of the test to predict the development of clinical disease.
DR. SKEELS: Ned, this is Mike Skeels. I didn't send this comment in writing but, along those same lines, this question and Question No. 5 are just elaborations on a concept of predictive value of a positive and predictive value of a negative result. Yet I don't see those phrases in here. Again, looking at it from a laboratorian's point of view, just how predictive is the test? I think we need to somehow weave that in.
DR. CALONGE: I'm happy to do that.
DR. SKEELS: I'm not a real epidemiologist like you, but I have those tendencies, so I think that would be helpful.
DR. CALONGE: I used to be a pure epidemiologist, but then I started working in public health and I have been tainted with politics.
DR. SKEELS: I hear you.
DR. CALONGE: I actually am very comfortable with putting stuff in to talk about predictive value if the rest of the group is comfortable with using those usual comments. The issue that strikes us about both metabolic screening and genetic screening is that the tests or testing algorithms detect something other than potentially a clinical disease itself.
So we actually have to talk about analytic validity. That is, does the test detect what it is supposed to test. Then, clinical validity: does the test predict clinical disease. Those two answers can be different in important ways. So, trying to capture that here is something I'm happy to try to do.
DR. CHEN: This is Freddy. Ned, you are absolutely right. In fact, there is a positive predictive value for both of those, right? For both the analytic validity as well as the clinical validity. I resonate with including the positive and negative predictive value language in there, but I don't want to lose track of the fact that the clinical validity and the point that you were just making is important in this.
DR. SKEELS: This is Mike Skeels again. I second that emotion, but I just also want to stay grounded here. This really comes down to, is this or is this not an actionable result when the screening laboratory has done its work. Are you or aren't you going to trigger a cascade of follow-up, tracking, possible treatment, confirmatory testing, repeat testing, all of that kind of stuff if you start from the point of view of the blood spot and work forward.
I like what Ned said about including some language in there about PPD. With that I will stop.
DR. CALONGE: I would like to move on to Key Question No. 5. There wasn't much in the comments. There is a wording addition from Coleen which I think is helpful, but I didn't get a lot of comments back that said that this is a section that needed change. Let me just step back. We edited it quite a bit by being less specific about what the

health outcomes we would consider would be. In other words, we talked about health outcomes I would say more generically, outside the usual morbidity and mortality descriptions. A lot of that had to do with this whole issue about important health outcomes.
Michele, correct me if I'm wrong. That probably required a separate and more detailed discussion by the Advisory Committee.
DR. LLOYD-PURYEAR: That is up to the Advisory Committee, but it seemed from the comments that were being received on the table that there were --
DR. BOYLE: We are not hearing you, Michele.
DR. LLOYD-PURYEAR: It is up to the Advisory Committee to decide on that. The reason why I rewrote this is based on the comments that were coming in. There were lots of revisions to the table and it was going in many, many different directions. It seemed that the next step would actually be to make this section briefer.
DR. CALONGE: Michele, some phrases drop out.
DR. BOYLE: I don't know what you are transmitting on.
DR. LLOYD-PURYEAR: I can't move. I'm in a cast. I don't know why the phone isn't picking me up.
DR. CALONGE: Again, I think what we decided is that, given the amount of interest that that table engendered, we might not be able to get that in this particular document and that it might be more appropriate for this document to point to something separate that talks about the important health outcomes we were talking about.
To be honest, that is what EGAPP did. The EGAPP methods paper just talked about the upcoming EGAPP outcomes paper, and those were two separate documents that were linked through the appendix or the referral approach.
As I looked at the comments, I agree with Michele that, depending on what the taskforce wants to do, this could engender a broader discussion.
DR. CHEN: This is Freddy Chen again. My question is about the overlap between Key Question No. 5 and Key Question No. 1 and the fact that, really, most of the issues with a lot of the proposed tests that we examine really do come into play around Key Question No. 5. I just wonder how you foresee these discussions playing out and whether or not we will be in a position to be specific about whether it is Key Question No. 1 that is the problem or Key Question No. 5 that is the problem. It just seems like there is a lot of overlap when you look at those two.
DR. CALONGE: I think that is a good point. The issue of Key Question No. 1 really comes back to the fact that you have a study whether or not screening makes a difference and do you have a study where you have screening and not screening. Clinical utility can be pieced together by looking at things a little bit differently, including the issue about are there treatments that are identified and useful and what are the outcomes of those treatments.
I think in looking at utility, though, then you start to say what are the health outcomes that the treatments lead to, and are there intermediate outcomes that I confidently assign to long-term outcomes. When I go back to Pompe disease, I was always left with the question once I stop giving you the enzyme what happens, how long do I have to give it to you, and what are the long-term ramifications of giving you the treatment. That was on the treatment end. I had this evidence that kids didn't die or stayed off respirators if you treated them.

So those are the treatment issues. Then the issue is, were these applied in a screening-detected group or a non-screening-detected group. I think that is another set of questions around clinical utility that we will need to wrestle with. The serious conditions in the spectrum of disease do become clinical manifest. The issue is, did newborn screening change when I started therapy in some meaningful way so that the delta between screening versus clinical detection is meaningful and should be pursued. That all gets rolled up in this clinical utility question.
It would be better if we actually had that overarching study in Question No. 1, but I'm willing to be that we will never have that.
DR. CHEN: I appreciate that. That helps clarify it for me, too.
DR. BOYLE: Ned, this is Coleen again. Even though I only had a small comment on this question, which is to change that one question to be not only timely but an accurate test for diagnosis, this came up with the discussion around Pompe. You weren't there. It sounded like there was something missing.
I guess when I was reading this weekend I was thinking it is probably captured under Question No. 5. But it really was the accuracy and our ability to diagnose the condition. That was very apparent when we were talking about early-onset Pompe versus late-onset and, even with an early-onset, separating out those who had a more severe clinical course.
In some ways, all the questions you have asked here under clinical utility do address that, but I don't feel like we get at the diagnostic testing attributes.
DR. CALONGE: Coleen, I think that is a great point. In Pompe it looks like there are two flavors. I think in other conditions we might wrestle with the issue of, yes, you have the condition but is it going to be clinically manifest or not. Given that we screen for it and detect it, do we have diagnostic tests that help us say this is one we need to intervene versus this is one that might not ever become clinically manifest.
So that clinical spectrum of disease does fit in here. I think maybe a discussion around diagnosis of clinically important disease would fit here.
DR. BOYLE: That was absent from the evidence-based review as well. I don't know how we reframe this question here. I think it falls under clinical utility, but I don't know how we reframe it so we really capture that aspect.
DR. CALONGE: That will be our challenge. I know we only have about seven minutes left in the discussion.
Now, there has been a back-and-forth around Key Question No. 7 and whether we should have this question in there or whether we shouldn't have this question in there. The concern, not just from Coleen but from several sources, is that we are just not going to have these data available to us. Yet I think it is in our charge to actually consider cost.
So I will just leave that as an issue. What we put down here is to try to use approaches that are in the medical literature now as trying to see can we make any statements based on what is in the literature about cost. I will open the discussion.
PARTICIPANT: Did we skip No. 6?
DR. CALONGE: I'm sorry. Yes, I did. Question No. 6 is a question about harm. Here we rolled harms together into testing, identification, and treatment, rather than pulling out separate harms questions.
DR. CHEN: This is Freddy again. The only point I wanted to make about No. 6 was the

point that I brought up in our discussion during our face-to-face meeting. There is a lot of evidence about harms of false positive testing that will not be specific to that particular test. For example, there isn't any literature on the harms of false positives for Pompe disease but there is literature on the harms of false positives for any other kinds of devastating diagnoses and testing.
So I don't think it is excluded in this. I just wanted to make sure that that came up in our discussion.
CHAIRMAN HOWELL: As we mentioned at the previous meeting, one of the issues is that we all expect that there will be some psychological harm. One of the terrible problems with the studies and the literature is that they almost never quantify or characterize how families were informed and by whom, which is a huge issue in informing someone about a potentially serious issue. That is an area of research that needs to be done carefully.
DR. CALONGE: Would it be okay with the Committee if I try to reflect in this section this issue seeing what we can learn from research for other diagnoses?
PARTICIPANT: I think it could be similar to what you did under Question No. 7. "There is little published empirical research." There you would put "harms and risk" for specific disorders and that you would be using proxies.
DR. CALONGE: Right.
PARTICIPANT: That would be great.
DR. CALONGE: That gets us back to No. 7 and back to this tenacious issue about cost effectiveness.
CHAIRMAN HOWELL: We clearly are not going to spend a lot of time on cost, but it is probably worth mentioning.
DR. CALONGE: I guess the issues often come down to; the cost of testing is small. I don't want to overstate that, but in general, for many of the metabolic screens, once you have the machine it is already doing the patterns for more conditions than we are currently identifying. You add to the follow-up cost depending on the state and the state approaches to newborn screening, counseling, follow-up, and referral to services. That is one cost.
The next cost is the actual cost of treatment, which again is very dependent upon the condition. Then there are the costs of not treating, which has to do with the implications of potentially institutional care or other issues that could be lifelong for an affected individual.
It is possible at least to make comments on those cost areas for the conditions that we look at.
DR. KUS: This is Chris Kus. The question is, in using the term "cost," are you just talking dollars and cents? People could talk about cost to the family, cost to society, and things like that.
DR. CALONGE: I think cost effectiveness is actually inclusive of all of the things you just mentioned, including opportunity costs, things we could be doing if we weren't doing this.
Could I just have a feeling from the Committee about changing this? I like Dr. Howell's comment: we're not going to spend a lot of time on it.
CHAIRMAN HOWELL: That's right. It seems to me you treat it fairly reasonably. I would think that as the document is published we obviously would not want to have references

in press.
DR. CALONGE: Right.
DR. KUS: This is Chris. One more comment, though, is that we have had this long-term discussion about a part of the newborn screening program that has not really been funded, the long-term follow-up in order to gain information and also to see how we are affecting it. I just want to make sure that that is reflected in this discussion.
DR. SKEELS: This is Mike Skeels. I feel like we have the expertise we need to address all the other questions on our Committee, but I'm wondering do we have someone who is an economist or a health economist in particular, to address this one. It seems like this is a resource where we would struggle a little bit, unless somebody has credentials that I don't know about.
DR. LLOYD-PURYEAR: No, that expertise is not on the Committee. But when you want this kind of analysis done, you can bring that kind of analysis to the evidence review or to the recommendation process. You don't necessarily need it on the Committee full-time.
CHAIRMAN HOWELL: You can bring it in at any and all levels that you might require that information.
DR. SKEELS: I would respectfully suggest that if we are going to take on the issue of cost effectiveness that we make sure we have someone with the right kind of training to help us frame those questions. As was just pointed out, it can mean a whole lot of different things and you can come to very different conclusions depending upon how you frame the question.
DR. WATSON: There is probably a snowball's chance that you will even find a cost effectiveness study. I don't know anybody that has been funding them or is doing them, outside of the one we funded to Steve Downs and Aaron Carroll.
DR. CALONGE: Let me make an alternative proposal to the Committee that we take Key Question No. 7 out of the analytic framework. Let me tell you my reasoning. The Committee would have to decide. I'm trying to think of whether we would change our recommendation on the basis of inadequate cost effectiveness analyses.
The Clinical Guide pays limited attention to cost. We might put it in the discussion, but we decided as a group not to let the cost effectiveness of a procedure color the actual recommendation.
DR. SKEELS: Ned, this is Mike Skeels again. It depends upon how much impact you want our recommendations to have on state-based newborn screening programs. One approach, which you just outlined, would be to just be silent on the issue of cost effectiveness and let every state sort it out for themselves. But if you create a recommendation for a panel of newborn screening disorders without being bound in any way to making a judgment about whether they are currently cost effective, then you have painted the state programs into a corner.
You have said, you should all be screening for this, we think, based on purely clinical and technical merits. Then we have to explain why we aren't. Then we each have to do our own cost effectiveness study, and so on and so forth.
I agree with you, but I'm really concerned about where it is going to leave us if we are completely silent on the issue.
DR. CALONGE: I didn't quite get through my whole recommendation, which is okay. That is the downside. The issue is that we would address cost and cost effectiveness

but it wouldn't be here in our decision process. It would be part of the discussion that we would have.
I honestly think that for many of these conditions what we will be able to do is elaborate on what the costs are as we can identify them and then maybe make some suggestions about the back of the envelope or whatever we can afford to pay for, the "what you spend for what you get" approach. It might be separate from the actual decision process.
I'm not necessarily advocating that. I'm just saying that there is a way to make sure we talk about cost effectiveness but it is not integrated into the analytic framework key questions and whether or not we recommend something. I'm happy to do it either way.
DR. SKEELS: If you go the other way and if you make a recommendation, say that this recommendation is based upon clinical and laboratory determinations, with some kind of disclaimer about the limitations of our cost effectiveness analysis. That would be helpful.
DR. CALONGE: What is the pleasure of the rest of the Committee?
DR. FREMPONG: This is Frempong. I would say that a detailed cost analysis to determine effectiveness I think is probably beyond the Committee. But I think that it is important to mention that in general even the human side of cost effectiveness would be driving, maybe, decisions that we make. If people are convinced that a condition is relatively common and that a screening can lead to improved morbidity and reduced mortality, I think people would like to see that as a general comment on the overall cost effectiveness.
Certainly, if the only test available for doing the test is prohibitively expensive, that too needs to be mentioned in some way, without going into actual details of lifelong cost effectiveness of any one particular child with a condition that is screened for.
DR. CALONGE: My worry is actually less in the test world than it is in the treatment world. If we have to manufacture something even for a very few number of infants, your cost per year of life saved could easily hit the millions of dollars range. It is problematic, I think, for the healthcare system, although not insurmountable.
DR. VOCKLEY: This is Jerry. I think we have to keep it in our analysis even if we don't have the likelihood for good data up front. That does two things. First of all, I think you can't talk about a newborn screening program without talking about cost benefit ratios. So that is important.
Secondly, it raises the flag to funding agencies to say, here is an important question that is not being addressed and is holding up the implementation of any one of a number of important screening tests.
DR. BOYLE: This may be a topic that we take up in a larger group or have a number of folks come and talk to us, or in one of our subcommittees. I agree with the statement as written that we are very unlikely to have this type of information. That is why I was suggesting taking it out as a key question. But I also feel like it is important to think about cost and cost effectiveness issues in terms of providing a context on which our recommendations are based.
DR. KUS: This is Chris. I would just also second the idea that it has to be included somewhere because of that discussion about having the states make some decision. The point of putting some of this out is that it is the expectation that this should be covered, which would require federal or state funding to do it. We have to have some of

the context of this even though we have limited information.
CHAIRMAN HOWELL: I think that we should certainly leave it in there. I think that we will need to be considering the total cost of the impact of these rare conditions that involve the families and things of that nature. I think it is much more than the screening test, which tends to be relatively inexpensive per person at the current time. But, look at the total cost of children who are missed and who do go on to have chronic disease and chronic disorders that largely fall back on the individual families and so forth. I would suggest we leave it as is.
Now, the other thing that we are dealing with right now, Ned, is that we are beyond our time. I wonder if we could try to come to some conclusion about this report in the immediate future.
DR. CALONGE: Yes. I have this issue about Key Question No. 7. The evidence comments have been mainly around the issue that when we cut this way, way back, we kept some criteria and we dropped others. I think, again, my suggestion -- and Michele and I need to work through this -- is that we appendicize the study quality grading and then make sure we have sections for each of the key questions.
The last issue is that the table has changed to reflect taking out the provisional status. I'm hoping that everyone is comfortable with the recommendation table, which is the last part of the document. Then I can be done.
CHAIRMAN HOWELL: About the table, I was pleased to see how it had changed. It was very nice. Any comments about the table?
[No response.]
CHAIRMAN HOWELL: So the fundamental plan as I understand it is you will take all this extraordinary wisdom that you have received this afternoon, Ned, and come up with a final document for the next meeting. Is that not correct?
DR. CALONGE: That is correct. In February. You may see some iterations coming from Nancy, Michele, and I. But again, what we will try to do is make sure we point to what has changed rather than expect you to read the whole document.
CHAIRMAN HOWELL: Right. The other thing is that I would think that we really do need to put this on the shelf. I'm sure most of you agree. So we should communicate in whatever means we need to so that come the meeting at the beginning of 2009 we can really finalize this and adopt this. Is that fair?
DR. CALONGE: I will just tell you that my schedule between now and that next meeting is going to allow for committing to getting that done.
CHAIRMAN HOWELL: Outstanding. We are delighted to hear that you are going to be snowed in and you will have plenty of time to work.
We had agreed to have a brief break after Ned's presentation. I would like to suggest that we take a break now for a period of 10 minutes. Why don't we plan to come back at just a touch past 2:30.
Stay on the line, please. If you could just mute your phones so we don't hear all your kibitzing in the background. But stay on the phone and we will resume at 2:33. We will then, at that point in time, hear from Dr. Perrin. Thank you very much.
[Break.]
CHAIRMAN HOWELL: Ladies and gentlemen, have most of you returned?
PARTICIPANTS: Yes.
CHAIRMAN HOWELL: I hear a lot of "yeses." I can't tell who is there and who isn't, and

so forth, but we need to zip along here and hear from Dr. James Perrin.
Dr. Perrin and his group have been working hard on the candidate nomination of severe combined immunodeficiency disease. Jim is going to give us a preliminary report today. Let me underline again, it is preliminary and they have not finished their work, but we are looking forward to hearing from Dr. Perrin and his colleagues in Boston. Jim?
Evidence Review Workgroup:
Preliminary Report on the Candidate Nomination:
(Severe Combined Immunodeficiency Disease)
James Perrin, M.D.
[PowerPoint presentation.]
DR. PERRIN: Thanks very much, Rod. I think they are putting up my slides and I can move the slides myself.
First of all, we very much appreciate the opportunity to share where we are with you all. We would appreciate feedback. Some of the comments just before in the report from Ned and his committee I think are comments that could help us in our work as well. Some of the things you were asking for in trying to get better evidence on particular elements of screening tests, for example, are things that we would appreciate your asking us at this point. We can try to deal with that in the final report.
Let me start by telling you where we are with the other reviews. We did submit through the bureau to the Committee our final report on Pompe disease. I believe that is available to you all and is on the website at the moment. We are going to talk about severe combined immunodeficiency disease today.
I think you know most of our team. The two key authors for the Report on Severe Combined Immunodeficiency have been Ellen Lipstein and Alix Knapp. Our other team members, though, have been very active in the discussion and the development of this report as well.
Just as quick background, SCID is a group of disorders really characterized by the absence of both humoral and cellular immunity. It results from a severe defect in T-cell production and function, with additional defects in B lymphocytes and/or in K cells, depending on the gene that is mutated. At least 15 genes cause SCID when mutated, so there are a variety of conditions within this group.
As protection from maternal antibodies wanes, infants with SCID develop infections due both to common and to opportunistic pathogens.
The rationale for review and some of the items that were in the subcommittee's report to the Advisory Committee recommending that this be sent to our workgroup for review are really that without treatment SCID leads to death in early childhood, that earlier treatment, particularly before the onset of lung infection, may decrease mortality and morbidity associated with SCID and with treatment itself, and that methods to screen infants for SCID using quantitative PCR for T-cell receptor excision circles have been developed. Indeed as we will mention a little later in the report, other methods have also been developed, but this is the one that was in the original rationale for review.
Our methods of review are much as we did with Pompe's disease. That is to say, we carried out a systematic literature review, which I will describe in more detail, summarizing evidence available from published studies. We also assessed credible unpublished data and data presented at recent meetings but not yet published from key investigators.

These were the key review questions that we dealt with. Let me just say that partly because of the discussions we have had based on the Calonge Committee work and the attempt to harmonize our work with the nomination form, we reordered these a bit from what we did in the Pompe disease report. We hope this will be a little bit more down the line of an organization that you will find helpful. But we are certainly prepared, once the Calonge report is in place, to go even further in trying to make our questions be highly comparable to the ones both in the nomination form and in that report.
We have tried to provide evidence as we could find it on incidence and prevalence of SCID, the natural history, with an emphasis on the timing of clinical onset, the severity of disease and its variations, and the genotype-phenotype relationships, especially as they might affect screening decisions.
We have also looked at a number of issues in screening, including methods in screening, the accuracy of screening with sensitivity and specificity, methods of diagnosis, and what evidence exists with respect to risks and the cause of screening.
The other sets of questions we have examined have been the methods of treatment, does treatment help, does early treatment help, something about the availability of treatment, and again, where it exists, risks and costs of treatment. We have tried to provide as well an overview of critical information that is still needed in the area of SCID.
Now, the materials that you have available for you besides the slides that we are going through at the moment include the draft review summary, very much like our earlier review of Pompe disease, and the evidence table with abstracted articles, which we hope will be useful to you. We would very much value review by members of the Committee and your thoughts on is this the kind of way you would like to have the evidence made available to you. The bibliography of all the identified articles is also provided, as well as the list of interviewees that we at least attempted to have some contact with in our search for more evidence relating to SCID.
The systematic review covered basically 20 years, January '88 to October 2008. We looked at MEDLINE, Ovid In-Process, and Other Non-Indexed Citations databases. We limited studies, as we have in the past, to English language only, human studies only. We eliminated reviews, editorials, other opinion pieces, and case studies of fewer than four patients and ones that included only adult subjects or not addressing one or more of the key questions. We also did check to make sure that all the references on the nomination form were included in our reviews, and we also looked at the references in review articles that we did find in our surveys.
We initially examined a little over 700 abstracts. From that initial review we selected 60 articles for more intense, specific review and abstraction.
We do have information on all of the assessments of the studies; for instance, the study design and to some of the details of the studies. We can provide you some of that evidence. Again, we would love some feedback as to whether the way we are providing this evidence is helpful for the decision-making by the Committee.
So these are the 60 articles we reviewed. These are not the specific articles, but it gives you some overview of the kinds of articles we found. Of the 60, cohort studies were 11 and case control studies were eight. The large majority, almost two-thirds, were case series follow-ups. We did find here, actually, one economic evaluation.
This is an overview of the kinds of papers that we found. It gives you some sense, I

think, of the quality of data available in this area. It would likely be true of most other reviews that we have done in the past and would like to do in the future.
Rod, if someone would like me to stop at any point through this, I would be glad to at least deal with questions of clarity.
CHAIRMAN HOWELL: I would suggest that you proceed unless someone has a clarification issue. Go through the whole thing. Then we have asked Jerry Vockley to lead the Committee discussion of your report.
DR. PERRIN: Excellent. Great. The additional expert communication was determined by our literature review, basically the people whose names continually came up in the literature on SCID, some discussion with a variety of experts around the country who are knowledgeable about this. It was in many ways a networking strategy for determining whom we should talk with. We included experts in, we believe, all the major issues relating to SCID. This indeed is a list of the people whom we contacted.
I want to stress that these are not necessarily all the people we actually had discussions with. Some people chose not to have contact with us or did not respond at all. Others suggested that there were people on our list who could provide better information than they could. But these are the experts whom we did contact, and we will be sharing some evidence from these people as I move forward.
Actually, let me go to the next slide first and then come back to this one.
These are really information on the studies we found leading to incidence, on the bottom, and genotype-phenotype correlation, on the top. Just to go to the bottom for the moment, the data that are obtained from whole population screening or comprehensive national surveys, we found about one study. With somewhat more limited geographic coverage, we found two studies. A fourth study is estimated from the number of cases clinically diagnosed in the United States.
I will focus on the bottom three first and then come to the top one as we talk about what we know about the incidence or prevalence of this disorder.
A study by Chan and Puck was based on extrapolation from laboratory samples sent to their lab, which they believe is the only lab that would really be getting these samples for XSCID, and then extrapolation from that to the likely large number of all SCID diseases, from which they estimated an incidence of about one in 105,000 live births.
A substantially earlier study based on five years of referrals to specialized units in France published back in 1993 came up with fairly similar estimates of one in 100,000 live births.
We know, however, that there are certain subpopulations that have substantially higher rates of SCID, predominantly in Native American families, Navajo in specific, and there are published reports of prevalence that are substantially higher, as high as 50 or 52 per 100,000 live births.
It is very important to note none of these come from screening. These are all from basically identified cases, and most of the people whom we have talked with and most of the publications would suggest that the rates are probably higher than this insofar as a number of children likely die without diagnosis from severe infections early in life and never reach the identification level. So estimates might be as frequent, therefore, as one in 50,000 or one in 40,000 live births. But at the moment there are no such data to really document that set of estimates.
I will go back in a few minutes to talk about some unpublished data from a single-state

study in a few moments.
Let me go from incidence and prevalence data to natural history data. Except for children who were diagnosed early in life who are essentially diagnosed because they had older affected siblings, most children are diagnosed after recurrent pulmonary infections. All of the SCID subtypes do exhibit infection with opportunistic organisms, although the timing of onset may vary somewhat by SCID subtype, not probably an important variable with respect to the importance of screening.
Without treatment of underlying immunodeficiency, i.e. well beyond simply antibiotics, children with SCID die in early childhood from infections. The known phenotype-genotype differences do not affect the main findings relating to infection and death without treatment.
Let me move on to some of the issues in screening tests. Here we have, again, not a large number of studies. We basically have three studies where we have sensitivity and specificity of screening in false positive rates, really from systematic studies but other than from whole population screening. Then we have one study which provides a little bit of, again, systematic information about second-tier testing with not a lot more data than come from the other three studies, however.
The main screening methods, at least that we have identified so far, have been a whole blood lymphocyte count, quantitative PCR, and ELISA strategies for dried blood spots. I apologize. I would be much happier in person show you this slide because there are too many lines to describe, but let's spend a few minutes on this. There have now been a number of strategies that we report here for screening. The first one and the last one are really basically strategies which look at different ways of amplifying DNA and using dried blood spots.
In the first study you had 23 children who did have SCID, two children who had non-SCID immunodeficiencies, and then 242 anonymized newborn screenings. Using this method, this particular study had a false positive rate of about 1.5 percent from children born in routine nurseries, i.e. of the 242 anonymized newborn screenings, and about 5 percent from special care nurseries. Our calculations of sensitivity were between 84 and 100 percent and a specificity of about 97 percent based on this particular study.
If you go to the very bottom of these four studies to the McGhee et al. study, this is, again, a similar study in a smaller number of children with SCID. It used a somewhat different strategy for the analysis of dried blood spots, but exceptionally pretty similar. Here again, their report -- this is not our calculation -- was a combined specificity in this strategy of about 100 percent, with a confidence interval of 97- to 100 percent, and a combined specificity of at least 85 percent.
The middle two studies are both studies using lymphocytes. The first one is, again, 45 children with SCID, 90 without. Using the first available lymphocyte count, this study had a false positive rate of about 8 percent. Sensitivity is also in the mid 80s. Specificity is a little lower, at the 94 percent level.
Finally, the Hennewig et al. paper is a very small study in 18 children with and 18 children without SCID. Again, somewhat similar, although here a much lower sensitivity and specificity, probably based on that this particular study is a very small study.
This gives you, I think, a range of a couple of strategies for screening and what we know from these non-population-based studies with respect to false positive rates and,

to a degree, sensitivity and specificity.
DR. BOYLE: This is Coleen.
DR. PERRIN: Yes, please.
DR. BOYLE: If we were to relate this back to our questions, this is the clinical validity issue here, right?
DR. PERRIN: That is basically correct. It will be helpful if we try to cross-walk, Coleen, back and forth among the terminology, which we will try to do as we harmonize our strategies better in the future.
Let me describe a little bit about the one population-based study that we are aware of, which has been going on in Wisconsin. It began population-based screening in January of 2008. These are data that were presented a few weeks ago by Dr. Mei Baker. She was kind enough to share this with us.
Basically, as of the end of August they had screened not quite 50,000 children. They had had 20 abnormal findings in this and 76 inconclusive results. That gives you some numbers to work from. Again, there were higher abnormal rates among premature infants than among full-term, although not strikingly different levels here.
I think it is important to realize that in these 47,000 children that there is not yet a case of SCID. The abnormal results are listed at the bottom of this table. I think this provides a little bit of information about potential false positive rates but so far there has not been a case of SCID determined in this population. That is not totally surprising given rates that are presumed to be about one in 50,000 or one in 100,000. We don't know much yet about sensitivity of this test given the current evidence.
This is, to our knowledge so far, the only currently ongoing or concluded population-based screening study.
Let me go from screening to treatment, unless there are questions about screening at the moment. We will have time at the end to come back to screening questions, after Jerry's presentation.
Treatment methods.
DR. van DYCK: Jim?
DR. PERRIN: Yes.
DR. van DYCK: This is Peter. Can you go back to the slide that says "Screening Tests"? The top row was the Chan and Puck row. Can you explain to me where it says "23 children with SCID, two without, and 242 anonymized newborn screening cards" just what that means?
DR. PERRIN: I'm trying to remember exactly what the two children with non-SCID immunodeficiencies were. They were obviously much less severe immunodeficiencies. The 23 were diagnosed children with SCID. This is an attempt essentially to look at dried blood spots from this population and then compare them to 242 children who presumably did not have SCID. This is an attempt to look at whether this particular strategy would adequately discriminate between normal newborns, i.e. the 242, and then 23 children with SCID. That is the basic strategy.
DR. van DYCK: Thank you.
DR. PERRIN: Sure. Let me move on, then, to talk about treatment. There have been three major modes of treatment that have been attempted. The first one, i.e. bone marrow transplant or stem cell transplant, is really by far the most studied of the treatment strategies for SCID.

There are a small number of studies for a very specific kind of SCID, the ADA-deficient type of SCID, where there have been some enzyme replacement studies done. That is not generalizable to SCID in general. There have also been some very small trials in gene therapy in SCID.
Let me talk about, again, the treatment trials that we were able to identify. Most of these are, as you can see at the bottom here, descriptive studies of the clinical experience of people having carried out the treatment. There have been a number of well designed cohort trials, of which almost all have been retrospective with concurrent controls. Again, this is not at all surprising for this rare disease, but this is where our data come from.
To give you some examples now, first of all, I'm going to go through a few slides on whether treatment seems to be effective for SCID. Buckley et al., a case series published in 1999, included not quite 90 children treated with stem cell transplant between 1982 and 1998.
Again, I apologize for these slides being too detailed in some respects, but I think the information is really pretty important here.
Of this group, 81 percent survived to follow-up, with a median follow-up time of 5.5 years. Children who had HLA-identical transplants from a related donor had 100 percent survival. Those with P-cell depleted haplo-identical transplants had about a 78 percent survival. Survival was not related to genotype. There was some variation in race and in gender. About 36 children developed GVHD disease, most of which did not create problems for the children.
DR. BOYLE: Could I just ask for a clarification? Was there any explanation for the difference by race and gender?
DR. PERRIN: I believe it was not in this publication, if I remember correctly. I think it was a finding but not explained beyond that. We can ask Dr. Buckley, I think, in a few minutes, and she can tell us otherwise. But my memory of that study was, no, there was not specific information. This was an empirical finding.
These latter two studies I'm going to show you on this particular slide probably overlap, so I can't be quite sure how many of these are really different information between these two studies.
Here again, with HLA-identical transplants they had less good survival, 84 percent, compared to Buckley's series above. A very small number of pheno-identical transplants had a 40 percent [survival rate], but we are talking about only two out of five. We are talking about small numbers.
From their study, T-cell depleted haplo-identical transplants had only a 56 percent survival compared to 78 percent in the Buckley numbers.
Again, going down to the one below, the numbers are pretty similar to those in the Stephan et al. series. I think the important things here are that HLA-identical transplants have a better survival than haplo-identical transplants do in general. But the one for which we have most data comes from the very top series here, which, as I said, has a median follow-up of about 5.5 years.
These are, again, similar kinds of studies, not a different type of study than the ones in the previous slide. Here we have European examples, a large sample from 1968 to 1999, of about not quite 500 patients. Here, three-year survival with sustained engraftment was 77 percent for HLA-identical and 54 percent for HLA-non-identical

transplant. If you look over time in this population from '68 to '99, improvement over time for both cohorts was improved.
As before, SCID genotype or phenotype was not associated substantially with differences in survival. Having a lung infection before treatment was associated with lower rates of survival.
Again, the next one I believe is also a European study. Patients who had myeloablation prior to their transplant did better in this particular study, but this will be an interesting issue for discussion as we get a little bit further along.
The very last study is a very small study, again. I'm not going to say much about it in specific because I think it generally supports the previous study findings there.
Similarly, some more recent studies here add a little bit to our knowledge. What they really say in general is children who were treated with transplant after they have had substantial infections did less well than the ones who were treated earlier, before they had substantial infections.
Let me talk a bit about the efficacy of stem cell transplant in neonates. Again, the first one is the same study as before, I believe, but here what is striking is that 95 percent of infants, i.e. children transplanted before 3.5 months of age, were alive at follow-up, whereas only 76 percent who received transplants at 3.5 months or older survived to follow-up. This is not, of course, a randomization to early versus late treatment but a finding in this particular study that children who were transplanted early did substantially better than children who were transplanted later.
Kane's study, the second one down, says pretty much the same thing: high rates of survival in children who are transplanted early. The Myers study basically says the same thing. Ninety-five percent of the early treatment children survived in this study but only 75 percent of the late treatment children survived in the study.
Again, none of these are randomized trials. These are cohort studies that we are sharing with you about early treatment and also long-term survival.
This is from Dr. Buckley's work. This is really just giving you survival curves. It is very similar to what I just said two slides ago, which is the survival rate for children transplanted in the first 3.5 months of life was basically 96 percent if you look at them over time, and only 71 percent survival in the late transplant group.
Let me move from treatment to talk a bit about treatment availability. This we learned primarily from our conversations with experts in the field. There are 15 major and 34 minor centers in the United States and Canada -- I'm not sure I can tell you exactly the difference between major and minor characteristics at the moment -- that are currently performing stem cell transplantation for SCID.
So at least one in every other state, apparently, exists for availability. We don't have any information about relative quality or survival rate by center, for example.
Harms and cost effectiveness. We found nothing in the area of either screening or diagnosis. In two studies of treatment three children did develop autoimmune hemolytic anemia in context with their stem cell transplants. Three of those died of complications.
PARTICIPANT: This is Jennifer Puck. I believe there is an ongoing web conference on whether SCID should be treated.
DR. PERRIN: Hello? I'm sorry. Someone seems to be talking in the background.
DR. LLOYD-PURYEAR: Somebody let the public in. Jennifer Puck shouldn't be being heard right now.

DR. PERRIN: Are we back okay now? Hello?
CHAIRMAN HOWELL: I think we are fine.
DR. PERRIN: There are also, in another study, four children of the nine or 10 who had had successful gene therapy, from the gene therapy study, who had developed leukemia between basically three and six years after therapy. Three of those four were successfully treated and did well.
We found only one study of cost effectiveness. Without going into too much detail, it was difficult to understand a number of the strategies used in this study. But basically, using a decision tree model comparing universal versus targeted screening approaches, this study assessed the threshold at which screening would be cost effective from a healthcare system perspective. At a threshold of $100,000 for quality-adjusted life-year, they estimated an 86 percent likelihood that screening would be cost effective.
I think we have a cost effectiveness person on our staff that had some real difficulties being convinced of the basic confidence intervals around any of these numbers in this particular study.
In summary, let me say that what I think we know is that SCID affects at least one in 100,000 newborns in the U.S. That is probably a very conservative estimate. Several population-based screening trials are underway in Wisconsin or planned in a few other states, but to date we have no completed population-based screening trial. We do know something about screening tests in non-population-based evaluations.
Without curative treatment the newborns develop severe opportunistic infections that lead to early death. Treatment, most commonly the stem cell transplant, decreases morbidity and mortality. There is some evidence from a few studies which supports the notion that earlier treatment leads to better outcomes.
There is a lot of stuff we don't know and we would like to know more about. I'm not going to spend a lot of time on this except to say these are the areas where it would be valuable to have more information.
One is really better information on the prevalence of SCID, which will come from some form of systematic newborn case finding. It may come from the Wisconsin study to understand more about that prevalence. But I think if you want prevalence that describes really variation by a variety of subpopulations, we are not very close to having that kind of information.
The accuracy of screening. Again, we have the initial pilot screening data from Wisconsin that do suggest a relatively low false positive rate, but the data so far are pretty limited. The data regarding accuracy of other screening methods in population-based protocols are not available.
Feasibility. The Wisconsin program suggests feasibility, but we would need to have more information about the ability of other newborn screening laboratories to offer the screening.
The acceptability. We did not find any evidence there. I think the question that we would ask you is, is the evidence for early treatment enough. There is very little evidence, really, about the cost effectiveness of screening and treatment. I shared what little we do know. As I said before, we don't know much about the adequacy, competence, success rates, et cetera, of available treatment centers, although there is some very promising grouping together from these centers which may allow the development of a much more serious collaborative strategy for gathering these kind of data in the future.

CHAIRMAN HOWELL: Jim, thank you very much. I would like to call on Dr. Vockley for the Committee to lead the discussion of this preliminary report on SCID. Jerry, are you there?
[No response.]
CHAIRMAN HOWELL: It seems like Jerry has fallen off the phone call, unless Jerry has been excluded from the call.
DR. LLOYD-PURYEAR: He is disconnected. He at some point disconnected from the phone line.
CHAIRMAN HOWELL: I wonder if someone could call him back to let us know that he was disconnected. In the meantime, let me accept commentary from the Committee about Dr. Perrin's very nice summary.
Committee Discussion on the Nomination of SCID
to the Recommended Uniform Screening Panel
Gerard Vockley, M.D., Ph.D., Discussant
CHAIRMAN HOWELL: Jim, let me comment that I felt the material you provided the Committee was really very nicely laid out as far as being able to go through and exactly see what was in each of these reports. I found that extremely helpful.
DR. PERRIN: Thank you.
CHAIRMAN HOWELL: Can we have some general comments from the Committee and questions of Dr. Perrin?
DR. CALONGE: Dr. Howell, this is Ned Calonge.
CHAIRMAN HOWELL: Yes, Ned.
DR. CALONGE: Jim, first of all, I have to reiterate that, because we don't always celebrate what good jobs we do. I thought this was laid out very nicely.
My question has to do, and I might just not have heard it in the presentation, with the diagnostic work-up of one of these positives and the potential harms associated with that. The reason is that, even at 97 percent specificity, a disease with a prevalence of one in 100,000 is going to generate lots of false positives. I just am trying to get a concept of how bad that is.
DR. PERRIN: We have asked that question of our expert because we actually find very little in the published research literature about even what is done for confirmatory diagnosis in SCID. That may simply be that this disease is one people have been examining and treating for many years.
So the simple answer is, we really don't know. We don't have good evidence about what are the risks of false positives in this particular disease. Again, you all discussed that a few minutes ago in the discussion of your report, but in the context of SCID we really just could not find good evidence.
DR. CALONGE: That is discouraging. I think if we had to bone-marrow all these kids, that is about the worst thing I could think of. I'm just trying to figure out what it might entail.
DR. BUCKLEY: This is Dr. Buckley. I have to first state that, obviously, I have a strong conflict of interest with this discussion. But the confirmatory tests can be done very quickly by flow cytometry because these conditions are all characterized by the absence of T-cells. So for example, within three hours after birth we can confirm a diagnosis of SCID if you just do flow cytometry.
DR. CALONGE: That is helpful. Thank you.

DR. VOCKLEY: Hi. This is Jerry. I'm back on. I had a little technical difficulty.
Jim, I had a question as I was pushing the wrong button and hanging up on you. The current Wisconsin study, the screening pilots, are they using the tiered approach that was referenced in Table 7 on your draft document or are they just using TREC screening?
DR. PERRIN: I'm embarrassed to say I can't remember that exactly. We can track that down. We do have that for sure. I'll look that up while you are talking.
DR. VOCKLEY: The only reason I ask is that the preliminary report has I guess they would say no false positives, which they report in their original pilot. But the original pilot had the two-tier screenings, I just wasn't sure whether we were dealing with two-tier.
DR. PERRIN: I think it is TREC.
DR. VOCKLEY: Why the difference, then? The Chan and Puck study reported a 1.5 percent false positive rate. Now Wisconsin is reporting essentially no false positives with that same technique, or is there something different there?
DR. PERRIN: No, no, they have false positives, too.
DR. VOCKLEY: Much, much lower.
DR. PERRIN: Yes, much lower. Right.
DR. VOCKLEY: A hundred-fold lower. The numbers don't jive.
I will tell you what. Since I'm back, what I would like to do is give the draft approach to dealing with this a dry run here. Ned, you can see how your document works.
We had seven key questions that are raised in the evaluation of our evidence-based information. I would just like to run through them.
Key Question No. 1 is, is there direct evidence that screening for a condition leads to improved health outcomes for the infant or child to be screened. Comments?
DR. CALONGE: Again, it is hard to answer this question with indirect evidence. Applying a non-biased approach to this, I think it would be hard to say we could adequately answer this question.
DR. VOCKLEY: I guess the key there is direct evidence. Since we don't really have anybody screen positive, we don't really have direct evidence for that.
Jim, can I ask you another question about that? Or, I guess, anybody on the Committee. For siblings and previously affected family members, they are in essence screened positive, although they would be treated from the earliest point in the same way that someone that was picked up by newborn screening would. Can we somehow elaborate? Do we have access to that kind of information, either formal or informal? Maybe Dr. Buckley would be able to help us out.
DR. PERRIN: My understanding is that indeed the younger children in the Buckley series in fact mainly are siblings who were identified for that reason. So I think you are quite correct in your assumption. Dr. Buckley, am I right in saying that?
DR. BUCKLEY: Rodney, am I allowed to speak?
CHAIRMAN HOWELL: You are not only allowed to speak, you are encouraged, as a member of the Committee. Everyone knows that you are a leader in this area. I think that when it comes finally to voting on SCID we will ask you to abstain, but in the meantime we would appreciate your wisdom.
DR. BUCKLEY: Yes, you are correct that these were identified because of either a family history or a previous death in the family that was of unknown cause. So these infants were tested because of that.

There were a few exceptions. We had a few alert pediatricians who picked up a low lymphocyte count. So currently we have treated 48 infants who were less than 3.5 months and we have only lost three. Of the three that we lost, two were from CMV and EBD, which they got at birth. The third one was in an older patient who was a rebellious teenager who refused to take his intravenous [medication] for lung disease. Those were the only three deaths we have had out of that group that you might call screen positive because they had either family history or were picked up early.
PARTICIPANT: Rebecca, do you have any information or data on it getting picked up early because they had a clinical change even in that under 3.5 months?
DR. BUCKLEY: I would have to go back and look and see whether any of the 48 that we had had any signs or symptoms at all. I think there must have been a reason for them to do a blood count. They could have had a URI or something like that.
DR. VOCKLEY: I think it would be very helpful to have the information on kids who were diagnosed strictly on the basis of family history because that is going to be the group that is going to look for children identified through newborn screening. That might be something you could add to the evidence-based report.
Any other questions or comments about Key Question No. 1?
[No response.]
DR. VOCKLEY: Key Question No. 2 is, is the condition well characterized.
CHAIRMAN HOWELL: Comments about that?
DR. BUCKLEY: Again, I would be glad to offer a comment about that. These people look like the Gerber Baby before they get sick. That is why no one really thinks about them having anything wrong. But once they get sick, there are typical characteristics.
DR. VOCKLEY: I think, Becky, the question here is more is it a distinct enough clinical entity to go after in a screening program and the overlap with any other condition that might be confused in the laboratory or clinically.
DR. BOYLE: This is Coleen. Clearly, we don't know what the incidence is and that is why it is important to be doing some population-based studies like we are doing in Wisconsin. We know what the prevalence is based on clinically identified cases.
DR. VOCKLEY: So we have a pretty characteristic clinical picture in the children that are identified via symptoms. What we don't know is, is there a milder variant which plagues most disorders once the screening is in place.
Key Question No. 3, is there a test for the condition with sufficient analytic utility and validity. Never mind the language. We are going to have that changed a little bit. I think in light of what we discussed earlier, do people feel that we have enough data? I guess I think of it in terms of how many babies are going to have to be referred into an immunology clinic that ultimately don't have a real need in order to treat that one baby that does.
DR. SKEELS: This is Mike Skeels, Jerry. I think that the jury is still out on this one. There is some promise. It looks like pretty good discrimination between infected and uninfected kids using some of these tests, but I for one would like to see a lot more data before I think I could answer this.
DR. BOYLE: I think the studies are ongoing to be able to address this.
DR. VOCKLEY: That was my question about the current Wisconsin data. There seems to be a fairly significantly lower level of false positives in that study than in some of the earlier data. I think we need to see that before we will have the opportunity to really be

able to talk about it with the analytical utility and validity.
DR. PERRIN: That may fall out in the Massachusetts pilot that is starting up.
DR. CALONGE: I think that in general when you are identifying these issues you need to look across the breadth of the available evidence. This would raise levels of uncertainty that could be decreased by more evidence.
DR. VOCKLEY: I think the other half of that -- and I keep forgetting where it is. It is probably more like Question No. 5 -- is where you are going to go in and actually diagnose the disease after the screening. So the TREC PCR testing certainly seems to be robust in that setting. It is a very good test from that standpoint. We don't quite have the information yet in screened populations, as has been noted.
CHAIRMAN HOWELL: But there is nice data that may be forthcoming.
DR. SKEELS: Jerry, this is Mike Skeels again. This is out of left field, so bear with me here. It seems to me like infants who are getting white cell counts and differentials ought to be less lymphopenic enough that you could tell it if you are doing that test on their whole blood. How many babies get that?
I'm just trying to think of some other way that you could screen kids for low lymphocyte counts. I understand that it is just T-cells, it is not all lymphocytes. But is there some other way to skin this cat?
DR. BUCKLEY: Could I speak again? This is Rebecca Buckley.
CHAIRMAN HOWELL: Absolutely. You have been thinking about this and working on it for years.
DR. BUCKLEY: This is what I have been recommending for the past 11 years, doing a white blood cell count and a manual differential on the cord blood. We haven't published it, but we have a lot of data. Actually, it has been partially published in one publication. Anyhow, we have a lot of data on babies who had white counts and manual diffs done because they were relatives of babies that we have treated. What we found is that if you do a white count and a manual differential, the SCID baby will have not only a low total white count but also it will be profoundly lymphopenic because T-cells represent 70 percent of your and my circulating lymphocytes. If you are missing 70 percent of your lymphocytes, you are bound to be lymphopenic.
But when I proposed this as a screening test to several different groups, I have been told that the neonatologists don't want to do that. Then I have been told that the HMOs don't want to pay for it. Then the third thing I have been told is that it has to be done on a dried blood spot.
DR. VOCKLEY: Mike, what do you think about that?
DR. SKEELS: First, I want to give credit. It was actually Cheryl Hermerath [ph] who thought of that question. I don't know that newborn screening has to be done on a dried blood spot. That happens to be what we are doing now because it is multiplexible and convenient and all of the above. But I'm just saying [maybe] there is some other way to at least identify kids who are at risk and then pursue them. I'm, frankly, heartened to hear that Dr. Buckley already thought of this.
I'm not sure how that fits into our committee process in any way, but I just want to throw it out there.
DR. VOCKLEY: I think the way it fits in is to say that if the current screening method that is being proposed ends up not being robust enough then perhaps there are other ways to go at it. But I think it restarts the process. At least that would be my interpretation. At

the very least, if you are going to start proposing additional or different tests, then they have to be validated in the same way that the originally proposed test would have been.
DR. PERRIN: We did tell you about one study that we did identify, which was a lymphocyte county study, but we did not find others. There certainly is one that could merit more evaluation.
DR. SKEELS: This is Mike again. I don't think flow cytometry on all newborns is ever going to happen. But if there is some other, more mundane routine test such as a white cell count that could be done, that is a possibility, too. We should put that one in the parking lot, I think.
CHAIRMAN HOWELL: I would agree with putting in the parking lot. I think you have to look at a variety of logistics about white cell counts and small community hospitals and manual diffs and a variety of things. I think we should put that in the hopper and think about it. Jerry, can you proceed?
DR. VOCKLEY: Question Nos. 4 and 5 I'm going to lump together. No. 4 is the clinical validity of the testing and determining is that validity adequate. No. 5 is what the clinical utility of the screening test is. I think we are coming back to questions of the test. Are we comfortable with the screening test that we have and do we have enough information to be able to comment. I think the intent here is the follow-up testing. Once you are screened positive, do we have enough information on what that means to proceed.
No. 5, remember, was that one that covered all sorts of things, including treatment. That is a big one.
Ned, I'm going to prod you. Since you have been thinking about this outline, if you could get us going with your thoughts.
DR. CALONGE: I guess the first question to Jim would be, the separation between the early and late treatment graphs.
DR. PERRIN: Yes.
DR. CALONGE: Can I understand how many cases that is actually based on and if you actually ran Kaplan-Myer statistics on it to get confidence intervals, or how clear we are that those two graphs are really separate? They look impressive, but I always worry. If 161 is the total number, how many kids is that based on and what do the stats tell us about the difference?
DR. PERRIN: It is actually the Buckley et al. study going back a little bit. I think these are actually including the most recent numbers from the Buckley population. It is more than is on two or three tables before. My memory is, a little less than a third of these are children who were transplanted early and two-thirds are late transplants.
DR. BOYLE: It is 48 and 113 in the report.
DR. BUCKLEY: If I could add something else, we have recently done a statistical comparison of the Kaplan-Myer, and it is highly significantly different.
DR. CALONGE: All the other caveats aside about us talking about whether the testing is ready, whether or not we need continual information to specifically answer the question about clinical utility of early detection, this was a key point for me. I think understanding how many cases it is based on and seeing the statistics leads me towards thinking that this is a level of adequacy that at least I'm feeling comfortable with. I'm trying to decide what we would expect to see in another population that would be anticipated to wipe out this effect.
That is where I come down in terms of looking at this specific key question and the data

that are available to us.
DR. VOCKLEY: Other comments?
DR. BOYLE: Is there a way we can get more information on this graph? I guess I'm still going back to the varied survival by race and sex.
CHAIRMAN HOWELL: We can see if we could get access to the raw data there.
DR. BUCKLEY: Actually, I can tell you the answer. There is no difference between race and sex.
DR. CALONGE: The real issue is, are there additional sources of bias that we can imagine or envision that underlie the separation of the two graphs in these cases that would say this isn't really accrued to screening, this is accrued to some other associated correlational fact.
DR. BOYLE: One big one would be the recency of cases. These both extend out to 26 years, which I guess is counter to what I'm going to say. But if more of the children who received a transplant early are more recent cases where the technologies and treatments are better versus those who received them late, clearly that would result in a bias in terms of survival. The survivorship goes out to 26 years in both of these.
DR. VOCKLEY: For me, this is actually one of the stronger points for going to screening. That is, there does seem to be some difference between early and late treatment. That is really what you want to see in a disease that you are going to be screening for. Of most of these points, I was probably most convinced of that one.
DR. SKEELS: This is Mike Skeels. Was antibiotic therapy started at the same time for each of these two groups of kids? That is one thing that comes to mind that could be an underlying variable that is unrelated to the age at which they received their transplant. In other words, are the ones who got transplanted earlier more likely to have been started on antimicrobial therapy earlier?
DR. BUCKLEY: I can comment on that. Once you make the diagnosis of SCID, generally you are put on prophylactic Septra to prevent PCP. But of course, the ones who were not diagnosed until late may have been treated with antibiotics for the various illnesses that they had before the diagnosis was made. So it is really hard to say that there is a difference there.
The one main difference is that the group that was transplanted early, those infants basically remained well babies throughout the post-transplant course, whereas the group that was transplanted late came in with viral agents on board and often had a rocky course.
DR. CALONGE: Dr. Howell, this is Ned. I apologize. We have a budget crisis, so I'm going to have to leave. I wonder if I could just make a few comments real quickly.
CHAIRMAN HOWELL: Please do.
DR. CALONGE: I think that, again, this is an important difference that helps point toward the efficacy or the clinical utility of early detection. I think, again, looking at all the challenges to internal validity are important.
I think there are additional questions for SCID that have to do with the testing platform, uniformity of testing, and making sure we are generating not very many false positives. I think that the discussion we have had today hopefully will help Jim in the final report round that out a little.
I guess the last question that I think we are going to have to wrestle with is external validity, or the ability for the treatments to be widely available for states who are trying to

do this testing. Again, I think that is a timing issue.
As I went through this whole review, I felt that if we could answer a few basic questions and move a little farther down the road that this looked pretty positive to me. But I wasn't quite certain whether we were going to have all the questions answered in this particular review.
That is my overall summation in looking and listening to the discussion about the areas where we still have questions.
CHAIRMAN HOWELL: Ned, your thoughts on the key areas where we believe evidence would be?
DR. CALONGE: I think one is decreasing the variation around the testing utilities, specifically specificity -- I actually need to look at the paper. I apologize for not doing that -- and any other threats to internal validity of the separation of the survival curve based on early detection, which again, I just have to tell you, looks pretty promising and pretty compelling.
Then, at what point would the states that would incorporate the recommendation actually be able to provide the treatment necessary for these kids.
So the identification of the condition when you don't have availability of the curative strategy is not necessarily helpful from a public health standpoint. It is like identifying a problem without a solution. You know there is a solution, you just don't have it.
CHAIRMAN HOWELL: Thank you.
DR. CALONGE: Thank you.
DR. VOCKLEY: As I looked through the Evidence-Based Review Committee's report, the thing that struck me the most was one that we talked about in relationship to I think essentially every disorder that we have discussed thus far, and that is really the lack of screening data. Here we have at least pilot data from one program. That is a real plus. But we still don't have a positive out of that program, so we don't know the incidence yet. It is hard without a real positive to know what the false positive or false negative, specificity, sensitivity, whatever measure you want to apply, is going to be.
I think Ned already commented on the issue of how the experience is going to translate to other programs.
I do think there are some unanswered questions that are outstanding. I know there was a mention in the report of a pending program in New England. That is something that will really lend, I think, some weight to the decision on screening for this disorder.
CHAIRMAN HOWELL: Jerry, thank you very much. Jim, thank you very much. This was an excellent discussion and a wonderful report. Our plans will be for Jim to finalize his report and we will discuss this in February. We have a formally scheduled meeting February 26th and 27th that will be a face-to-face meeting here at the Pooks Hill Marriott in Bethesda. We are excited to look at those questions and so forth. Thank you very much.
Public Comments
CHAIRMAN HOWELL: We have a considerable number of public commenters today, and I want to be sure that we get to them. So I would like to, with your permission, modify the agenda slightly and go to the public comments section.
If we could get the folks downtown to connect Mickey in, we would like to hear from her.
PARTICIPANT: I'm actually not seeing that person still dialed in.
CHAIRMAN HOWELL: Let's continue to see if someone can find Mickey. In the

meantime, let's go to Ron Laessig, who is the director of the School of Medicine and Public Health at the University of Wisconsin. Let's see if we can find Dr. Laessig.
PARTICIPANT: That person is no longer dialed in, either.
CHAIRMAN HOWELL: Well, we should get through our comments quickly, then. The next one is Marcia Boyle, president of the Immunodeficiency Foundation.
MS. BOYLE: Guess what? I'm here.
CHAIRMAN HOWELL: Congratulations.
MS. BOYLE: I just came back about three minutes ago from another call, so I'm glad I made it. Do you want me to just read my comments?
CHAIRMAN HOWELL: Five minutes, please.
Comments by Marcia Boyle
Immune Deficiency Foundation
MS. BOYLE: I want to thank the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children for giving me the opportunity to comment in favor of adding severe combined immunodeficiency to newborn screening programs. I truly can't express strongly enough how important this would be to our community.
By way of background, the Immune Deficiency Foundation is the national patient organization dedicated to improving the diagnosis, treatment, and quality of life for persons with primary immunodeficiency diseases through advocacy, education and research. Since 1980 we have been dedicated to providing accurate and timely information to the nearly quarter million Americans who have been diagnosed with a primary immunodeficiency disease.
We are governed by a board of trustees, supported by a medical advisory committee of leading clinical immunologists. Plus, we have hundreds of grassroots volunteers and a compassionate professional staff.
We have provided individuals and their families with vital knowledge in helping patients and the medical community gain broader understanding of primary immunodeficiency diseases through education and outreach, promoting and participating in research to characterize primary immunodeficiency diseases, and give patients improved treatment options, and conducting public policy programs on issues vital to enhancing patient access to treatment.
I have to say that newborn screening for severe combined immunodeficiency is absolutely central to our mission and critical to our patients.
I think, as you know, babies born with SCID have the most severe of the more than 150 recognized primary immunodeficiencies. They die from infection before their first or second birthday if not given immune reconstitution by bone marrow transplantation.
If a SCID baby receives a bone marrow transplant in the first 3.5 months of life, the survival rate can be as high as 97 percent. However, this rate falls dramatically after that time.
Many children with SCID who are successfully transplanted had earlier siblings who died of SCID, thus alerting families and physicians to look for SCID at birth of before.
Newborn screening for SCID would save the lives of SCID babies and give them normal lives. Without newborn screening many of these children will either die before diagnosis is made, receive a diagnosis too late to save their lives, or will be diagnosed after irreversible damage to their bodies has occurred that severely impacts the quality of life.
Another threat to SCID babies are live-virus vaccines such as rotavirus which are being

administered in infancy. They are not going away. Only newborn screening can protect these vulnerable babies from receiving a live vaccine that could potentially kill them. Since SCID is fatal, a highly successful therapy exists and screening tests are now available, I cannot imagine a more important disease to include in newborn screening. On behalf of the Immune Deficiency Foundation, I urge the Committee to immediately add SCID to newborn screening programs.

I also just want to add personally, in August I attended a conference for families with severe combined immunodeficiency. IDF was very proud to be a sponsor of this and supporter of this. A hundred and forty people attended, 35 families. What I was struck by was many of the families attending had around their neck a picture of the child who passed away. Those families who had a child who was healthy after a transplant had generally lost a child before, so they were looking for that at birth.

There were some children there who had been, luckily, transplanted and survived but who had been diagnosed quite late. Some of these children were teenagers who were half the size of a normal teenager and had to deal with multiple health issues, emotional issues, et cetera. Again, all of them could only pray for newborn screening that would prevent these kinds of problems.

Thank you for your attention to this life-and-death situation. Please let me know if the Immune Deficiency Foundation can ever be helpful to the Committee in your endeavors.

CHAIRMAN HOWELL: Thank you, Ms. Boyle. The next person who would like to comment is Heather Smith, who is cofounder of the Angels for Life Foundation. Again, we will need to stick quite rigidly to five minutes, Ms. Smith. Thank you very much.

Comments by Heather Smith

Angels for Life Foundation

MS. SMITH: I want to thank the Committee for this opportunity to represent the families of children with severe combined immunodeficiency. My name is Heather Smith, and I am the mother of two children both with X-linked SCID, although one has passed away. I'm on the Immune Deficiency Foundation's SCID Initiative Oversight Committee, the cofounder of SCID Angels for Life Foundation, and recently I hosted and funded through educational grants an international conference for families who are affected or have been affected by SCID.

Our first son, Brandon, began his battle with SCID in November of 1993, when he came down with his first cold. He was six months old at the time and appeared up to this point to be a very normal baby without any infection. We quickly learned that he did not respond to a cold like a normal baby would. He was admitted to the hospital when he showed failure to thrive. He had a difficult time eating, a rash on his face, and thrush in his mouth, and his fingernails had turned blue.

Immediately the doctors began testing him for everything they could think of under the sun, including cystic fibrosis and AIDS. Although all the tests came back negative, Brandon did not respond to treatment and was quickly transferred from hospital to hospital while the doctors battled for answers and some kind of a diagnosis.

[Interruption.]

MS. SMITH: [In progress]-- 3.5 week hospitalization, and that does not include any treatment such as a bone marrow transplant. In fact, at this point the idea of a bone marrow transplant wasn't even an option presented to us for consideration. Instead, we were told that we had to say goodbye to our only child and turn off all machines. Three

and a half weeks after initially becoming ill, our precious Brandon passed away and became our SCID angel for life.
It took over six months for geneticists to confirm that Brandon had died of SCID and that I was a carrier of this deadly disease. Because of this, when we became pregnant the next time, we immediately had a CDS test done to see if this child would be --
[Interruption.]
MS. SMITH: [In progress] -- didn't look so good. Three weeks later, we got the call from the doctor that this baby also suffered from SCID. Immediately, we started to make a plan. We had already done quite a bit of research on SCID after we lost Brandon, and we knew that a BMT shortly after birth was our only option to treat and possibly cure our new baby boy.
However, what we didn't know was that the bone marrow transplant could actually be done in utero while I was still pregnant. If that wasn't amazing enough news, the transplant could actually be done in Detroit, Michigan, just two hours away from our home.
The only catch to this story was that the procedure had never actually been done successfully on a fetus before. Our physician, Dr. Alan Slake [ph], had been doing research in the lab and was waiting for the perfect patient. That would be us.
At 16, 17.5, and 18.5 weeks gestation, three separate stem cell transplants were performed, with his father being the donor. If the procedure didn't work, our plan B was to do a traditional bone marrow transplant within the first three months of life, and we would travel to Duke for that.
At 36 weeks, Taylor was born via C-section, weighing 4 pounds, 3 ounces, and 17.75 inches long. The cord blood was immediately tested at birth and the preliminary results were extremely positive. His transplant was a success. Now, 13 years later, Taylor is a thriving and healthy teenager with a life full of possibilities ahead of him.
Unfortunately, a tragedy had to happen in our family and in so many other families in order for us to know about this devastating disease. If Brandon could have been diagnosed at birth, before the onset of a life-threatening illness, his pain and suffering could have been stopped. His life could have been saved. It has been almost 15 years since we lost Brandon, but I can remember it like it was yesterday.
I would like to share a comment from one of the mothers that was at the conference this summer. Her name is Mary and she said, "Had my son been diagnosed as a newborn, I would have never had to endure threats from the State Department of Health and Rehabilitative Services that my child would be taken away from me for neglect due to his failure to thrive and repeated infections. It was months after his death before I learned that he had died of SCID and was able to clear my name."
I appreciate your time. Thank you.
CHAIRMAN HOWELL: Thank you very much for your thoughtful comments. I think your comments also underline the fact that although this is an incredible tragedy for the families and the children, you have also emphasized that associated with that tragic illness are extraordinary costs to society of the hospitalizations that preceded your son's unfortunate death. Thank you very much.
MS. SMITH: Thank you.
CHAIRMAN HOWELL: We will next go to Dr. Jennifer Puck. Jennifer, are you there?
DR. PUCK: Yes, I am here.

CHAIRMAN HOWELL: Thank you. Please comment.
Comments by Dr. Jennifer Puck
DR. PUCK: I appreciate the consideration of SCID by this Committee. I want to own up to the fact that I was the nominator of SCID. I did want to share just some brief comments with the Committee.
First of all, I don't think the discussion really got into these two comments, but I will share them anyway. There are several different protocols to do the transplants for SCID now. Many institutions have developed their own rather than having a standard protocol at this point because the disorder is so rare.
I would like to emphasize that all the protocols, though, are extremely successful at saving lives of SCID infants in contrast to no treatment, which we have just heard about from Heather Smith. Failure to diagnose and treat SCID is fatal.
Furthermore, the infectious complications that are present at diagnosis in all the cases of SCID except those with a known family history or a prior death decrease the likelihood of successful outcomes no matter what treatment regimen is used.
Experts in hematopoietic stem cell transplantation continue to refine their therapies, such as using different donor sources, whether or not they use chemotherapy, and in some cases whether to use enzyme replacement therapy for ADA-deficiency or gene therapy, every current regimen saves the lives of infants with SCID.
The distinctions between the regimens are much smaller compared to the improvement in survival when the diagnosis is made before versus after the infections have set in. So, in my opinion, it would be wrong to delay institution of newborn screening until a single ideal treatment is arrived at.
Secondly, although outcomes following successful treatment for SCID are not always complete cures, the overwhelming majority of children who receive these treatments develop, thrive, attend school, go to college, and end up with jobs and paying taxes. So their intellectual function is normal or near normal. There was a recent publication from England confirming this in a large series there.
Residual impairments that SCID children have can almost always be attributed to the infections that were present due to the delayed diagnosis rather than the SCID itself or treatment. I therefore think these impairments can be predicted to be lessened with implementation of SCID newborn screening because then children will be treated before they develop infections.
While many surviving SCID children presently continue to require long-term therapy -- for example, immunoglobulin supplementation -- this treatment is arguably, I would say, no more burdensome than a PKU diet or galactosemia diet. Therefore, I think the advent of affordable, sensitive, and specific screening methodology that we now have with the TREC test should make the addition of SCID testing an important public health measure at this time.
I would also quickly like to add, because the head of the Wisconsin Program, Ron Laessig, was not on the call, I am in communication with their program and know that they are using just the TREC test. They have refined the test from my original publication. I have also done that so that we have similar indeterminate rates now to the ones that you saw on your screen. That is with simply using the TREC test.
I'll stop there. Thank you very much.
CHAIRMAN HOWELL: Jennifer, thank you very much. As you know, Dr. Perrin and his

group are in close contact with the Wisconsin group. I'm sorry that Dr. Laessig was not on. He signed on several times but apparently has departed.
We had one final person who had signed up to present, but I do not see her on the sign-in screen. That was Dr. Priya Kishnani [ph], who is head of genetics at Duke. Dr. Kishnani, are you there?
[No response.]
CHAIRMAN HOWELL: I don't think so. So that will end our public comment. Thank you very much. That was excellent.
We have just a few minutes left on this call. We want to end promptly on time. I wonder if there are additional items from the Committee that should come before the Committee at this time.
[No response.]
CHAIRMAN HOWELL: I'm listening carefully. Hearing none, we would like to look at some potential dates. I realize that we probably won't finalize a date today. But the two potential dates we are looking at for May for meeting is the 12th and the 13th. Please look at your calendars for that, Committee folks. We will be in contact with you.
The other time that we need to meet --
PARTICIPANT: We are having a little trouble hearing you. If you could get closer to the microphone?
CHAIRMAN HOWELL: This microphone needs to be carefully directed today.
The dates that we are looking at for May are the 12th and 13th. Look at your calendars. The folks at HRSA will be in contact with you to verify that.
PARTICIPANT: Those are the confirmed dates.
CHAIRMAN HOWELL: So if you can put that on your calendar, that will be great. The 12th and 13th. There had been a circulation looking for the best dates.
Then the date that we don't have a final date for is September. Please look at that. Now, I'm aware that early in September happens to be the International Society for Inborn Errors of Metabolism in San Diego. That's going to take out the first week for practical purposes, I think, for a number of members.
Again, then we come to Labor Day, which is the 7th. So we probably are going to be looking somewhere from the 10th and beyond that. Yom Kippur is in there toward the end of the time. Please let us know about that. There are a number of Islamic holidays, for those of you who might celebrate that.
Anyway, let's look at the calendar. We will be in contact with you about September.
PARTICIPANT: Can you please confirm our February dates?
CHAIRMAN HOWELL: The February dates are confirmed, and that is February 26th and 27th. Again, that will be a face-to-face meeting in Bethesda at the Pooks Hill Marriott. That is firm at the current time.
PARTICIPANT: I'm sorry. What is the name of the Marriott again?
CHAIRMAN HOWELL: Pooks Hill, P-O-O-K-S, Hill. It's the one that is right off Wisconsin Avenue, not too far from the NIH. It is a very good location. It's also nice because once you get there you can't get away. It's not close to any activities whatsoever.
PARTICIPANT: Thank you very much for that, Rod. That gives us something to look forward to. Will Gary or Tamar be sending us the information for registration at the hotel, or have they already done it and I missed it?

CHAIRMAN HOWELL: They have not done that. I'm sure they will do that.
PARTICIPANT: The sooner the better. A lot of us are facing long travel approval times and one thing and the other out here in state-land, especially with budget cuts. So the sooner we ask, the more likely it is that we will be able to actually attend.
CHAIRMAN HOWELL: I think that would be wonderful. We look forward to all of you.
Is there any additional business that should come before the Committee at this time?
[No response.]
CHAIRMAN HOWELL: Let me thank the Committee for a very successful meeting today. I think we made a great deal of progress. We will look forward to seeing the final report on SCID in February and having the Committee's decision on that and, obviously, a lot of things in the meantime.
Unless there is further discussion and so forth, let me thank you and we will end our meeting. Thank you.
[Whereupon, the meeting was adjourned.]
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