P R O C E E D I N G S (1:12 p.m.)
DR. HOWELL: Let me welcome you to the 14th meeting of the advisory committee, which now has a new name you probably noticed. It's the Advisory Committee on Heritable Disorders in Newborns and Children. So our name has shrunk, and certainly our mission has expanded. But let me welcome all of you.
I'm calling from a rainy Miami. I hope the weather is less rainy where you are.
+ Michele, would you please make a roll call currently so that we're clear about who is on the call?
DR. LLOYD-PURYEAR: So I'm going to go through the roll again. Ned Calonge?
(No response.)
DR. LLOYD-PURYEAR: Rodney Howell?
DR. HOWELL: Yes.
DR. LLOYD-PURYEAR: Jana Monaco?
MS. MONACO: Here.
DR. LLOYD-PURYEAR: Piero Rinaldo?
DR. RINALDO: Here.
DR. LLOYD-PURYEAR: Mike Skeels?
DR. SKEELS: Here.
DR. LLOYD-PURYEAR: Tracy Trotter?
DR. TROTTER: Here.
DR. LLOYD-PURYEAR: Gerry Vockley? Gerry?
DR. VOCKLEY: Here.
DR. LLOYD-PURYEAR: Duane Alexander?
DR. ALEXANDER: Here.
DR. LLOYD-PURYEAR: Coleen Boyle? Coleen?
DR. BOYLE: I'm here.
DR. LLOYD-PURYEAR: Denise Dougherty?
DR. DOUGHERTY: Here.
DR. LLOYD-PURYEAR: Joseph Telfair?
DR. TELFAIR: Here.
DR. LLOYD-PURYEAR: Peter van Dyck?
DR. van DYCK: Here.
DR. LLOYD-PURYEAR: And then representatives. Al Berg?
DR. BERG: Yes.
DR. LLOYD-PURYEAR: Tim Geleske?
(No response.)
DR. LLOYD-PURYEAR: Mike Watson?
DR. WATSON: Hello.
DR. LLOYD-PURYEAR: Tom Musci?
(No response.)
DR. LLOYD-PURYEAR: Jane Getchell?
(No response.)
DR. LLOYD-PURYEAR: Chris Kus?
DR. KUS: Here.
DR. LLOYD-PURYEAR: Bennett Lavenstein?
DR. LAVENSTEIN: Here.
DR. LLOYD-PURYEAR: David Louder?
DR. LOUDER: Here.
DR. LLOYD-PURYEAR: Ethan Hausman?
DR. HAUSMAN: Here.

DR. LLOYD-PURYEAR: Sharon Terry?
MS. TERRY: Here.
DR. LLOYD-PURYEAR: Alan Fleischman?
(No response.)
DR. LLOYD-PURYEAR: Barbara Burton?
DR. BURTON: Here.
DR. LLOYD-PURYEAR: Okay.
DR. HOWELL: Thank you very much, Michele.
Ladies and gentlemen, let me welcome you to this 14th meeting by teleconference of the Advisory Committee on Heritable Disorders in Newborns and Children.
As those of you who were on the line earlier during the roll call noticed, Dr. Tom Musci has replaced Dr. Tony Gregg as a ACOG representative. Dr. Musci is in the San Francisco Perinatal Association and is chair of the ACOG Committee on Genetics. And we'd like to welcome Dr. Musci. He will not be on the call until later, but we do expect him later.
+ Our first order of business is the approval of the minutes from January 14 and 15, 2008. They're in tab 5 of the book. They're also posted on the material that you have on the website, for those of you who are looking there. And we need to formally vote on these, and the only way I know to do that is to have our able executive secretary to go through the membership again. Michele?
DR. LLOYD-PURYEAR: Yes.
DR. HOWELL: Michele will zip down the list and those favoring the adoption of the minutes, which we have to formally approve, please speak out.
DR. LLOYD-PURYEAR: Okay. I'm calling those that I know that are on the phone currently or in the meeting.
Rod Howell?
DR. HOWELL: Yes.
DR. LLOYD-PURYEAR: Jana Monaco?
MS. MONACO: Yes.
DR. LLOYD-PURYEAR: Piero Rinaldo?
DR. RINALDO: Yes.
DR. LLOYD-PURYEAR: Mike Skeels? Mike?
(No response.)
DR. SKEELS: Sorry. Say again?
DR. LLOYD-PURYEAR: This is about approval or disapproval of the minutes.
DR. SKEELS: I'm sorry. This is Mike Skeels. Did you call my name again?
DR. LLOYD-PURYEAR: Yes, I did.
DR. SKEELS: Well, I voted yes. You must not have heard me.
DR. LLOYD-PURYEAR: No, I didn't.
Tracy Trotter?
DR. TROTTER: Yes.
DR. LLOYD-PURYEAR: Gerry Vockley?
DR. VOCKLEY: Yes.
DR. LLOYD-PURYEAR: Duane Alexander?
DR. ALEXANDER: Yes.
DR. LLOYD-PURYEAR: Coleen Boyle?
DR. BOYLE: Yes.
DR. LLOYD-PURYEAR: Denise Dougherty?
DR. DOUGHERTY: Yes.
DR. LLOYD-PURYEAR: Peter van Dyck?
DR. van DYCK: Yes.

DR. LLOYD-PURYEAR: So I'm just calling for the voting members. We have a unanimous vote of approval.
DR. HOWELL: Thank you very much, Michele.
I'm pleased at this time to welcome Mr. Dennis Williams for his comments, and Mr. Williams is the Deputy Administrator of the Health Resources and Services Administration, who obviously oversees this committee. Mr. Williams, welcome.
+ DR. WILLIAMS: Thank you very much, Dr. Howell. And I bring greetings from Dr. Duke, the Administrator from HRSA, to all the members of the committee.
I'll keep my remarks very brief. This meeting is notable for a couple of very different reasons. One, as you've just been going through the roll call, this is a virtual meeting. This committee, like many other advisory committees, has traditionally met face to face incurring travel costs and hotel costs to do so. But it was done so that these advisory committees could do their work effectively.
We're experimenting in the face of the budget limitations with these kinds of virtual meetings, and we look forward to your feedback on these meetings. We want them to be effective meetings. We want to make certain that you can do your work, but if we can accomplish that and save money at the same time, that's good for everybody. So I think we're probably still working the kinks out of some of this process, but we welcome your feedback and hope that these kinds of meetings can work. We're asking all of our advisory committees to experiment with this over time. We hope this will be a workable process.
Secondly, a major part of this agenda is on processes and aspects of the recently enacted Newborn Screening Saves Lives Act of 2008. That is a major piece of legislation that affects this committee, its relationship with the Department and with newborn screening policy more generally.
This legislation was enacted quickly in the Congress. I regret to say we were not totally on top of it when it was first enacted. But Dr. Duke has, with Dr. van Dyck's help, assembled a business team inside of HRSA that is very much focused on what needs to be done to implement this legislation. Dr. Duke chairs weekly meetings on this topic so that we can get HRSA's work done along the time table expected by the Congress. So we look forward to working with you on this.
The speed with which this was enacted has resulted, I think, in some aspects of the law which will require some interpretation. That's why we're having a lot of meetings. But as we work through all of that, I think we expect to have a good implementation within the time frames laid out by the law. And Peter will talk more about this later in the agenda.
So I welcome everybody to this meeting and I look forward to a good session. Thank you.
DR. HOWELL: Thank you very much, Dr. Williams, and we certainly appreciate your support and the support of Dr. Duke in making this committee function efficiently and effectively. And we'll look forward to your continuing thoughts and wisdom about this new major legislation that you have already alluded to.
Our first item on the agenda is a review of the committee nomination and review process. And for those members who have the big, fat book, that's tab 6. I welcome Dr. Nancy Green who's in the Division of Pediatric Hematology and the Associate Dean for Clinical Research Operations at Columbia University Medical Center. Nancy, can you share your thoughts about the nomination at the current time?
+ DR. GREEN: Sure, Rod, and I guess it's best if I don't take questions during the presentation. Right? But wait till after if there are any questions.
DR. HOWELL: Well, I would think that after you make your presentation, if there are questions, it would seem prudent to do it at that time.
DR. GREEN: Very good.
DR. LLOYD-PURYEAR: Nancy, we cannot hear very well.
DR. GREEN: Can you hear me now?
DR. LLOYD-PURYEAR: Yes, very well.
DR. HOWELL: And you're having trouble with me too?
DR. LLOYD-PURYEAR: Just for a moment. You weren't speaking into the phone directly, which is a problem.

DR. GREEN: So go to the slides. So this would be slide two out of only five. Thank you, Rod, for the opportunity to review the nomination and evidence review process to date, and I will now do so. So for those of you who have been assiduous attendees of the meetings, this will be a review.

So the nomination form, which is available on the HRSA website, is submitted to HRSA for administrative review, and then once that form is complete, including filling out all of the requisite aspects required on the form and also submitting references to substantiate the data on the nomination form, that is then forwarded to the advisory committee. This is sort of an overview, and then subsequently I'm going to expand on some of these aspects.

Then the advisory committee will decide which of those nominations will be reviewed by the Nomination Review and Prioritization Workgroup with some back and forth with the committee. And then with input from that workgroup, the committee will decide which nominations and in which order would be submitted for an external workgroup, which is the Evidence Review Workgroup headed by Jim Perrin.

That group will then perform its duties and prepare a report that is also preliminarily reviewed by both an external advisory committee and then subsequently by the Nomination Review and Prioritization Workgroup and then presented to the advisory committee for its deliberations on the potential outcomes for the nominated condition. Those potential outcomes are listed, including from the one extreme of universal newborn screening, so added to the existing universal minimum panel of newborn screening disorders; potentially targeted screening, pilot studies that would need to be undertaken prior to further recommendations, or other kinds of critical studies needed. The advisory committee would also potentially recommend against newborn screening for a variety of reasons, and those would have to be spelled out. And again, as the slide suggests, as part of that advisory committee recommendation, there would be identification of data that are lacking of a variety of types and potentially further specific studies that should be done prior to reconsideration. And then the advisory committee will ultimately make recommendations on nominated conditions to the Secretary.

So this slide just describes in a little bit more detail kind of the flow of nominations and the additional point to be made here is that the committee chair, so Dr. Howell, oversees the decision about when to forward these nominations to the Nomination Review and Prioritization Workgroup, which is a subgroup of the advisory committee. And the tasks for that workgroup have been to date to, number one, list criteria for readiness for evidence-based review -- and I will go over that in a moment -- and then to make a recommendation to the advisory committee about whether or not to submit any nomination to evidence-based review. And I will again update the group where we are to date in a minute.

Again, the advisory committee would then ask the Evidence Review Group to review. This is an independent group external to the advisory committee, although there are some liaisons. Specifically, Marie Mann from the Bureau and I participate in the biweekly meetings of the Evidence Review Group. This group has, thus far, defined terms from the nomination form that required some clarity, and the criteria for evidence, including evidence in their review, and then for each of the nominated conditions will produce a formal report that will be submitted to the advisory committee.

So in all of this flow, one of the points is that only the advisory committee may make decisions. The other subgroups, workgroups are really advisory, if you will, to the advisory committee.

Again, this was reviewed and endorsed by the advisory committee a couple of meetings ago, and the question is, is it a nominated condition ready for evidence-based review? So this is, again, a structured review process with a form that asks these six questions.

Is the nominated condition medically serious, number one?

Number two, are there prospective pilot data either from U.S. or international sources available from population-based assessment for this disorder?

Number three, is the spectrum of this disorder well described? And that would be to help predict the phenotypic range of those children who would be identified based on population-based screening.

Number four, is there a screening test that's capable of identifying the condition?

Number five, if the spectrum of the disease is broad, would there be, through testing and evaluation, the

ability to identify those children who are most likely to benefit from treatment, especially if the treatment is onerous or risky?
And then lastly, are there defined treatment protocols available, and if applicable, is there FDA approval or clearance for those treatments?
So overall, the Nomination Review and Prioritization Workgroup comes back to the advisory committee with this form filled out and summarized and presented to the advisory committee with a recommendation consisting of one of two options: either the condition is ready or not ready for evidence-based review and then with this supporting rationale.
So the next slide. This is slide 5, the last slide. To date, the nominated conditions that have been submitted and reviewed up to now are, number one, SCID. And that is currently undergoing evidence-based review. You'll hear from Dr. Perrin later on. Pompe disease, which is also in review by the evidence-based group. Number three, Krabbe disease, which the advisory committee has deemed ready for evidence-based review, and that is in the queue for evidence-based review. The Nomination Review and Prioritization Workgroup has deemed Fabry not ready for evidence-based review. And then lastly, Niemann Pick. That review is just wrapping by the Nomination Review Workgroup and will be discussed in this meeting of the advisory committee.
Thank you very much.
DR. HOWELL: Are there questions of Dr. Green about the nomination? This was basically a review of an agreement that had happened some time ago, but it's a refreshment.
DR. SKEELS: Yes, Rod. This is Mike Skeels.
Can you remind me whether our advisory committee is supposed to consider issues of cost-benefit related to population-based screening of newborns, and if so, where in the process we do that.
DR. GREEN: Can I answer that, Rod?
DR. HOWELL: Please.
DR. GREEN: Mike, that's an important question, and the Evidence-Based Review Group has that in its purview and will be presenting that to the committee, again, based on evidence. And certainly your well-informed question might suggest there may be some other input required. But anyway, the Evidence-Based Review Group does consider that.
DR. SKEELS: Thanks, Nancy. I've been inert on this committee for a few months because of another job assignment, and I was just trying to remember whether that was actually considered part of the evidence-based review or if that was a different issue relating to sort of operationalizing these things at a population level. But I'm happy to hear that it is in the EBR process. Thanks.
DR. HOWELL: Are there other questions?
DR. BOYLE: Yes. This is Coleen.
Nancy, I had a clarification, and it may be just I misinterpreted what you said. For Krabbe and Fabry, do they have to actually come back to the committee for the decision, or does the decision lie with this Nomination Review Workgroup?
DR. GREEN: Thanks, Coleen. All of the decisions are made by the advisory committee. The nomination committee would simply make recommendations.
DR. BOYLE: Okay. So then on your chart, which is slide -- the second one, the one with the more --
DR. LLOYD-PURYEAR: Coleen, can you speak up please?
DR. BOYLE: Sure.
DR. GREEN: Slide 3?
DR. BOYLE: Yes, slide 3.
The lines that -- the arrows that go back and forth between the external review group and the Nomination Review and Prioritization Workgroup -- I guess I'm not quite sure why they would sort of go back and forth between that. Would there be communications? I mean, I can see that once there's a nomination, it goes to the advisory committee, and then it goes to the external review group. I wasn't quite sure why there's this back and forth communication. Maybe I'm not understanding the process well.

DR. GREEN: Well, Coleen, for an example, when the Evidence Review Group makes its report to the advisory committee, perhaps the advisory committee would want additional information or some clarification or something like that.
DR. BOYLE: I can see that exchange, but it was more the exchange between the external Evidence Review Workgroup and the Nomination Prioritization Workgroup.
DR. GREEN: Okay. Well, that's a good question. So those are separate groups.
DR. BOYLE: Right.
DR. GREEN: Although, again, Marie and I sit in on those meetings.
DR. BOYLE: Correct.
DR. GREEN: So when something is nominated, the Evidence Review Group would define the main issues. The Nomination Review Group would have the opportunity to refine those key points, for example, and then go back to the Evidence Review Group. And then once the review is completed, the Nomination Review Group would like the opportunity to review that report, again ask for clarification or additional information. So the groups are separate, but there is some opportunity for advice and recommendations. I don't know if anybody else would like to clarify that.
DR. HOWELL: Any comments about that, the double arrow between those two groups? It would seem that certainly the major arrow would be the Nomination Review and Prioritization Workgroup with a big arrow going to the external evidence group, if you wanted to quantitate those arrows, and a small one perhaps going the other way. I think Coleen is pointing out that the communication there should be largely one-way.
DR. GREEN: I'm happy to make that revision.
DR. BERG: This is Al Berg. I have a question.
I wonder if there's a mechanism for periodic reconsideration or review of topics that the committee has already considered. The National Guidelines Clearinghouse, for example, requires a review every four to five years in order for things to be continuously posted. And I wonder if there needs to be a process for that in this as well.
DR. HOWELL: Comments about that?
DR. CALONGE: Hi, Al. This is Ned Calonge.
It's certainly something that we've committed to continuing to look at, tests that are in the recommended set, but we've not put a periodicity to it. And there's a little problem with the periodicity because the conditions are rare. We may have to figure out how long it takes us to get enough cases to have enough additional information for a re-review to make sense. But the committee has committed to looking at topics that are on the list as new information becomes available.
DR. HOWELL: One subject that's still in development is the NIH-proposed effort with the Translational Research Network to follow in a research mode some of these rare conditions. That particular group may produce information that would require that the committee go back and look at these. That would be one source of information.
DR. CALONGE: But that's an interesting question, and I wonder if there should be some kind of surveillance process that, with some kind of periodicity, tries to look at, reach out, and summarize what we know about what we've already recommended.
DR. HOWELL: Do you have a specific suggestion on how that might work?
DR. CALONGE: Well, the Clinical Task Force actually uses medical officers and members of the committee to kind of scan the literature to look for landmark articles. I think, Rod, talking about a specific process where, on an every five-year or some other periodicity, we have a process where we do a literature search to see if there's anything that's hit the literature new about the conditions that are on the list, it would require resources, but I think it would greatly improve what we know about what we've already recommended.
DR. HOWELL: Are there suggestions about how that might be accomplished? HRSA folks, do you have any ideas? Peter?

DR. van DYCK: Well, I think it's something that we should discuss. I think the Nomination Review and Prioritization Workgroup could discuss that. I agree with Ned a little bit that because the conditions are rare, that just a set time period is probably not the answer and it's better to respond to when something is new, when there's new information. And I think that's worthy of a discussion to determine what that review process would be and who would do it.
DR. TROTTER: This is Tracy.
Just an outline of how the American Academy of Pediatrics does it with their statements, they do have a periodicity of three years, but it doesn't require action. It requires somebody looking at it or a group looking at it and coming back to the committee and saying, we've looked at it; it doesn't need revision at this point. We've looked at it; it needs just an additional statement. Or we've looked at it, and it really needs to be looked at completely again. And one of those three tracks then take place.
Again, periodicity for something like this is probably not going to be as soon as three years, but I think there should be a structure where some expert group says we don't need to do this right this minute or there is something new. If we sort of wait for something new to happen, I'm not sure how you monitor that.
DR. HOWELL: I think that I hear general agreement that there's interest in a periodic review and so forth. And I guess that the question at this point in time is how do we move from that feeling that this is worthwhile to coming up with a specific idea of how to do that. Does someone have a specific suggestion on how we do that?
DR. van DYCK: Well, Rod, this is Peter.
It might be the same group that Nancy chaired because those conditions are going to have to be re-queued into the Evidence-Based Review Group, and I think we're going to have enough new conditions over the next couple of years to stay busy. So there would have to be some thought given to how to re-queue those that really need review into the queue.
DR. BOYLE: This is Coleen.
It's not just those that didn't have enough evidence to move forward. It's all of the conditions because of the rarity of them. So as we get new information on follow-up, that information needs to be brought into this process.
DR. CALONGE: This is Ned again.
Rod, I wonder if once we get the process done for moving from the evidence review to a recommendation, that same workgroup can take on this process. There are a couple of things I could think about, I mean, trying to assign a condition to a committee member, for example, to just do a literature search on, or the committee members who are able. I mean, that might be one way of doing it. But I think spending some time thinking about what kind of new information would cause us to remove a condition from the list is important, and I don't think we've given a lot of thought to that.
DR. HOWELL: I don't think so either.
Maybe we could ask Nancy's group to think about these issues with time to think about it and talk with the committee members and so forth and come back with a thought about how we do this. Can we settle on that, Nancy? Would your group do that?
DR. GREEN: Sure.
DR. HOWELL: Let's do that.
Let me ask you one question. Can you review your final slide exactly for everybody so that we're crystal clear? It's clear that SCID and Pompe are currently with the Evidence Group. Clarify exactly where Krabbe, Fabry, and Niemann Pick are.
DR. GREEN: Okay. Well, you'll hear about the evidence-based review for the first two conditions, Rod, as you know.
DR. HOWELL: Yes, right.
DR. GREEN: Krabbe. Correct me if I'm misspeaking. I believe that the advisory committee recommended evidence-based review for that.

DR. LLOYD-PURYEAR: No, no. This is Michele, just to clarify. And it's because we haven't had a meeting since January that I think people have forgotten.
DR. GREEN: That's why I asked the question.
DR. LLOYD-PURYEAR: So Krabbe and Fabry -- that's what Piero is presenting today. The internal workgroup has reviewed, but they have not gone back -- those reviews, which are being presented today for the first time, have not been seen formally by the advisory committee. So the advisory committee at this point has to make the decision whether or not to send them forward for evidence review or not.
DR. HOWELL: So that's where we are, and then Niemann Pick is still with the Nomination Review and Prioritization Workgroup.
Are there further questions of Nancy? If not, I'll --
DR. BURTON: I just have a quick question of clarification. Barbara Burton here.
DR. CALONGE: And Rod, I'd like to add one after Barbara please.
DR. HOWELL: Okay.
DR. BURTON: So will we be hearing then during Piero's presentation -- I wasn't able to get it off my computer, which is why I'm asking -- why Fabry, for example, was not deemed suitable to be put forward? Will we be going through each of those six questions?
DR. RINALDO: This is Piero. That's what I'm supposed to try to do.
DR. BURTON: Okay, very good. Thank you.
DR. CALONGE: I had a couple questions.
Some of the six questions on the nomination list are ones for which there might be evidence available, like the spectrum of disease is broad so that those most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky. So should that be a key question that we're considering in the literature review? I'm just trying to make sure that if there are parts of the nomination questions that we should be basing our decision about recommendation on, that those are included in your evidence review.
DR. HOWELL: And I think they are. Jim, you're on the phone. Would you comment?
DR. PERRIN: Yes, they definitely are, and I'll describe that in my presentation a little later.
DR. CALONGE: All right, and I should remember, but there are too many evidence groups.
DR. PERRIN: Of course.
DR. CALONGE: The other question has to do with cost, and what I heard you say, Nancy, is that reviewing cost effectiveness of population-based strategies is within your purview, but you may end up with cases where there's no literature that's been published. And do we have the resources then at that point to do at least an outcomes table based on prevalence, cost of therapy, marginal cost of other follow-up issues so that the task force can at least have a ball park understanding about the up sides and down sides of the costs? That's different than looking at evidence.
DR. PERRIN: So this is Jim. If I can respond to that, Ned.
I think that's an incredibly important question. The reality is, as you've said, at least from our experience so far, there is painfully little published evidence with respect to cost. We do hope to provide the kind of tables you're talking about. So it may be that we'll be able to provide at least on a crude level these kinds of data. But I think that the strength of the evidence is pretty limited in most of those areas.
DR. GREEN: This is Nancy.
The Evidence-Based Review Group may, in fact, make that recommendation or list that question amongst its recommendations to the advisory committee; that is, there needs to be some assessment of the cost impact, for example.
And, Ned, if I may just go back to your first question addressing the question of spectrum of disease. So all of those six questions that the Nomination Workgroup is considering are addressed based on the nomination form and the references submitted with that form by the nominator.
DR. CALONGE: Right. I understood that.
DR. GREEN: Okay.

DR. HOWELL: If there are no further questions, I think that we probably should try to move along. I would like to then move on to our substantive discussion this afternoon on decision criteria and the process workgroup, and that is headed by Bruce Nedrow Calonge, better known as Ned. It's in tab 7 of my book, which has nothing in it. But I'm sure Ned will tell us all about it.
+ DR. CALONGE: Well, and I apologize for that. I'm up in the mountains and I thought I would have Internet access and I don't. So I was unable to get these materials down to you.
DR. HOWELL: Well, I've been hearing you on the news all week talking about prostate.
DR. CALONGE: Yes, I have phone contact, as you can tell.
So what I'd like to do, after that apology, is kind of describe where we are and hopefully give the rest of the committee enough information on the topic for us to move ahead with some discussion.
So the idea is that we will be presented with evidence reports from Dr. Perrin's group that will give us the opportunity to make a decision about whether or not we want to recommend or not recommend. I think the first substantive part of the discussion for the Process Workgroup is that we were a little uncomfortable with just those two decision points because we worry about the times where the strength of the evidence isn't strong enough for us to be certain and yet there's some promise in the condition that makes us uncomfortable in not recommending it or waiting longer. So that's kind of the setting I'd like to start in.
In the other evidence-based groups we look at, our preference is to have direct evidence or a randomized controlled trial, that screening for a disease or a condition leads to improved health outcomes. And we recognize that that is unlikely or maybe extremely unlikely in the case of these rare disorders.
So what we're trying to do is put together an approach that will allow the workgroup to use indirect evidence to put together a chain that, with a level of certainty, will allow us to say, yes, we should add the condition; no, we should not add the condition; or one of these two kind of states in between that I'll talk about in a minute.
So the six questions in the nomination list look a little like what the other evidence-based groups use as what we call key questions to organize the literature search around. And so I'd like to talk about the key questions that we have discussed so far in the group putting together the decision-making process.
And the first question is, is the condition well-defined and important, which I think mirrors number one, the nominated condition is medically serious. And again, I think that most of that will have occurred before we ever send a recommendation to the Evidence-Based Review Group because we'll be making the decision based on the nominating form.
I think this next question, which we need to talk about, is what do we know about the natural history of the disease and what do we know about the treatment history of the disease. So I think flushing out the evidence about what is known about the condition, its spectrum, and whether or not there's sufficient evidence or at least hopeful-enough evidence that there's an effective treatment available will be an important issue. And that's a key question that isn't currently in the draft that we didn't send around that I've been working on since our last discussion.
Then we kind of move into a set of questions that look very much like the ACCE questions that are currently used by EGAPP in their methods. And EGAPP is the Evaluating Genetics Applications for Practice and Prevention group that I think Al Berg still chairs. Isn't that right, Al?
DR. BERG: I do. Thank you.
DR. CALONGE: And so the first question in that set is, does the test have sufficient analytic validity? Now, this is a question that we find more important in these metabolic tests and genetic tests as the laboratory methods might vary from laboratory to laboratory and there are things such as home-brewed tests, et cetera, that the secret of population screening would depend on the replicability to other testing centers or laboratories. So while this is not normally a question that the Preventive Services Task Force asks, it is very important in both metabolic and genetic screening. And the idea is that you ought to make sure that the test is actually measuring what it's supposed to measure and that it could be replicated in other laboratories.

And I've asked Dr. Rinaldo to take the lead in writing this section. I've drafted the section that is based primarily on EGAPP's genetic testing with some high level discussion of metabolic tests from tandem mass spec screening. And Dr. Rinaldo has agreed to kind of flesh this section out. But we want to make sure that the test has the simple values of accuracy, validity, reliability, and replicatability across laboratories.

Now, analytic validity is different from clinical validity. So clinical validity is really the test results translate to disease. And so that's where you start to get into the other issues about penetrance and other parts of whether or not, if a person is a positive, first of all, are they a true positive, and second of all, are they being diagnosed with a condition that's going to require treatment, or is it on part of the spectrum what would never require treatment, or in the case of a genetic test, is it only an increased risk of disease and not a disease at all. So, therefore, clinical validity will have kind of different attributes whether we're doing genetic testing in newborn screening or metabolic testing in newborn screening, but a lot of the issues around false positives, false negatives, and overdiagnosis are issues that I think we'll need to bring into the clinical validity discussion.

And Piero has gone as far as to say we might try to work with consistent cutoffs for the clinical positive predictive value/negative predictive value or kind of an acceptable level of false positives that we're willing to accept in diagnosing a condition in a newborn. And those are discussions that I think we have just started on and haven't gone very far because your willingness to accept a false positive may often be based on how onerous or risky or expensive the treatment is, or are there other harms associated with making a false diagnosis.

So that's the issues of clinical validity.

And then finally, clinical utility comes to the issue if you actually do the test and then treat those who are positive, do you make a difference in terms of important health outcomes. And in the draft -- and when we send it around -- you can actually see it now, if you wanted -- there's a list of health-related outcomes for genetic screening that the Secretary's Advisory Committee on Genetics, Health, and Society has put together in their report, "Oversight of Genetic Testing." And it has four major groups of health information impact, therapeutic choice, patient outcome impact, and familial and societal impact. So if you've looked at that report, you've seen those outcomes, and I think our job will try to be to weigh those outcomes in terms of the potential down sides to the testing.

So that gets us to our final part of decision-making. We'll have the information to answer these questions about the importance of the test, the availability of treatment, the analytic clinical validity of the test, and what evidence we have on clinical utility. And the decision we need to make hinges on trying to weigh benefits and harms. In a lot of the cases, it will be potential benefits and potential harms.

So we'll be using, I believe, estimates, or the best evidence available I guess is the optimistic way of looking at it, looking at the up side of testing as well as the down side of testing. Weighing those two, we will have to make a judgment based on whether or not we think the benefits outweigh the harms. And you could greatly outweigh the harms, as we believe we are right now with PKU testing, but you may have more closely balanced benefits and harms, in which case I think we'll have to almost look at those on a case-by-case basis to try to think of how to push our decision one way or the other. And there may be areas or there are expected to be areas where the harm is extremely small or is zero -- I'm sorry. The net benefit is extremely small or zero, or even more harmful than beneficial where we don't think we should recommend the test for addition.

We need to apply those decisions of net benefit with a level of certainty. We can either be very certain or moderately certain or uncertain. And I would kind of lump any moderate certainty or above together to say, yes, we think we're unlikely to be making a mistake. In the uncertain area, we're really in that insufficient evidence, and that's an area where we need to have additional choices on what we're going to do with the final outcome.

So I'm going to close by trying to describe *[1B flip] to add or not add.

The first would be that we believe the magnitude of net benefit is at least significant, so that we believe

that doing the testing will lead to more positive health outcomes than it will lead to any adverse outcomes. And our level of certainty is sufficient. So if you have sufficient certainty of significant net benefit, we would recommend adding the test to the core set.
On the flip side of that, we could have sufficient certainty of zero benefit or even net harm; that is, doing the testing actually does more harm than good. And for those cases, we would recommend not adding the test to the core set.
So those are the easy ones. Then we are into the insufficient evidence area.
So in talking with the group, we believe there will be tests that will have potentially significant net benefit, but the research isn't finished yet or that it doesn't meet our criteria for saying the evidence is adequate. But we believe the potential for net benefit is compelling enough to add the test now with the commitment to evaluate the experience with the test over time. So I'm suggesting we have tests that are added with a provisional status with the express expectation that the advisory committee will update looking at the evidence in the future to make sure that we've made the right decision or remove the test from the core set if future evidence suggests that we've done the wrong thing. So that's the provisional status.
And then the last status would be we just don't know enough about the net benefit. We really need more evidence to even make a decision about adding something to a provisional status, and instead we recommend pilot studies.
So let me go over the recommendation choices one more time, and then I'll open to questions.
We can recommend the test to the core set because of sufficient certainty of significant net benefit.
We can recommend not adding the test to the core set because of sufficient evidence of zero benefit or net harm.
We can recommend adding the test with provisional status where the certainty is insufficient, but the potential for net benefit is compelling enough to add the test now with the commitment to evaluate the experience with the test over time.
And then finally, recommend not adding the test now but instead recommend pilot studies.
With that, Rod, I'll open the floor for questions.
DR. HOWELL: Questions of Ned? You had a very lucid presentation, Ned.
DR. CALONGE: Well, I have a great slide set. You guys just don't have it.
DR. HOWELL: Well, once you get connected, we'll have it made.
DR. BOYLE: This is Coleen. I'll ask a question.
Ned, I have the benefits of having your --
DR. LLOYD-PURYEAR: Coleen, can you speak up a little bit please?
DR. BOYLE: Sure. Sorry.
I have the benefit of having what you had drafted last time for our committee meeting, which I missed.
DR. LLOYD-PURYEAR: I still can't hear.
DR. BOYLE: I guess in looking at it on paper, I see a challenge between the two recommendations, the provisional status and then the one with pilot studies, and trying to distinguish between those two I think is going to be a particular challenge. And I see us perhaps leaning more toward sort of a provisional status. Had you thought or had the workgroup thought, even though I'm a member of it, but I missed the call, of trying to combine those two somehow and calling it all pilot?
DR. CALONGE: You know, it's interesting. I think we saw more of a separation of those two, and I guess I was heartened by the people on the group like Piero who do this work who felt that it might be a little easier to separate those out. And I think it's a reasonable question.
I think you might say that there is something that we feel is so compelling that it should be added and that we think that waiting for pilot studies would be the wrong decision. And I think that's what that provisional group was for.
I think all of us would prefer to have pilot studies and have some evidence in our pocket before we add something to the list, but both the groups I've worked on, EGAPP and the task force, have always talked about tests where the evidence wasn't there but we were pretty optimistic that when the studies were

done, they would be positive studies. I was trying to capture that insufficient but optimistic category in this provisional issue and trying to operationalize it in a way that would make sure we kept ourselves from being wrong, but didn't slow the process of adding conditions to the list.
DR. BOYLE: I guess I see a little bit of the distinction there for EGAPP, and that's a clinical test versus this is sort of a public health mandate or a public health program.
DR. CALONGE: Right.
DR. BOYLE: So I don't know.
DR. CALONGE: Well, I think it's a reasonable point of discussion. I wonder what other committee members think.
DR. TROTTER: This is Tracy.
I am on your subcommittee, as you know, and I was on our last meeting when we discussed this decision matrix and came up with the wording for it. I really do think in the kinds of things we're likely to be dealing with, the evidence is frequently -- and this is I guess probably true of molecular genetic testing in general. So it expands to EGAPP as well. The kinds of evidence, as we're finding, are frequently small in number. Often one researcher or two researchers are really the only people who really know about it. And yet, I think there are differences in being compelled to not leave the test off for any longer period of time but not so sure that we say it's in that first category.
We talked about it a lot at our last meeting. I really do think the four possible recommendations is probably -- I think it's the best way to sort of meet that challenge for now.
DR. CALONGE: There was a different criticism I heard from someone else about the provisional status, that once you put something on, it's extremely hard to take it off. And I think that's just something we will have to be committed to be willing to do. Colorado, after 20 years of not a single positive test, took one of the core set off the list when were doing it, not tandem mass, but the other methodology. And I think that being willing to look at those issues is important.
DR. BOYLE: I'd just mention one last thing for me, and this is an important distinction. Maybe I'm reading a little bit too much into this, but I see sort of the provisional status as being something that's a public health function, so exempt from informed consent, whereas I see the pilot as being within the context of informed consent and research. Again, I feel like some of these issues that we're talking about are very gray issues, and there is a sort of ethical/legal aspect of informing people about the lack of knowledge.
DR. LLOYD-PURYEAR: Coleen, I'm sorry.
DR. BOYLE: No. I'm sorry.
DR. LLOYD-PURYEAR: I think it's that you fade and what's happening is the transcriptionist can't hear.
DR. BOYLE: Okay.
DR. CALONGE: Well, I can repeat what she said.
DR. BOYLE: Thank you because this is my phone. I don't have another choice here.
DR. CALONGE: She said that there seems to be a bright line in terms of research versus public health between adding something with a provisional status and recommending something for pilot studies such that for the pilot studies, we fully inform people about the uncertainty of the knowledge base behind the testing strategy. And I think that's a reasonable issue to talk about.
In the provisional status, it might not have met the bar for us to say, yes, we're certain we should add this because the evidence is adequate. We're saying we think we should add it because we think the down side of not adding it is great enough, we're unwilling to wait.
And the question I think Coleen was asking is the ethics of adding a test in a public health population-based strategy where there is still a level of uncertainty but we're not informing patients of that.
PARTICIPANT: Ned, I hate to even bring this up, but how many of the current panel do you think would meet that criteria?
DR. CALONGE: Yes, I think that's a good question.
DR. SKEELS: This is Mike Skeels.
I just want to support what Coleen is saying. I think she's making a really good point.

On the other hand, remember, there are 51 different jurisdictions that will have to make the decision about what is and isn't screened for in their population anyway. So even if it makes the provisional list, there's nothing binding about that. We'd like to work toward a more uniform national panel, but I don't see it as something that would happen overnight.
DR. CALONGE: Well, and it may always have that star or asterisk associated with it. I guess this is a good discussion for me because it says we may use that category rarely.
Al, I hate to pick on you, but you thought about insufficient pluses for a long time.
DR. BERG: Well, what I can say is that this discussion is being held with lots of other evidence groups in many other clinical domains in this country, and I think everyone is struggling with the criteria that you use to make a recommendation not only clinically but for a public health intervention. I think in general the bar keeps being raised, and it does raise that interesting question about, as this group considers its criteria, what you do with things that have already been reviewed but now, with new criteria, may not have met the same standards.
So what I can say is I can sympathize, but I'm too new to this committee to -- it would be presumptuous of me to make a suggestion at this point, but I do think the general direction of the discussion is right at the cutting edge of where these reviews need to be. And the question of putting some kind of status on it that lets the horse out of the barn is a big question for those of us in clinical medicine and public health in general. So that bar keeps being set higher and higher in the groups that I at least have seen working on this problem.
DR. HOWELL: Any further questions for Ned?
So, Ned, what are your specific plans for the document you're working on?
DR. CALONGE: Well, I had a specific and, I would say, a very good recommendation from Michele to flesh out kind of the earlier questions, is the disease important, what's the natural history, and is there a treatment available. So we will do that.
I think I need to rework this provisional stuff a little bit to make sure that everyone from the public health and the ethical standpoint feel that they can be comfortable with it. I think a lot of it will be in the implementation, but I do think there will be conditions that we will recommend that we're all feeling good about but we wish there was a little bit more evidence for. I hate to not have the ability to say we really think you should screen for those even though we can't quite get the evidence together to meet our criteria.
And I guess spending some time to work on that, having a second round of the draft document to the rest of the committee probably within a week or during the national convention when I'm watching CNN all day. I will commit to that and will try to get that draft vetted by the group and then out to the rest of the committee for review.
DR. HOWELL: I think that your committee, during its telephone conversation, had a lot of discussion about the provisional designation, and I think there was a considerable sense that that did have relevance. And I would urge you to continue to do that but take into consideration the important points that Coleen talked about.
DR. LLOYD-PURYEAR: Ned and Rod, Ned won't be there at the October 1st or 2nd meeting because of a conflict.
DR. CALONGE: Yes. I'm trying to see if I can draft Nancy Green to present in my place.
DR. LLOYD-PURYEAR: Well, that's what I was going to ask. Do you want to ask somebody else to present?
DR. CALONGE: Nancy, is that something -- if you and I work close enough together and I write the slides?
DR. HOWELL: Nancy, are you there?
DR. LLOYD-PURYEAR: Nancy is still there.
DR. GREEN: Can you hear me now?
DR. LLOYD-PURYEAR: Yes.

DR. GREEN: I'd be happy to do that, Ned.
I just want to point out we have to be careful with nomenclature because I think your document and the discussion reflects accurately the struggle to kind of make gradations, which is very important. But the states may interpret that differently. I'm thinking of Wisconsin with its current pilot on SCID does not require informed consent. So we just have to be careful with the semantics.
DR. CALONGE: We may not use those words. I was thinking about the risk-benefit of putting those in the document.
DR. GREEN: Yes, happy to do it.
DR. HOWELL: So Ned will have an opportunity to circulate his document to his committee and the committee as a whole, and then Nancy will have a chance to present that at the October meeting. So is that where we are with this?
Any further comments that should be in Ned's document?
DR. CALONGE: I'm sorry you all didn't have it, but I'll get you a version as soon as possible. And I have to sign off now.
DR. HOWELL: I guess Ned we will miss. Back to the mountains of Colorado.
Our next presenter is Piero Rinaldo, who is obviously a member of the committee, and Piero is going to go through the Nomination Review and Prioritization Workgroup and report on the candidate conditions of Krabbe disease and Fabry disease. I think that all of the members of the committee got Piero's slides. Is that correct?
DR. RINALDO: That's correct.
DR. BOYLE: Yes. I did not.
DR. HOWELL: You got an email today, Coleen. So you might check your email today.
Piero, are you ready?
DR. RINALDO: Sure.
DR. HAUSMAN: I just forwarded the email to you, Coleen. This is Ethan.
+ DR. RINALDO: Well, I guess this being the first time that we do this, and I sort of improvised on the format of this presentation. It certainly shouldn't take 45 minutes.
So besides the title slide, the second slide I think is actually timely because it goes back to some of the points raised by Nancy earlier and some of the questions asked by Coleen and others. And I realized that my recollection -- and I emphasize this is a personal recollection -- of the status of nominated conditions -- that's the second slide. And I realized that probably based on something I heard from Michele is not correct. What I did I think was a correct understanding that the Review and Prioritization Workgroup essentially decides to make a recommendation to the full committee, and that will basically have to be done. And so on the fist three conditions, SCID, Pompe, and Krabbe, I think I probably had it right for SCID and Pompe, but based on what Michele said, apparently there has not been a vote of the full committee to send Krabbe disease to the Evidence Review Group. I was under the impression, but obviously I'm mistaken. So I can certainly edit this slide to make it correct. Perhaps that will happen today. I don't know if we have time later.
Then there are two other conditions -- actually three. Fabry has been mentioned earlier. According to the nomenclature used by Nancy, it was declared not to be ready to proceed to the Evidence Review Group. I thought that the same had taken place -- but perhaps we are not there yet with the process -- for the nomination of Niemann Pick. So my presumption was that, again, the next level of action was supposed to happen today.
I also heard that there is another application, another nomination, brewing, and that's for SMA. Maybe I misunderstood that an application has been submitted already to HRSA and is being reviewed. Michele, please tell me or let me know what is all wrong in this.
But I did this really mostly for myself just to get a sense of where we are, and clearly the time line for the two top conditions, SCID and Pompe -- probably something we'll learn more today from Jim Perrin. But my job is to really summarize what we have talked about and discussed at the Review and Prioritization

Workgroup for Krabbe and Fabry.
The next slide is actually a step back in time, and it's a slide that shows the scoring of all the conditions considered by ACMG/HRSA Expert Panel. I hope you can see the animation. There is the original figure with an animation that actually highlights, let's say, at the time the not exciting performance of the lysosomal storage diseases. And in fact, you can see that they all score pretty much low. Krabbe actually happened to be the lowest scoring condition.
The next slide -- the next two slides actually show the fact sheets that were part of the ACMG report. This is a summary, again, of all the criteria used there to evaluate the condition, the test, and the treatment. And clearly here, the show stopper for both Krabbe disease and Fabry disease -- and you should see highlighted by a red rectangle -- is that at that time the consensus was that there was no sensitive specific population-based screening test available and validated.
Because I will touch on it later, I also want you to look on the right page. There are the criteria of least consensus, and I will revisit them later. So you can just see for Krabbe disease are benefits of valid identification and confirmation of diagnosis.
On the next page is the fact sheet for Fabry disease, and again, the conclusion was that there was no clinically validated test. However, in the case of Fabry disease, there was a mention of a specific reference out of the Seattle group that there are tests. Well, at the time, the definition was in clinical trial. In the case of Fabry disease, the two criteria where the least consensus was observed -- and you know, there were about 50 responses to a survey for each of these conditions -- was actually in the incidence. And this also will be an interesting point to touch later.
The next slide shows the algorithm that was included at the end of the executive summary of the ACMG/HRSA report, and that was really to emphasize the fact that this is now, but the future may be different. And there is a red animation that highlights the bottom right corner of the algorithm to say, okay, there is no test or even condition deemed to be only secondary targets, but there are arrows that point to the possibility that this condition may be reconsidered based on the description. This is, again, a point that was touched earlier about new things happen all the time. So it could be new screening methods and new treatments or a better understanding of the natural history. So that really was meant to activate that sort of back to the top system.
Yes? Sorry. I thought somebody wanted to say something.
And it obviously means that significant new findings can and should trigger reconsideration. Obviously, it's not going to be done by the same process used then, but by the evidence-based review. And you should see a box appear in there on top.
So the strategy was clearly delineated at that time that this is a continuum and is really what is feeding the activities of the things we're doing now.
The next slide is just to remind, I don't think members of the committee, but perhaps somebody among the public that may not have seen the paper where the first author was Nancy Green where we are sort of describing the process and some of the things we're doing in this very moment.
The next slide is a simplified version of the process. You have seen the slide made by Nancy earlier. It just really shows how the nomination goes through administrative review. Then eventually it comes to the advisory committee, and then there is interaction and we talk about the bidirectional arrows, and eventually leading to a decision by the advisory committee and leading to a recommendation to the HHS Secretary.
The next, if you sort of click or move the arrow, you will see this red circle with a number 1 appearing. That's really one of the two steps that were deemed necessary to be added to the process, and that, indeed, is the Nomination Review and Prioritization Group. The concern was that it could certainly happen that within a relatively short period of time, multiple conditions could be nominated and clear the administrative review.
And at that point, we are all aware that the Evidence Review Group and Jim Perrin really cannot handle an infinite number of nominations, and probably not even a double digit number. And so it was wise to

think that there should be a process to decide in what order this condition will be sent to the Evidence Review Group, but also one of the possibilities -- and that's what we're here to talk about -- was that something might be sort of put on standby or sent back for the time being because this group felt that you may reach a conclusion that not really everything seems to be there. And certainly this is not * in any way but is more of a measure of appropriateness in terms of timing.

There is a group here. The next slide shows the members. We have sort of a * consistent participation, but overall, I think we're being able to do what we're supposed to do.

The next slide actually shows at the bottom a scan of the Krabbe nomination. The nominator was Micki Gratzke on behalf of the Hunter's Hope Foundation, although my understanding is she is no longer associated with that group, and I don't know if this is in any way relevant. But anyway, it was submitted in September 2007. The administrative review was concluded in January, and I believe was reviewed by the Prioritization Group in March.

The point I want to make here is that clearly, despite the effort to really try to encourage people to stick to the format, you can see this application was spread over four pages. Again, I think it's something we might want to be a little stricter. For example, if you go to the next slide, although it's completely unrelated to this presentation, but I was really impressed by the way the SCID nomination was put together. It was just two pages, packed with information, and frankly, I think is really something that should be used almost as a template, as a model to encourage others to follow.

The next slide is again a scan of the recommendation to the advisory committee. Clearly, it is not readable. Maybe you can try. But what I really want to highlight -- I hope you can see the animation that brings up a simple table where it summarizes the questions being asked and addressed and, again, is a totally personal interpretation.

But the conclusion was that the condition, yes, is medically serious. Yes, there is prospective more than pilot data at this point actually. There is now a population-based screening going on in New York. Yes, the clinical spectrum is well described. Again, on the positive side, certainly we have now good data about the performance characteristic of the screening test. I didn't interject earlier in the presentation by Ned. This goes back to the concept of analytical validity and having some standards for performance metrics, which is something I very strongly believe that it really should be done in an objective and consistent way.

On the other side, there were clearly issues about the clinical spectrum, ability to predict a phenotypic range, the identification of cases most likely to benefit from treatment, and finally, the defined and available treatment. I thought pretty much in a short summary, the group felt that there is evidence and certainly questions. And so I sort of decided to punt and say, well, this is going to be up to the Evidence Review Group to decide.

In the end, the highlight shows at the very bottom, and if you again click, the next animation is just * what the bottom of the form says. The disorder meets the criteria for evidence-based review and recommend a clarification of identifying those infants most likely to benefit and the efficacy of treatment. So there were two specific points that the Prioritization Working Group felt it was important to make again in sending this to the next level. And according to Michele, this still must be formally voted and approved by the committee.

And I highlighted those because the next slide is actually -- again, going back to the expert panel survey, it's interesting because you see one of the criteria listed here that is in the middle highlighted with a green background was, indeed, the benefits of early identification you see where the scoring was 100 points or whatever units for evidence of clear benefits, 50 for some benefits, and 0 for no evidence of benefit.

So going back and pulling out the data, you go to the next slide. It turns out that already at that point, there was clearly an indication here of a lack of consensus between the people who responded to the survey. You see that the three levels were equally represented, 0, 50, 100. And also it was interesting. Actually somebody felt to create an intermediate category of 25. So I think that the key issue was evident and clearly recognized already at that time.

Now, Fabry again was nominated by Maryam Banikazemi and Fabry Information and Support Group, again submitted at the end of '07, reviewed pretty quickly, less than a month, and again reviewed by the Prioritization Group -- I'm sorry. March, not in "Mare." Again, I think a form could have been formatted a little better, but maybe I'm just too much of a perfectionist. But I certainly hope that they can be kept to the recommended format of two pages because one of the things really was to avoid very extensive descriptions and really trying to encourage nominators to condense information here.
The next page is again the scan of the summary of recommendations to the advisory committee from the Nomination Review and Prioritization Group. Again, if you go to the next animation, you can see now, comparing the impression of the working group comparing the two conditions. Clearly here, the most notable differences are, one, that differently from Krabbe disease -- right now prospective studies, pilot studies have not started in the United States. We know they've started in Italy, in Taiwan, and in Austria, but that has not yet happened, unless I'm missing something, in the United States.
On the other hand and quite differently from Krabbe disease, we have an FDA-approved treatment. So clearly, I think that this shows the differences with the current stage of evaluation of sort of more of an evaluation of sort of progress toward implementation of newborn screening.
On the other hand, there are significant issues related to the clinical spectrum of the condition and the correlation between phenotype and what type of clinical presentation. And you can see those three boxes at the bottom also including the identification of cases most likely to benefit from treatment.
So the recommendation I actually tried to summarize to make it fit in one page, but you should see an animation that on top has underlined and in red fonts is that it is not recommended. And maybe, Nancy, we probably should agree it is not recommended or not ready. I don't know if it's just a matter of semantics. It is not recommended this condition go forward to the expert review group at this time.
And the four major issues were highlighted there. The late and variable onset of disease. Unclear if those at highest risk of serious symptoms can be discerned in newborns. The lack of published data of preventive treatment early in life. And the undetermined risk of immunological response to ERT. I think the *outcome was that premature treatment may lead to immunological response and might actually become -- could neutralize the effectiveness of treatment at a later time.
Also, I think the point is that a prospective study of screening and therapeutic intervention is needed to demonstrate the benefit of newborn screening. This goes back again to the discussion led earlier by Ned about where you set the threshold for significant evidence or adequate evidence. To me, I think it's still an important point of the fact that still in the United States this is not yet operational in any state that I know of.
The next slide is just something I took straight out of OMIM and more to really emphasize the fact that if you just scanned this remarkably long and most intimidating list, there is clearly a lot of signs and symptoms. They are clearly things that *want us back to seeing adult patients. And so we talk about hypertension. We talk about heart failure and all sorts of things.
This actually brings back one of the key observations. The next slide shows the title of a paper probably most people in the field are aware. It's the paper published in 2006 in the American Journal of Human Genetics by Marco Spada, Alberto Ponzone, and their colleagues, in collaboration with Bob Desnick.
The first animation actually brings up the full abstract. And the next one highlights a specific section, and that's the one that shows that they clearly have a total of 12 cases picked up in this pilot study. It was perhaps a remarkable finding and probably exceeding any expectation. And some were clearly at the genotype level, indicating late-onset patients.
The second animation brings back another section, and I'll just quote it. "The incidence will be approximately 1 in 4,600, 7 to 1 ratio of patients with the later-onset versus classic phenotypes." And that goes on. "Results suggest that the later-onset phenotype for Fabry disease is underdiagnosed."
Now, this brings back one of the points. The next slide is actually the criteria and scoring system of the ACMG survey. There was a scoring for incidence of condition on the top. And it's interesting that if you go to the next slide that shows each and every one of those red dots represent a different respondent. And

it's interesting. On the one hand, there was significant lack of consensus, but it turns out that there are five individuals. The one at the top, they gave an incidence greater than 1 in 25,000. They probably had it right. And so it's interesting to see that the group that was numerically the smallest is the one who actually was closest to the truth.

So to conclude, I show you again that simple summary with the green and orange boxes. Again, the conclusion of the Nomination Review and Prioritization Group is to send forward the nomination for Krabbe disease, again I understand for a vote by the full committee, and to sort of hold -- I don't know what technically is the next step. Well, to recommend holding Fabry disease. Again, I presume that the full committee is certainly in a position to override this recommendation, but I'll wait to hear from Rod and Michele what's exactly the process.

And going back to some of the uncertainties that were discussed earlier, some of the comments, the last slide is a bit of a provocative one, but I think it would be one of the most challenging, also most important tasks that this group and the whole committee could undertake because this late onset dilemma, if you want to call it that way, is certainly not unique to lysosomal storage diseases. And I have on this slide the abstract of a paper that appeared in 2007 in Circulation where it clearly shows that -- you know, the title is pretty self-explanatory -- treatment with statins in children with familial hypercholesterolemia, the younger, the better.

And then there is a cartoon. Well, it's actually a picture. It was advertising for a company that I found intriguing that shows a pretty chubby and beautiful baby, and the legend at the bottom says, "Heart attacks should be treated early. Say, 50 years before they happen."

So it's important I think, and I wanted to have this slide to say that it's important we keep in mind that our discussion about what to do with conditions where there is a component of late onset is something that is not really unique to lysosomal storage diseases. And we'll have to have a broad understanding and really consideration of all these conditions because I really believe that it is extremely important that whatever we do has to be done in a fair and consistent way.

And that's all I have, and thank you.

DR. HOWELL: Piero, thank you very much. And let me remind the committee, members got an email from HRSA yesterday or today that had actual copies of the nomination form and also summaries of Piero's committee, both the recommendation about Krabbe and about Fabry disease.

I would suggest that we begin. We have not formally voted about Krabbe disease before, and I would suggest we begin our discussion right now with Piero's first recommendation about Krabbe disease.

DR. LLOYD-PURYEAR: Rod, this is Michele.

Just to refresh everyone's memories about what happened with the nomination review process before, to go into the minutes from the January meeting, and on page 40 -- and you don't have to do it now, but just after the meeting, you can go through with what happened with Krabbe disease. In fact, we didn't get that package completed until right before the January meeting. So the internal review group did not review that condition with a final recommendation until March, and we have not had a meeting since January.

DR. HOWELL: Right.

DR. LLOYD-PURYEAR: So the committee has not voted on Krabbe yet.

DR. HOWELL: Right, fine. And you've heard Piero's recommendation and each of you should -- well, each of you does have a copy of the actual Nomination Review and Prioritization Workgroup recommendation.

Can we have your comments about this, please? No comments about the recommendation to send the material on Krabbe disease to the Evidence Review Group?

DR. VOCKLEY: This is Gerry Vockley.

It's a very well-reasoned recommendation, and I think we should follow it.

More broadly, we need to come back to, maybe after this discussion, the issue of the terminology that we're using because that should be standardized. I don't think it's a trivial point. Whether we're saying not send it forward or rejecting it is more than a matter of semantics.

DR. SKEELS: This is Mike Skeels.
I agree. I think that someone should make a motion to move this forward as recommended.
I would also like to echo the concern about terminology, although this is probably not what you meant. We need to use the terms, "sensitivity," "specificity," "false positive," and "false negative" and "predictive value," in the same way throughout all of the different analyses and recommendations. I don't want to get into that now, but I just hope we can work toward uniformity there.
DR. HOWELL: Gerry has made a motion that we recommend.
DR. SKEELS: I second it.
DR. HOWELL: And Mike seconded that, I think.
Is there further discussion about sending the Krabbe recommendation forward?
DR. BOYLE: This is Coleen.
I have just sort of a clarification about the procedure. Piero, I think you did a very nice job on your presentation. Thank you. I finally got it to open up.
Again, this is just in general. When your committee is reviewing the nomination, are you really sticking to what is in the nomination form and the references that are provided by the nominator?
DR. RINALDO: I believe so. What we did was basically we had a series of conference calls. Ahead of the conference calls, we always see the full printed packets.
DR. BOYLE: With the --
DR. RINALDO: And all the references.
And then each member -- again, we didn't have complete participation, but all members were submitting their own comments using the form devised by Nancy. And Michele did compile in a common document all the recommendations, and that was what was discussed in conference calls to a point of reaching an agreement.
I have to say that I agree with Gerry and others that we better come up with a standardized nomenclature.
The process -- I do not recall any formal dissent in the conclusion. There was discussion in the group, but I believe we discussed this in January about the prioritization.
DR. BOYLE: My one concern -- I guess that's why I bring this up and also look at the date that Krabbe disease was nominated. It's almost a year ago now. It was 9/9/07 on the form. And clearly the major population-based or the prospective data comes from the New York experience, and I feel like there's a lot more information in there. Again, this is more of a procedural issue that we're reviewing something where -- I mean, at least I heard a presentation by someone from the New York group back in March, which sort of raised issues of concern for me, and that all isn't included here. So I'm not quite sure. I mean, that may all come out in the evidence-based review.
DR. RINALDO: That's the idea. The idea is really -- I believe that around March we did get an informal update on the status of the New York screening, and that was taken into consideration in our discussion. Now, in terms of the effectiveness of treatment, yes, probably you have heard -- and I think that there was a very interesting discussion. At least the last I heard was at the ACMG meeting in Phoenix. So clearly, there is a lot of relevant information that is becoming available, but personally I think this is what the Evidence Review Group --
DR. BOYLE: When you folks reviewed this, you had knowledge of that information.
DR. RINALDO: Well, this was happening, Rod, just before the ACMG? Michele, maybe you can tell me what was the date.
DR. LLOYD-PURYEAR: No. You did not have the evidence. I think there were rumors, but this all happened before ACMG.
DR. RINALDO: So I think that probably some of the more recent data about treatment effectiveness we were not exposed to. But that really goes with the time.
I think what is a bit unusual in this year, again, the schedule of our interactions of the committee have somewhat had a few hiccups.

DR. BOYLE: Of course, of course, and I'm not criticizing that at all. I was just trying to see whether or not that would have changed the decision process.
DR. LLOYD-PURYEAR: Except that, Coleen, going forward for an evidence-based review does not mean that the internal review group is saying you should screen for it or not screen for it.
DR. BOYLE: I realize that.
DR. LLOYD-PURYEAR: Yes, but I think --
DR. BOYLE: If the nomination form was more current and included that information, would a different decision have been reached?
DR. HOWELL: I doubt it as far as going forth to the evidence group.
Is there any further discussion? Are there any more questions or anything?
(No response.)
DR. HOWELL: We've had a nomination and a second, and I think we're ready to vote on this. Michele, I think you'll have to call the -- I think the only way we can vote is for you to go through the voting members and ask for their recommendation.
DR. LLOYD-PURYEAR: I know Ned has gotten off the phone to go on his vacation. So I'm going to begin again with you, Rod.
DR. HOWELL: Yes.
DR. SKEELS: Rod, this is Mike Skeels.
Could either you or Michele read the motion that we're voting on to us?
DR. LLOYD-PURYEAR: The motion is to send the Krabbe nomination package forward for evidence-based review.
DR. HOWELL: Is everyone clear about that? It's basically to send it forward to the ERG, Jim Perrin's group. And I would vote yes to that, Michele.
DR. LLOYD-PURYEAR: Jana Monaco? Jana?
MS. MONACO: Yes.
DR. LLOYD-PURYEAR: Piero?
DR. RINALDO: Yes.
DR. LLOYD-PURYEAR: Mike Skeels?
DR. SKEELS: Yes.
DR. LLOYD-PURYEAR: Tracy Trotter?
DR. TROTTER: Yes.
DR. LLOYD-PURYEAR: Gerry Vockley?
DR. VOCKLEY: Yes.
DR. LLOYD-PURYEAR: Duane Alexander?
DR. ALEXANDER: Yes.
DR. LLOYD-PURYEAR: Coleen Boyle?
DR. BOYLE: Yes.
DR. LLOYD-PURYEAR: Denise Dougherty?
DR. DOUGHERTY: Yes.
DR. LLOYD-PURYEAR: Peter van Dyck?
DR. van DYCK: Yes.
DR. LLOYD-PURYEAR: And that's the members.
DR. HOWELL: So we have a unanimous vote of the members on the call, and so we will recommend that that go forward to the evidence-based group. Thank you very much.
And now, Piero, we come to your second document which is that of Fabry disease.
DR. BOYLE: I'm sorry to be the interjector all the time, but one last comment on Piero's recommendation. There was a second part of the recommendation to recommend clarification --
DR. RINALDO: These are not my recommendations.
DR. BOYLE: Your workgroup. I'm sorry.

DR. RINALDO: And what was your question?
DR. BOYLE: It was, the second part of the overall recommendations for the workgroup was to recommend clarification of identifying those infants most likely to benefit and the efficacy of treatment.
DR. RINALDO: That was more of a placeholder, if you want. I'm pretty sure that we wanted to convey in the language of the recommendation that those are issues of paramount importance in our opinion --
DR. BOYLE: And I would agree with you, Piero.
DR. RINALDO: -- when it comes to the work to be done by the Evidence Review Group.
DR. HOWELL: And I think we would all agree with that, Coleen. Thank you very much for bringing that up.
Any more comments before we go to the Fabry issue?
Piero, do you want to make a few general comments about Fabry?
DR. RINALDO: I really want to speak to what I said repeatedly before, that this is not a race, and it's important to really make decisions when there is evidence that comes directly from the United States. And so to me, to proceed with -- also, being aware of how precious is the time of the Evidence Review Group, I really hate the idea of having them going through their effort and missing a critical piece of information.
To me, this nomination -- I don't want to use the word -- is "premature," but I think this nomination must be fortified by evidence of a prospective population-based pilot screening somewhere in the United States. Until then, I think it's probably not the best use of the time and effort of the Evidence Review Group to work on it because although it is true that -- I believe it's one of the slides by Jim Perrin -- to identify gaps, but this is really a very large gap.
And that personally I don't think in any way should be perceived as a negative evaluation of the chances of Fabry disease to be included in the newborn screening program. The reality is that the data coming out of Italy are so provocative and really with so far-reaching consequences, that at a minimum they should be reproduced.
And so for these reasons I am comfortable with the conclusion of the Prioritization Group that at this time we should not activate the Evidence Review Group. And I think that the message should be to the people who have an interest in this condition to basically focus their effort and energies and resources to have a pilot study starting in a U.S. program.
DR. HOWELL: Comments about that? No comments on Fabry?
DR. ALEXANDER: This is Duane Alexander.
I think that this case illustrates the wisdom and the value of a two-committee/two-step process, an initial screening process and then a more intensive evaluation one. And I think in this case, the committee has done its job well and acted wisely, and I think we should follow their recommendation that this one is not yet ready for prime time review by the external Evidence Review Group. Its time may come, but in order to get to that point, the advice of the review committee is that there needs to be a prospective trial somewhere in the U.S. And I think that's sound and I think that's what we should go with.
DR. SKEELS: If that's a motion, I second it.
DR. HOWELL: So Duane has made a motion that this nomination not be sent forth to the Evidence Review Group at the current time and that the folks working with this proposal be advised to work as best they can on a prospective trial here in the United States that would underpin many of the issues that are here.
Is there further discussion of that nomination? Is there any comment about how this should be worded? We should be sensitive to how we word these motions.
DR. SKEELS: This is Mike again.
I think you said it very well, Rod, that at this time we don't recommend that it be sent forward for the review process but that we consider it to be an important issue that is worthy of study on a pilot basis. I think we need to make it clear that we're not shutting the door on this one, but that we really need more information.

DR. HOWELL: I'm very sensitive to the fact that obviously the folks who did this nomination are knowledgeable and expert in this area and we would like to be constructive. I think that that's the reason that we should say that this is our opinion at the current time, but please continue your work and come back at this point in time.
So far, we've heard obviously from Piero and his workgroup and from Duane and Mike. Are there further comments either for or against this thought?
DR. KUS: This is Chris Kus.
The comment was made that there had to be a prospective study in the U.S. The explanation for that? Would another country's study not be applicable?
DR. HOWELL: Piero, would you comment?
DR. RINALDO: It's not that they are not applicable. It's that, again, we're talking about quite a critical decision, and to me to proceed to make a decision where nobody -- nobody -- in the U.S. is doing it will actually create a dangerous precedent. In other words, there must be something credible going on. And again, it goes back to the maturity of their nomination, not on the merit. I think it's premature personally.
DR. WATSON: This is Mike Watson.
I think there are also going to be circumstances in which it's going to be important that it be done in the United States. There are things like G6PD where dietary lifestyles and things vary considerably between countries, and you get a very different perspective on a disease in Southeast Asia as compared to the United States.
DR. ALEXANDER: This is Duane Alexander again.
I think that what we're trying to encourage here is the Krabbe model where there has been a prospective study in the U.S. in one state, and we're going to get very valuable evidence to assist our decision from that process. And I think that that's the kind of model that we need to encourage and that there is extreme value in doing that in the U.S. in the conditions that we operate under domestically so that we can get the best information on applicability here to guide our decision.
DR. HOWELL: And I would also think that the members of this committee, wearing multiple other hats and not necessarily as the responsibility of this committee, would try to work with groups such as the Fabry group to try to accomplish some of these pilot studies in their regions.
Is there further discussion?
(No response.)
DR. HOWELL: If not, I think that we're ready to take a vote on this. Michele, could you please poll the members of the committee?
DR. LLOYD-PURYEAR: Sure. First, Rod Howell?
DR. HOWELL: I would vote not to send it forward.
DR. SKEELS: I'm sorry. This is Mike. Could you say what the motion is so I know what a yes vote means?
DR. LLOYD-PURYEAR: That the nomination package for Fabry -- that the Fabry nomination package not be sent forward at this time for evidence review.
DR. HOWELL: And I voted to support that.
DR. LLOYD-PURYEAR: And you voted yes to that.
DR. HOWELL: To support that recommendation.
DR. LLOYD-PURYEAR: Jana Monaco?
MS. MONACO: Yes for the recommendation.
DR. LLOYD-PURYEAR: Piero Rinaldo?
DR. RINALDO: Yes.
DR. LLOYD-PURYEAR: Mike Skeels?
DR. SKEELS: Yes.
DR. LLOYD-PURYEAR: Tracy Trotter?
DR. TROTTER: Yes.

DR. LLOYD-PURYEAR: Gerry Vockley?
DR. VOCKLEY: Yes.
DR. LLOYD-PURYEAR: Duane Alexander?
DR. ALEXANDER: Yes.
DR. LLOYD-PURYEAR: Coleen Boyle?
DR. BOYLE: Yes.
DR. LLOYD-PURYEAR: Denise Dougherty? Denise?
(No response.)
DR. LLOYD-PURYEAR: Peter van Dyck?
DR. van DYCK: Yes.
DR. HOWELL: Well, all the members voting have supported that recommendation so that that recommendation will stand.
Piero, thank you and your committee very much. That was a very good exercise. And then in the future we have the Niemann Pick and the SMA nomination which, indeed, is at HRSA, that will need to be looked at.
With that, we're absolutely right on the minute. My clock says 2:59. And so at this point in time, I'd like to call on Jim Perrin who is Professor of Pediatrics at Harvard Medical School and Director of the Division of General Pediatrics and of the Center for Child and Adolescent Health Policy at Harvard Medical School at the Massachusetts General Hospital for Children.
And Jim is going to report on the Evidence Review Workgroup, report on the candidate nominations. Those two are severe combined immunodeficiency and Pompe disease. Jim?
+ DR. PERRIN: Thank you, Rod, and thank you very much to the committee for the hard work and for the help many of you have provided to us in our work so far.
I think you have my slides, and we'll start with the first one. And I will apologize for not having shortened the name of the committee yet, but we will do that in future slides for sure.
As you know, our purpose is to provide for the advisory committee a systematic, reproducible, thorough, and transparent process for gathering, organizing, and analyzing available data concerning conditions that have been sent to us by the advisory committee for in-depth evidence gathering and evidence review.
If you go to the next slide, you can just see the members of our team here. Again, I think many of you have seen this before, but we've developed within our own team in the Boston area -- predominantly in the Boston area -- forgive me, Nancy -- a group that works actively together and things that are really diverse to the backgrounds to the activity that we're carrying out here. But Marsha Browning is a geneticist on our staff, and Comeau is at the New England Newborn Screening Program. Nancy Green has been a very important conduit of information back and forth with the committee and the subcommittee. Alex Kemper is a methodologist and screening expert at Duke. Lisa Prosser, who actually is at Henry Ford Health System now rather than Harvard Ambulatory Care and Prevention with a background in cost-benefit analyses. Denise Queally who is a consumer, and then staff members here on our staff who are working on this project regularly. And Marie Mann has been an ex officio member of our work team.
The next slide. Just to remind you, we have an external advisory group. These people actually will review our procedures, which they've already done, but also will review our reports before we send them off to the committee for a formal examination by the committee.
Again, let me just stress at this point that I am predominantly talking about the processes that we have put into place. I will give you an update toward the end of my presentation about where we are on the SCID and Pompe reviews, what our time line is, as we have learned recently and really begun work on those two conditions in some substantial depth. So much of my talk is really going to be more process than outcome at the moment, but hopefully as we move forward together, there will be some outcomes for you as well.

And please do stop me at any point as we go through.
We have talked before with this group about some of the issues in evidence review. I think Ned covered some of these really very nicely in his earlier presentation, but what really differs in evidence review here compared to, for example, the use of statins in certain kinds of cardiovascular disease -- I'm not going to talk about that in children, but in adults -- there may be vast numbers of very good trials that allow us to make some very clear judgments. In this case, we're dealing with a generally really sparse evidence base, and that evidence base with rare conditions means that in many cases there are not randomized trials.
There is, as I said in a comment before, very limited information on costs and benefits across all potential outcomes, the main ones being, of course, true negatives, true positives, false negatives, and false positives. We just don't really have very good evidence on the true cost and benefits there, and much of what we'll have to do, given the limitations in those data, is come up with some best guesses to share with the committee.
There also are some very important issues in access to evidence, and we've had some more recent experience with that that I'll share with the committee shortly. Obviously, the published evidence is easy -- well, relatively easy -- to get. There are, however, a couple of other sources of evidence, evidence from investigators who are actively working in the field but may not be published. We'll talk about our strategies for making use of that kind of evidence now. And there's proprietary data which so far we have not had direct experience in trying to get our hands on.
So our first year, which is really now over, we were very much assisted by members of the advisory committee. We developed an extensive data abstraction form for the kind of evidence that we're putting together. So this will be systematic. We have not, I believe, shared that form with the committee. We would, of course, be glad to do so, but this is based on both our own previous work in related areas, but in other evidence review groups' efforts to develop consistent management of data. And this is the form that is used for each of our reviews at this point.
We spent a good deal of time developing a very clear conflict of interest policy. We had a requirement that anyone involved with any of the reviews must fill this out. That again has been an interesting experience that I'll share with you in a few minutes' time. But we are interested predominantly both in fairly traditional financial conflicts, which are the ones one typically gathers information on, but also on direct intellectual conflicts of interest. So I may have no financial conflict here, but I may have very strong beliefs, very strong opinions about a particular policy or program or plan. We attempted to assess the presence of those conflicts as well.
Again, as I said, everyone involved with the project, the staff, the consultants, that we're talking with, et cetera must fill out these conflict of interest policies.
And I would also say -- and I'll repeat this a little later on when I talk especially about the Pompe disease case -- our goal in working with external investigators, who have a substantial amount of knowledge and experience in these fields but also often an extensive amount of strong beliefs as to what should happen by the advisory committee, is not to ask them for advice to give to the committee. It's rather to help them tell us more or less two major things. One, is there something new that we haven't been able to track down through an evidence review that we should know about in providing evidence to the committee? And the second is really to check whether we have correctly identified the evidence that does exist in a particular field. So we're not asking for them in any way to analyze the evidence or even to organize the evidence -- that's really our job -- but to help us understand that we have access to the best available evidence.
We did provide for you in the past and we have revised -- and I will discuss it again in a few minutes -- what we propose to provide you with in the sense of the organization of the evidence reviews that will be coming forward to the committee.
And I can go to the next slide now. This is really starting to go into more depth about the evidence review rationale and objective. And you will see again some real similarity to the kinds of discussions that both

Ned and Nancy and Piero led already. These are some of the critical questions that led the advisory committee to send these for review. So in fact, the first part of what we will write back to you is in many ways a replication of your rationale presenting it to us. So it will be the presence of the nomination form and consideration by the committee. And then these three or four questions that you've addressed that, in general, has led to your recommendation that we review this.

The other thing in general will be that there have been some recent changes in treatment and/or screening that will direct the rationale here for you to send it to us.

But again, our objectives, as I said a few moments ago, are to provide timely information to the committee to guide your recommendation decisions for a specific screening program. Again, our purposes ought to be systematic, reproducible, thorough, and hopefully transparent for you and other people who will be interested in this work.

The main questions that we will then address in the body of the review are, indeed, as comprehensive a view as possible about the natural history of the condition, including variations in phenotype, the best possible evidence on incidence of the condition, and again, those data, as possible, relative to genotype, phenotype, and phenotypic variations, what evidence there is about the impact and severity of the condition. And then moving on from some condition-specific things to issues in the methods of screening and diagnosis, screening initially and diagnosis in screen-positive individuals, then some of the screening test utilities that we actually have already talked about earlier today, sensitivity, specificity, predictive values, as well as the evidence on the feasibility and the acceptability of screening. So we will be gathering a lot of information on the screening tests.

And if you move to the next slide, we will then move on to what's known about treatment, its benefits, and we'll be interested in knowing what evidence we can pull together both for the evidence of treatment in screen-positive individuals, as well as, of course, individuals who are diagnosed in other ways, which is where more evidence typically tends to exist.

We will be gathering information and sharing it with you on the apparent harms or risks of screening, of diagnosis, and of treatment.

And where cost data exist -- and we've been struggling on this one -- in any of these categories, the costs of screening, the costs of diagnosis, the costs of treatment, the costs of late treatment, i.e., later than current recommendations, and the costs of the failure to diagnosis in the newborn period are all elements we are seeking for but we do not know that we will get a great deal of evidence in those areas.

We will then, in the report that we provide you, provide a description of the decision model that we use in the development of the evidence questions. Many of those really come out, frankly, from the work that the subcommittee that Piero reported on has already done because in many ways, as that committee has become more and more sophisticated, it provides us with the kinds of evidence questions that seem to be most critical for answers for the particular condition.

We will describe for you, of course, the search methods that we used in the review and our general strategy is a literature review time frame that is typically no more than 20 years. We'll describe the search engines used and methodology there.

And then for the actual review process, we'll describe for you the study selection, the actual data abstraction, and the review. And inclusion and exclusion criteria, ones we've discussed before with the committee, are peer-reviewed published literature in English only. The gray literature, i.e., unpublished, will be limited to pharmaceutical companies and unpublished studies and related data. And I will get back to that a little bit when we talk about our experience with this. We will exclude very small case studies, although we will provide you the bibliography of the case reports that we were able to find. We will review consensus statements and review articles as guides, not for direct abstraction, but we'll also use those lists, of course, as all of us do in this field, to identify other articles that need to be abstracted.

The actual data abstraction and quality assessment. We do have a method for assessing the quality of studies. This we're having some interesting experience in trying to apply because most standard quality assessment methodology really relates to more traditional randomized controlled trials and similar

epidemiologic studies. There are ways of doing this. We have done this in the past and we're doing it now, but we're working on that.
We have offered the opportunity to analyze additional raw data that may arise from unpublished sources. So far that has not come up in our work.
And we are doing focus groups and/or interviews of experts, both investigators and family groups regarding some of the impact and severity estimates, as well as other evidence they may provide for us.
And then finally, there will be some data synthesis. This, given the limited amount of data, is going to be predominantly in the form of evidence tables rather than a traditional evidence review that has 20 or 30 RCTs to review.
Then finally, this is the summary of the evidence report we will provide to you. We will provide you results which will follow the order and content of the main questions and basically our statement that we believe that, for example, the current weight of the evidence suggests that the prevalence or incidence of this condition is X and that the rates of these different phenotypes based on the genotype are Y, that the weight of the evidence currently regarding the screening test experience has been in population studies and smaller studies, et cetera. So we'll provide those kinds of results based on the reviews that we do.
Again, our decision analyses, as I said a moment ago, are more likely to be in the form of outcomes tables, given the kinds of data that we are finding and expect to find.
We will provide then key findings in summary and table form, and we will critically indicate where evidence is absent and what information would be most critical. We think it's very important for you people to know what we think about what we don't know and what would be most helpful in order to really answer the key questions for evidence review in this particular area. So it's what we don't know and the level of uncertainty and what new information and studies would most help your decisions.
I want to stress, as Nancy did a few moments ago, that all decisions, of course, are made by the advisory committee. We make no recommendations. We give you the best possible -- at least we hope it's the best possible -- evidence that we've been able to put together.
Let me just stop for a moment before we move on to where we are, what we've actually begun doing, to see if there are questions or comments about the processes and procedures, the members of the groups, the conflict of interest questions, the basic structure for our reports.
DR. HOWELL: Any questions or comments for Jim at this junction?
DR. BERG: This is Al Berg.
I'm struck by the addition of the focus groups of experts, investigators and families. It's a novel addition to this kind of review. I'm wondering what your experience is and what you expect this to contribute to the review. It's often precisely these groups that have some of the -- they're not conflicts of interest, but as you pointed out, they're sort of intellectual conflicts of interest, people who have strongly held views on one or another issue. I'm curious how you expect that to help in reaching your --
DR. PERRIN: Yes. So I think we have not yet done this, number one. Lisa Prosser, who is one of our team members, has done this in other circumstances. What it really provides to us is mainly the best estimates where there is lack of good evidence relating to, for example, mortality; for example, rates of improvement; for example, costs and so forth. So where those pieces of evidence are simply not available from the literature, they become sort of pieces of evidence based on that kind of best wisdom. We will make it very clear that that is the kind of evidence we have, i.e., highly limited, but that sort of evidence. And that will lend itself then at least to some of the rough estimates of costs and benefits. That's the main kind of evidence we think we can get that way.
DR. BERG: Thank you.
DR. PERRIN: Other questions?
DR. HAUSMAN: Hi, Jim. This is Ethan.
I wanted to just make a comment. I think it's an excellent idea in the gray literature category to try to access pharmaceutical company data and just to state my own bias working for FDA, I would --
DR. LLOYD-PURYEAR: Excuse me. Can you identify yourself?

DR. HAUSMAN: I already did. This is Ethan. I'm sorry.
DR. LLOYD-PURYEAR: We couldn't hear.
DR. HAUSMAN: Oh, I'm sorry.
I think using pharmaceutical company data is excellent, and I acknowledged my bias of working at FDA because my comment would sort of -- I'd try to caution the Evidence Review Group or guide them. When accessing pharmaceutical company data, the richer the data that will be made available, the better. The best scenario is if the company were willing to share basically raw data rather than cleaned up data just to make sure the committee gets the most accurate picture possible of what bits of information relate to the process.
DR. PERRIN: Yes. So I couldn't agree with you more, having sat on some FDA panels, and recognize how much you folks work so hard to get as clean data as possible in this context. That is certainly our goal. The problem I think we face is really knowing whether we've achieved that goal because even in the best possible circumstances, it may be that data are still not being provided for a variety of reasons, many of them very good. So it's hard to know if we've achieved that goal. So I couldn't agree with you more. That's the way we'd like to be going.
I will tell you a little later, as we get into the Pompe's description of where we are, that we are struggling with the best way to get access to unpublished data, including pharmaceutical data, and how best then to report that back to you folks. It's a critical question but it's very, very important to deal with.
Other questions at this stage? We'll obviously have time later on for others.
(No response.)
DR. PERRIN: So let me move to the next slide then, which is really the next steps.
Our year two really began in June with a new contract from the Bureau through a variety of mechanisms, and we then began these two reviews, i.e., SCID and Pompe's disease.
The Pompe's disease is really aided by the earlier work that Alex Kemper already did and published, and the need there is really mainly to update the earlier work. We have already done all of the abstraction of more recent literature in this area, and Alex and Marsha Browning have carried out a series of conversations with investigators in the field. And Denise Queally is in the midst of setting up similar conversations with Alex's help but with some of the interest groups involved in Pompe's disease.
We expect very clearly we will have a report to the advisory committee at your October meeting, October 1 and 2, from the Pompe's review. It will have gone through review by our external advisory committee hopefully in late August, or early September more likely. So that should be available to you.
The SCID, which is sort of a de novo new review, is a longer time line for us than the Pompe's is. The SCID review, just to let you know where it is. We have carried out the data abstraction, i.e., the review of published literature. The data abstraction has all been carried out. We are now in the midst of contacting the key investigators relating to SCID for our discussions with them about what information they can add to our review. So we expect that the SCID report will not be that much later than the Pompe's report, but we do not believe that it is likely that we will be able to provide that to you at the October meeting, having also been reviewed and revised based on our external review committee.
So this is a little different, Piero, from what you had put down. I think you were hoping we'd have reviews to you by today, if I read your slide correctly.
DR. RINALDO: No, no. But this actually brings up an interesting issue because in a sense what has happened is that the prioritization done by the working group has been voided.
DR. PERRIN: Well, in the sense that SCID was first, yes. Is that what you mean? "Voided" is perhaps a stronger word than I would use. We are simply doing what is really feasible given the fact that Pompe's had a head start because of its previous work by Alex. If you'd prefer, we could obviously present you SCID first, but it will not be available by October since we really only began this review in June.
DR. RINALDO: Well, I'd be curious to know what the rest of the committee thinks of this.
DR. PERRIN: I'm happy to stop at this point and get some discussion of that, if you want to, or we can go forward and put that at the end, whichever you prefer.

DR. TROTTER: I defer to Rod and Michele for this.
DR. HOWELL: Why don't we go ahead and proceed with the review, Jim, and then we'll come back to that.
DR. PERRIN: Okay. Let me go ahead then.
So I want to talk with you about really what we've learned and the challenges from the Pompe's disease activity. I would say that I'm not going to give you many of the similar challenges from the SCID review, but they're somewhat similar, at least back at the level of data abstraction and data collection. We believe we have done a systematic review of all the potential literature in this area. There's always the risk that we may have missed something, and we have that anxiety as we move forward from that piece of it.
But the bigger problems with each of these reviews is really identifying and evaluating unpublished data. So we're trying to identify the unpublished data. From the Pompe's review, I think this is relatively straightforward to figure out who these people are. Our solution has really been to identify most of the researchers working in this area by previously developed relationships, by discussions at meetings relating to Pompe's disease, and of course, by citations and reviews and from advocacy groups. So that's how we find the investigators who are working in this area.
Now, when I say previously developed relationships, remember that our own group includes people who work in this field as geneticists. It includes Nancy Green, and we do get advice from our Bureau contacts as well to make sure that we haven't missed any obvious investigators in a particular area.
The second issue that we have faced -- and investigators have really responded to this request -- is we have asked them to fill out conflict of interest declarations before we even will talk with them. So in our initial contact with investigators with whom we've discussed Pompe's disease, we send them out the conflict of interest form and ask them to fill it out in advance. That is a little bit overwhelming for investigators, although essentially all investigators do have to provide conflict of interest forms, of course, for their own institutions at this point and for other committees that they may be involved with. We try to make this as easy as possible, but on the other hand, it is absolutely critical that we get at least statements of the data from the people we will be talking with. When I say investigators, this is really also for the family groups with which we're working too.
So, indeed, sending this form seems to be an invasion for some investigators. We cannot, of course, evaluate the completeness of the information provided. So we are beholden to the investigators being both forthright and comprehensive in their provision of this information to us. So far, we have gotten this, by the way -- I want to assure you of that -- from everyone we have talked with. But this does take work on the part of the investigators in order to do that.
Of course, we are struggling to understand the impact of conflicts on subsequently shared data.
Obtaining data. This gets back to the comment from the FDA a few moments ago. Unpublished data -- it's fairly easy to get investigators to tell us sort of high level summaries of their current findings. Our recent data suggests that the prevalence of condition X is substantially higher than previous data shows by this amount. However, trying to get the absolutely firm data, the actual data on which those statements are made has become quite difficult. Investigators are not terribly comfortable sharing that level of data with us because, among other things, we're required under our work to share those data then with you. And we would, obviously, want to do that, but that then creates some conflict for investigators who have some interest in publishing these data in a reasonable period of time.
So this has been an issue, and I'll tell you how we are approaching this in the drafting of the Pompe's report at the moment. We do use follow-up interviews to clarify written data that we request. The written data really does reflect the sort of basic questions in each of the reviews. But again, the data that we've gotten even on the follow-up interviews lacks the granularity that we would like to have in order to say we believe there's some validity to the comment, for example, the prevalence is different from what previous reports have shown.
I think this is going to leave us in a somewhat difficult position because what we will say, I believe, in our reports is here's the evidence that we have from the actual literature review. In addition to that, our

discussions with key investigators in the field would suggest that there may be some new evidence leading to a change in the prevalence. We will not, in fact, even provide those numbers because we don't have those numbers to provide. *[2b flip] the real serious evidence that says this is the change you can expect.
Now, it may be that in some certain circumstances, we'll be able to get better evidence than that, but I'm just sharing with you where we are today with respect to our ability to obtain unpublished data with respect to the Pompe's situation. We actually may go back to some of these investigators one more time and see if we can do that, but that's really where we are today. It's been a real struggle to get good data at that level.
So, again, for systematic evaluation, the level of detail is not sufficient to fully assess the evidence. It does allow us to understand the direction of research, and we will highlight findings that may differ from what the evidence review, the actual in-depth review, shows.
We feel that is really not going to be data sufficient for the "Results" section. It will be an important component of the "Discussion," especially if the findings, the high level findings, suggest new methods for screening, diagnosis, or treatment are otherwise different from published findings.
But this is a critical issue, and I want you folks to understand where we are. And again, any additional advice you can give us would be very useful here.
So a couple of issues that you may want to focus on. One is the time frame that we're proposing and working on, and the issue that Piero raised, the additional advice you may have as we struggle to get data that we can be fairly comfortable with their validity from unpublished sources. You may have other questions as well that you want to ask.
Thank you so much for your listening and thank you very much for the support that we're getting to do what we think is an extraordinarily interesting process.
DR. HOWELL: Jim, thank you very much.
Why don't we hear comments about both of those areas? Piero had raised the question of the fact that Pompe seems to be a bit ahead of Krabbe.
DR. PERRIN: Of SCID.
DR. HOWELL: SCID. I'm sorry. Excuse me.
I think everyone is aware of the fact that our meetings, as well as the contracts for these reviews, were somewhat delayed because of budgetary issues. And so one of the issues is the fact that we're behind on all of these things. But it would appear that your recommendation on SCID will be relatively soon after October. Is that correct?
DR. PERRIN: That's correct, yes. So we certainly expect that by October 1, we will have a well crafted report to share with our National Advisory Committee. We just don't believe that we will have gotten it back from them and able to, therefore, make the revisions and get it to you by then. So we're talking probably -- probably -- I don't want to commit to this -- November 1 for that one.
DR. HOWELL: Can we have some comments? Piero had raised the question about this order. Any further comments about that? No comments?
DR. WATSON: I don't have a comment on the order, but I do have a question.
DR. HOWELL: Please.
DR. WATSON: This is Mike Watson.
You've nailed down a lot of the problems that you're facing with rare diseases, and I just wanted to see if it was possible to bring some, I don't know, rationale or order to one of them that I think is going to be among the more difficult, and that is sort of the conflicts that people bring to this, especially when you're getting gray literature.
DR. PERRIN: Right.
DR. WATSON: Have you thought about how to rate conflict? I mean, there are people who work for companies. There are people who work with foundations, and this is very common in rare diseases. People who get grants to do work in particular areas, people who run clinical laboratories that have

revenue that's tied to doing testing on things that get recommended.
And then the big one for us, when we do guidelines, has been the impact of the orphan drug legislation which essentially gives a company a monopoly on the sale of a particular drug, and when approved by FDA, they often get a phase IV surveillance band aid of doing long-term follow-up, which brings everybody who treats patients into the clinical trial activity of the company.
So I'm wondering if you've thought about how to sort of grade or rate these various kinds of conflicts so that when you state that somebody has one, when you bring forth a report, there be some way of sort of grading it.
DR. PERRIN: So I think that's an incredibly interesting question, Michael, and I don't think that I've seen anyone with methods of grading conflict of interest.
In thinking it through, most of the people we will talk with have substantial conflicts of interest because they are investigators, for example, working in this area, so they have usually research grants that come both from public and private sources. They may be involved with work with a for-profit company in a variety of ways. I'm not sure how best to rank them and say this is a person with more or less conflict.
We can separate conflict into, I suppose, a clear financial conflict versus a clear intellectual conflict. But even that, as you start to think that through, isn't that clear.
DR. WATSON: I agree. I've been slapped around on all of these, and it's very hard for me to bring order to it.
DR. PERRIN: Again, if anyone has any advice, we are certainly open to it in this context.
DR. VOCKLEY: This is Gerry Vockley.
Regarding the issue, though, of how to get the quality of data that you want, Jim, you know, we actually, it would seem to me, have some pretty good leverage here. That is, you can simply say, give me your data, or we table the proposal.
DR. PERRIN: Yes.
DR. VOCKLEY: So I'm the last person in the world to be heavy-handed usually, but you are going to be inundated with these proposals. And we can't afford to futz around. I mean, I think we just need to say here's what you gave me. Here's what we need. Make up the difference, or else we move on and you go to the back of the queue.
DR. PERRIN: So we have basically said that. And you're absolutely right. What we've heard in the Pompe experience so far -- and it may be very different as we start this in the next few weeks in SCID -- is no one seems to have data that would change the weight of the evidence in a particular way. So they can say, yes, well, we have data that's interesting, but it's not really going to change the kind of evidence you provide to the committee. So you're absolutely right. Where they think they have something that will change the likelihood of the committee making a certain recommendation, I think they will be under tremendous impetus to provide us those data.
DR. VOCKLEY: But are you comfortable with them saying we have data but it's not really pertinent? I mean, if it's not pertinent data, they should never mention it in the first place, I would think. They should show it and then you can decide. You can say, do you have anything more? And again, the answer is yes or no. If the answer is no, then they've been forthcoming.
DR. PERRIN: See, that's very good phrasing and we should use that phrasing. I would agree with that. Again, I think the experience in Pompe's so far is really that we don't have -- the investigators that Marsha and Alex have worked with suggest that there is no new information in their armamentarium of unpublished data that would change the basic level of evidence that we have in areas like prevalence, screening tests, et cetera.
DR. VOCKLEY: Yes, that's fine.
DR. PERRIN: Again, I think we will test this as far as we can, I assure you, and we will certainly get back to you folks both with the successes and failures in our ability to gather these data.
DR. HOWELL: Jim, let me make a personal observation about the order. I think that the Evidence Workgroup should be very attentive to the recommendations of the committee about the order in which

these reviews go forth.
DR. PERRIN: Sure.
DR. HOWELL: Having said that, I'm sympathetic to the complexities, shall we say, of the summer and the fact that you had some data on Pompe that would really permit you to move ahead at a time when it was fairly complicated to move, shall we say. I'm not terribly put off by the fact that one will be slightly ahead of the others. If we were talking about great differences, I'd be very concerned.
DR. PERRIN: Thank you, Rod. I appreciate that. I think we have had some problems, given the sort of budget and so forth, in sort of being able to move forward. When we did get the go-ahead to move forward, we've been trying to move as quickly as we possibly can.
DR. RINALDO: Jim, this is Piero.
If I understand correctly, I understand that the committee will be in a position to vote at the October meeting on Pompe while SCID will go to next year. So, Rod, I don't know if that is in a sense is not the timing of the completion of the matters, rather the timing of committee action. And we're talking about several months.
DR. HOWELL: I'm sensitive to that. I think the practicality is that because of previous stuff, they're able to get Pompe's ahead enough to see in October, and they could not do SCID, even if they started today. I think that's the problem.
DR. PERRIN: Yes. So again, if I can say it, Pompe's has the advantage of previous work being done and thus a significantly easier strategy with respect to literature review than SCID did. It's simply a vastly easier activity, a third of the time, if even that, required to carry out the systematic review. So the other way of saying it is, given the time frame when we were permitted to start this process, that we would have neither SCID nor Pompe's available for the October 1 meeting if we hadn't had the head start.
It's the committee decision about what mechanisms there are for you to review these reports as we provide them to you.
DR. RINALDO: No, but you realize -- and I'm the first one to say we're all learning how these things will connect together, but then in reality we should change the name of the working group, no longer review and prioritization, but will only be review. I think that was exactly the reason why that working group was -- we felt a need to have it because we knew that there will be congestion. So in a sense, what we're learning is because of sort of downstream circumstances, all the prioritization that was brought forward can be reversed.
DR. PERRIN: Piero, I would probably -- again, this is a committee decision, but I would probably not consider it that general. I think this is a specific issue relating to the lateness of a budget on the part of the government and the fact that there had been some prior work specifically for this group, for the advisory committee, on Pompe's disease. So I would expect, in fact, the prioritization function is very important and will likely be adhered to actively in the future because I would expect that future reviews will vary in the amount of time they're going to require, undoubtedly, because of different characteristics of the investigations, investigators, and the data that are existing and the kinds of critical questions that need to be answered. But in general, I would expect they will take pretty much the same amount of time and therefore, this working group will definitely follow the prioritization of your group.
DR. van DYCK: This is Peter.
And we know the work can be done between meetings.
DR. PERRIN: Right.
DR. van DYCK: So when the evidence-based review report comes in to the chair, that can be sent out for review and we can hold a special session to vote, if necessary. And that will help ameliorate that kind of unevenness that probably won't occur again.
DR. RINALDO: That's fair enough because I was concerned of a difference basically, the fact that a decision could come to fruition in October for Pompe and only in January or February for SCID. I thought, again, it was significant. But, Peter, if you're saying that between October and January, by teleconference or whatever other means, it will be possible to act, then I definitely have much less of a problem.

DR. HOWELL: We clearly can have a conference call if we get the information and it's ready to go. There's no question about that. I have the same feeling of urgency you do about the SCID document. So certainly if Jim and his group finishes, we certainly will do that.
Are there other questions of Jim? Thank you very much. I know you've had a complex time getting started, but now we're on the ball. So hopefully you will go zipping along.
DR. BOYLE: This is Coleen. I did have a question not for Jim but maybe for you, Rod.
DR. HOWELL: I'm all ears.
DR. BOYLE: So when Jim's group finishes their report and it comes back to the advisory committee, it sounds like the intent -- I'm just trying to understand the process a little bit more. The intent is to have the report reviewed at the October advisory committee, and hopefully we will get it as a committee in advance so we can spend some time reviewing it. But I'm assuming that then we're going to use the process that Ned described for us that's sort of still being finalized in terms of making it an official recommendation. Is that correct?
DR. HOWELL: I think so. Ned's group should, however, have that material to us fairly soon so we could review that.
DR. BOYLE: Then how does that happen? Does Ned's group sort of make a tentative or a presumptive recommendation and the advisory committee considers that? Is it the whole advisory committee that's going to make the recommendation? At our October meeting, how will that process occur?
DR. HOWELL: I would assume so. Michele, do you have any comments? I would assume we will get the documents well before time and review it at the October meeting.
DR. TROTTER: Rod, this is Tracy. Let me just comment on Ned's group that I'm in. We are not going to make any recommendations about any specific nomination. It is merely going to be what we hope will be a process that will be useful to the committee as a whole to then look at each nomination as it comes forward.
DR. HOWELL: Yes, and that format should be available before the meeting, and we'll have a chance to discuss it at the meeting in October.
DR. TROTTER: I think we'll have it in the next few weeks.
DR. HOWELL: Yes, right.
Did that answer your question, Coleen?
DR. BOYLE: So then at the October meeting, committee members will have Jim's report well in advance so that we can have time to review it, and we'll also have an opportunity to re-review Ned's decision matrix. And then somehow we'll put the two of them together as a full committee in October.
DR. HOWELL: Right. That would be my thought.
Any further comments?
DR. ALEXANDER: Yes. Rod, this is Duane.
I just want to make a comment to Jim. Sitting and listening to the presentation, I was just very, very impressed with the thoroughness and completeness with which you approached this task. I couldn't think of anything that you hadn't thought of and dealt with in a creative and appropriate way. You're really breaking new ground in this whole area and providing a major service to the committee and to pediatrics, and I want to thank you for the way you're doing this because this is an activity that's under intense public scrutiny and it's so important for us to do well. And you're going to allow us to do it better than we could otherwise. So thank you very much.
DR. PERRIN: Thanks, Duane. We've tried to learn a lot from you guys in how to do it, and we appreciate your help.
DR. HOWELL: Well, I think that this is, obviously, a ground-breaking effort to look at -- a sophisticated, careful look at rare data, data on rare diseases, and it will be special and will be very carefully looked at and will be valuable to the committee and to the community. So thank you again, Jim.
DR. PERRIN: Thank you.
DR. HOWELL: We now move on. I'd like, if we could, to have Peter van Dyck review with us the Newborn

Screening Saves Lives Act of 2008, the new legislation, and a summary of this legislation and the implications to this committee. Peter?
+ DR. van DYCK: Thank you, Rod.
The law is under tab 10. You have a summary of the provisions of the law. You have a new law that's labeled Senate 1858, and you have an older law which the Senate 1858 replaced. You have three pieces of information. You have a summary of the provisions of the public law, which I'm going to go through briefly. You have a new law, the Newborn Screening Saves Lives Act of 2008, and you have an old law which was amended by the new law.
So you have a complete set of materials, but what I'm going to do is go through the summary of the provisions, and I'm going to go skipping sections for the sake of time and highlighting those areas that seem to involve the advisory committee most intensely.
So on the first page, second paragraph, the act reauthorizes and expands the role of the advisory committee, establishing an interagency coordinating committee, creates an Internet-based information clearinghouse to provide information about newborn and child screening for heritable disorders.
It requires the Secretary to ensure the quality of laboratories and to develop a national contingency plan for newborn screening.
And finally, it gives NIH the authority to carry out research in newborn screening, including identifying new screening technologies and researching disease management strategies for conditions that can be detected through screening.
If we turn the page, I'm going to talk about section 2. Section 2 authorizes the Secretary acting through HRSA and in consultation with the advisory committee to award grants to improve the ability of state and local public health agencies to provide screening, counseling, or health care services to newborns who are at risk of heritable disorders; to assist in providing health care professionals and laboratory personnel education and training in newborn screening; to provide educational programs to parents, families, and patient advocacy groups; and four, to establish and operate a system to assess and coordinate treatment relating to congenital, genetic, and metabolic diseases.
In addition, section 1109 provides that an application for grants contain assurances that the applicant will adopt guidelines and recommendations of the advisory committee that have been adopted by the Secretary and are in effect at the time that the grant is awarded or renewed. And it requires coordination between grantees.
So that's an amended grant section, and that section is called 1109, and when you hear people talking about section 1109, which the legislature or Congress often talks about, that's that section.
Then I'm skipping to section 4, and you have all the materials and can read them, and if you have questions about other sections, please bring them up after I'm finished.
Section 4 is devoted to the advisory committee. So it authorizes new duties for the advisory committee, which can include recommendations, advice, or information on certain diagnostic and screening activities. And it expands the membership of the advisory committee to include the Commissioner of the Food and Drug Administration, as well as to assure that we have expertise in infectious diseases and ethics who have worked or published on newborn screening.
It also expands the duties of the committee to include making recommendations that include the heritable disorders for which all newborns should be screened. Two, developing a model decision matrix for newborn screening expansion. And you'll see that the bulk of the meeting today was around these elements. Three, considering ways to ensure that all states attain the capacity to screen for the recommended conditions. And it also requires the advisory committee to continue to operate for a five-year period beginning on the date of enactment of this act. Enactment of this act was April 24th, 2008. This process includes an evaluation of the potential public health impact of such expansion and for the advisory committee to periodically update the recommended uniform screening panel as appropriate, based on the decision matrix that we've discussed.
It also amends section 1111, which is the advisory committee section, to require the Secretary to adopt or

reject recommendations made by the committee within 180 days, including recommendations pending at the time of the enactment of the act, which was April 2008.
Section 5 forms a clearinghouse and is a new section. It requires the Secretary, acting through HRSA, in consultation with CDC and NIH, to establish and maintain a newborn screening and information clearinghouse which will include ensuring that the clearinghouse is available on the Internet and is updated at least quarterly, contains an interactive forum, provides links to websites that have expertise in newborn screening, provides information about newborn conditions and screening services available in each state, provides current research on conditions for which tests are available, and provides for the availability of federal funding, the sources of available federal funding for newborn screening for heritable disorders.
Section 1113 requires the Secretary -- and this is about laboratory quality -- acting through the Director of the CDC and in consultation with the advisory committee, to provide for quality assurance for screening labs and appropriate quality control and other performance test materials to evaluate the performance of new screening tools.
And then at the bottom of the page begins 1114, which is the Interagency Coordinating Committee, which requires the Secretary to establish an Interagency Coordinating Committee on Newborn and Child Screening for the purpose of making recommendations on programs to collect, analyze, and make available data on certain heritable disorders, including data on the incidence and prevalence, as well as the poor health outcomes resulting from such disorders; and to work on the establishment of regional centers to conduct epidemiological research on effective interventions to prevent those poor health outcomes; and to provide information and education to the public on what these effective interventions might be.
It specifies who should be on the Interagency Coordinating Committee -- CDC, NIH, AHRQ, and HRSA -- and that the ICC will report to the Secretary and appropriate congressional committees on its recommendations.
Section 1115 is on contingency planning, and you remember we've discussed and had presentations on the contingency planning around Katrina a couple of years ago. This section requires the Secretary, acting through the CDC Director, but in consultation with HRSA and state departments of health, to develop a national contingency plan for newborn screening for use by states in the event of a public health emergency. I might add that that requirement also is to be done within 180 days of the enactment of the act.
And then the last section authorizes the Secretary working with NIH and again taking into consideration the recommendations of the advisory committee to carry out, coordinate, and expand research in newborn screening to be known as the Hunter Kelly Newborn Screening Research Program, including identifying, developing, and testing the most promising new screening technologies, and experimental treatments and disease management strategies for conditions that can be detected through newborn screening for which treatment is not yet available.
And that's the highlights of the bill. You can clearly see that there are some additional or expanded roles for the advisory committee.
If you have questions, I'll be happy to try to answer them.
DR. HOWELL: Questions of Dr. van Dyck about this fairly broad, new bill that's been passed and signed by the President?
Peter, I would appreciate hearing from you -- I know that Dr. Williams mentioned earlier that there had been a lot of planning meetings at HRSA -- about what specific areas are advancing in your planning at this current time, what is really afoot and what things have been done and what do you see as your top priorities right now.
DR. van DYCK: Okay. Dennis Williams is still here. He's been attending the whole meeting.
DR. HOWELL: Oh, good. Maybe we can call on Dennis and you to please bring us to date on that.
DR. van DYCK: But what we are doing is preparing responses and material for all elements of the bill. So

we're looking at recommendations from the advisory committee. We're looking at developing guidance for state grants. We're looking at implementing the newborn screening clearinghouse. We are beginning work with CDC on the contingency planning. So it's not necessarily focusing on any one section. It's trying to focus on all sections and trying to implement the bill to the best of our ability in the most efficient and effective way.
Dennis, do you want to have any additional comments?
DR. WILLIAMS: No. I think that covers it pretty well. There are, as Peter summarized, a large number of activities that we have to get done. Some of them have specific time limits on them, the 180 days. We're focusing obviously on those that have very short time frames, but others require developing working relationships with CDC or NIH in implementing some of these sections. So we're trying to establish those relationships, and we're working to accomplish what the legislation envisions.
DR. HOWELL: The bill authorizes in several areas specific funding that's substantial and so forth. Has there been any evidence of any new funds appropriated to help carry out these missions?
DR. van DYCK: So far, Rod -- and that's an important distinction, that the bill is an authorization bill, and you'll see amounts after each section that are fairly significant. So far in the appropriations process for 2009, the Senate has provided an earmark. It's at the same level as last year, around $1.8 million, and the House subcommittee in their markup has provided $5 million, which is about a $3.1 million increase. So this is very preliminary in the process, but those are what the full Senate and the House subcommittee -- or I should say the full committee in the Senate and the House subcommittee have recommended in their markups.
DR. HOWELL: Both of those figures being substantially below the authorization language of the bill.
DR. van DYCK: Correct.
DR. HOWELL: Are there other questions or comments of Peter about this very important bill which obviously had a great deal of support because of the rapidity with which it went both through the House and the Senate and through the President's office?
DR. BERG: This is Al Berg.
I guess it's a follow-on to the last couple of comments about possible funding. Are there particular areas of the bill where the match between the authorized level and the task is pretty close, and were there others perhaps where there's more mismatch?
DR. van DYCK: The markups both suggest that the money goes toward section 1109. 1109 is that first section which has the four elements which is related to grants to states. So that's where both the House and the Senate have chosen to place their earmarked money at the present time.
DR. HOWELL: Any further comments or questions?
DR. SKEELS: Yes, Rod. This is Mike Skeels.
I don't know if this is a question for you or for Peter, but I've been trying to get my mind sort of wrapped around this bill and the direct impact it will have on the way our committee does its business. And I guess until we have some appropriation, it's going to be hard to really meet all the expectations that are set forth in the bill. But can you just talk for a moment about how you think this will change our committee, our approach, our mission, our composition? What do you think will be the biggest impacts as we move forward?
DR. van DYCK: Well, I think the biggest impact is putting into legislation the process that has begun around the committee's work on evidence-based review. Before it was a process that we all thought was a good idea. Now it's a process which has been sustained by legislation and requires certain elements, if we read the bill closely.
It also requires a report on the work of the committee that the committee must write. So that will have an impact on the committee as well.
And it puts legislation around the formation of the Interagency Coordinating Committee which is a workgroup of the federal agencies but works in concert with the advisory committee.
DR. HOWELL: And the committee structure will change with some additional persons. Is that not correct?

DR. van DYCK: The requirement is that FDA be added to the committee without changing the number of the committee. The committee has 15 members and will still have 15 members.
DR. HOWELL: And what about the requirement that's stated concerning persons who are expert in infectious diseases and ethics?
DR. van DYCK: Well, as the people on the committee turn over -- we do have people that represent some of those areas now, and as the committee turns over and new people are appointed, we'll be sure that recommendations go to the Secretary that include that expertise.
*PARTICIPANT: What about the degree of, let's say, citizen involvement or liaison with other organizations and so forth? Would we still be following basically the same model that we are now, or are there different expectations now that there might actually be some money attached?
DR. van DYCK: I think the expectations are the same. The committee and the chair with Rod have really been very aggressive in getting liaison members and other organizations involved with the work of the committee, and I see that continuing.
*PARTICIPANT: I agree. I wasn't implying otherwise. I just wondered whether there was --
DR. van DYCK: There's nothing specific in the bill that would change, I think, the activities of the committee in that regard.
DR. KUS: This is Chris.
There is a small section that talks about effectiveness of newborn and child screening programs which looks like long-term follow-up kind of stuff. Funding for that -- it sounded like there wasn't as much. Right? Is that correct?
DR. van DYCK: Yes. You're talking, Chris, about section 3, which is at section 1110. It's on the top of page 3 on the document I just went through. It says it adds a new authorization for grants for demonstration programs to evaluate the effectiveness of screening, counseling, and health care services in reducing problems related to heritable disorders.
At the present time, there is no earmarked money authorized for that or appropriated for that section.
DR. HOWELL: Again, unrelated to this legislation, I think that we've mentioned briefly the NIH plans to develop some translational research follow-up network that might respond to some of that. Of course, that is not funded in here, but will be an important project that's currently under discussion at the NICHD. Duane, would you like to comment about that at all and how that might relate to this?
DR. ALEXANDER: Yes. We have set aside some funds for that under a grant mechanism. We hope to use this to accomplish a number of objectives, largely providing a scientific and research basis for getting information on natural history of these disorders when they're detected, as well as responses to treatment, and hopefully even categorization of different phenotypes of these disorders as we diagnose them and differences in responses of the different phenotypes to treatment. So this is a long-term project that is very much related to the language in the bill. Its planning actually preceded the enactment of the legislation.
But what we really hope to do is organize the regional networks with some coordination by a national coordinating center in a research context above and beyond this primarily service context in which they currently operate so that we would add on that activity and funding for that activity to learn about some of the existing conditions but largely to be able to provide some of this long-term follow-up as we add new conditions to the screening process.
DR. HOWELL: Any further comments, et cetera?
(No response.)
DR. HOWELL: Peter, thank you very much for that very nice presentation. I think that everybody has access to this legislation, and I'm sure they'll be able to see it. And it will be very interesting to see. Obviously, this bill was generated by a lot of public advocates, as everybody knows, for newborn screening, and it will be interesting to see if this particular group also is effective in identifying additional funding for some of the fairly broad missions that are stated here.
Any further comments about that?

(No response.)
+ DR. HOWELL: On our agenda now, we have a period blocked out for committee discussion, and one of the things that we've done this afternoon is we really discussed the issues that we've gone through as we've proceeded through. And I wonder if there are other areas that should come before the committee for discussion at this point about anything that we've talked about or haven't talked about. Would anyone like to bring something up at this point in time?
DR. BERG: This is Al Berg.
It's just a question. I very much enjoyed some of the papers that were sent along as committee background material. Does the committee sometimes discuss those or have a process for reviewing those in any kind of systematic way?
DR. HOWELL: At our face-to-face meetings, Al, we have -- Michele and her staff at HRSA have been very good about including recent papers and so forth. In our face-to-face meetings, we have discussed these. We have not made it a practice to discuss them in detail. Is there one or more of the -- certainly if you would like to discuss anything that's in your folder today or in your thing, if you would make any specific points, we'd appreciate hearing from you.
DR. BERG: No. I found a number of them quite interesting. It's the sort of thing that one could spend a long time discussing. I was just curious about what the expectations of the committee and liaison members were with these papers that are just distributed presumably now just for interest rather than for a detailed discussion.
DR. HOWELL: Well, we certainly expect that everyone will read them and become much wiser. And we have mentioned them in passing. But on the other hand, if there's material that comes out that you think would be something that the committee would benefit from a discussion, I would certainly welcome having that brought forth.
DR. BERG: Well, I'll just make one comment, and the paper that Dr. Calonge and colleagues published in Health Affairs is certainly interesting background in the context of some of the issues that the committee has been discussing. I'm sure that's been part of the committee's deliberations in the past. The views expressed in that article seem to be somewhat at variance with some of the decisions made before the committee began.
DR. HOWELL: The material that's been provided historically have been in both agreement and disagreement with the committee. It's been, shall we say, eclectic and broadly based.
Any other comments about those?
(No response.)
DR. HOWELL: It would not be my feeling that we should necessarily use all the time allocated for this meeting. You've been extremely patient. What I would suggest, if we don't have some discussion at this time, is that we have two persons representing groups that have signed up for public comment, and I would like to go to those. Michele, can we connect our public commentators?
DR. LLOYD-PURYEAR: We are connecting the public commentators, but there's only one individual at this point now.
DR. HOWELL: Okay. There's only one person.
DR. LLOYD-PURYEAR: Jacque Waggoner.
DR. HOWELL: And is Jacque connected?
+ MS. WAGGONER: Yes, I am.
DR. HOWELL: Oh, Jacque, good afternoon. Jacque Waggoner is the Chief Executive Officer of the Hunter's Hope Foundation, and Jacque's written comments have been received. Jacque, let me welcome you to the 14th meeting, and we'll look forward to hearing your comments.
MS. WAGGONER: Thank you.
On behalf of Jim and Jill Kelly and the Hunter's Hope Foundation, I am grateful to have this opportunity for our voice to be heard today.
Hunter's Hope was founded in 1997 by Jim and Jill Kelly after their son, my grandson, Hunter, was

diagnosed with Krabbe disease at 4 months of age. Hunter went to heaven when he was 8 and a half years old.
The mission of Hunter's Hope is to find a cure for Krabbe disease and other leukodystrophies, heighten awareness, and support families affected by these diseases. Our main objective is to educate people about the importance of early detection through newborn screening. We believe Hunter may have had a chance for a healthy life if his disease was diagnosed in time for early treatment.
First, it is important for all of you to understand and appreciate the life-saving role that we believe, with all of our hearts, that you play as members of this advisory committee. It is because of the infrastructure that you have built to help expand and strengthen the states-based newborn screening programs that Hunter's Hope is able to step out with confidence and educate policymakers and families on the immeasurable value of universal newborn screening. We rely fully on the recommendations of the advisory committee and the information provided by the National Newborn Screening and Genetics Resource Center. And we thank you all for your commitment and perseverance.
The report from the American College of Medical Genetics, "Newborn Screening: Toward a Uniform Screening Panel and System," executive summary, page 11S, recommends that state newborn screening programs mandate screening for all 29 core panel conditions. It also recommends mandate reporting for all 25 secondary target conditions and that all clinically significant information discovered through newborn screening be provided to the relevant health care professionals and family. We are most concerned that assumptions are being made that the 25 secondary conditions will automatically be reported because they are revealed by the screening technology when the core conditions are screened. Therefore, Hunter's Hope is advocating that all states mandate screening for all conditions recommended for screening and reporting by the advisory committee and that states implement an ongoing process to ensure their state newborn screening program is always current with the advisory committee's recommendations.
Finally, and perhaps most importantly to the Hunter's Hope families, we appreciate your consideration of the Krabbe nomination to the recommended panel. We are eager for every newborn in every state to be screened for Krabbe disease but trust your recommendation. We will work hard to do whatever is necessary to ensure that every child born with Krabbe disease has a chance for hope and a future. Thank you.
DR. HOWELL: Thank you very much, Jacque, for that thoughtful comment. I think I can speak on behalf of the committee that we appreciate the *[3a flip] comments or not questions are commented after that. But I will make one brief comment as I assume that Ms. Waggoner was listening when the committee made a formal unanimous recommendation to send the nomination of Krabbe disease forward to the evidence-based group. And I'll just make that comment.
Thank you very much.
MS. WAGGONER: Thank you.
DR. HOWELL: We're expecting a second commenter who apparently is not here. Is that correct, Michele?
DR. LLOYD-PURYEAR: That's correct.
DR. HOWELL: Is there any other business that should come before the committee?
Our next meeting is --
DR. LLOYD-PURYEAR: Just a reminder -- this is Michele -- to send your calendars back to Carrie for January and May of 2008 so we can determine the meeting dates for next year.
DR. HOWELL: Now, our October meeting still does not have a space identified. Is that correct?
DR. LLOYD-PURYEAR: Our October meeting does have a space identified. No. Wait. We still need to identify a space. I was wrong.
DR. HOWELL: All right.
Is there further business that should come before this group?
(No response.)
DR. HOWELL: If not, let me thank you very much for your hard work and persistence on staying on the

phone this long. I'm sure your phone lines are ready for a rest. If there's no further business, I will call for a motion to adjourn.
PARTICIPANT: So moved.
DR. HOWELL: Second?
DR. RINALDO: Second.
DR. HOWELL: All in favor, say aye.
(Chorus of ayes.)
DR. HOWELL: And we won't count these votes *.
Thank you very much, and we'll see you all in October.
(Whereupon, at 4:40 p.m., the meeting was adjourned.)