U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE ON HERITABLE DISORDERS
IN NEWBORNS AND CHILDREN

Wednesday
October 1, 2008

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P R O C E E D I N G S (1:28 p.m.)
DR. HOWELL: Let me welcome everybody on this nice, sunny day to the Hilton Hotel, and I hope most people found the right Hilton. I was at a previous Hilton a few moments ago. But it is great to be back here.
At the current time, we have two new representatives to the committee. The first new representative is Frederick Chen from Seattle who is currently representing the American Association of Family Practice, and he has replaced Dr. Alfred Berg. Fred, welcome.
DR. CHEN: Thank you. I bring greetings from the University of Washington in Seattle. Al and I are still in touch.
DR. HOWELL: Thank you very much.
We also have a second new member who apparently is not yet here, but we are expecting him. And that is Tom Musci who is from the San Francisco Perinatal Association, and he will be the ACOG representative replacing Tony on this committee, et cetera.
The first item of business that we have to do is the approval of minutes from the August 2008 meeting, which is in your agenda book. Can we have a recommendation on the minutes?
Gerry has made a move that we approve.
A second? Coleen.
Those favoring it oh, Coleen had a change I think.
DR. BOYLE: I actually read them on the plane up. I remembered in our conversation from our telephone meeting that there was a lot of discussion around the issue of whether or not new conditions that would be reviewed as recommended conditions for the panel, whether there needed to be a U.S.-based population study. There was quite a conversation at the end of Piero's I think it was Piero's discussion. It may come up when Nancy presents the guidelines for decision, and it also may come up when we talk about Pompe's disease. So I thought it was an important issue, and I felt like we have some conflicts there. So the minutes reflect the conversation accurately, so I don't think there is problem with the minutes. But I did want to just highlight that issue so that we could bring it up for discussion later.
DR. HOWELL: I've read the minutes, but I forgot exactly what it said about the Pompe situation. What does it say?
DR. LLOYD-PURYEAR: So there's no change you want to make. You just want to
DR. BOYLE: There is no change. I just wanted to note that I feel like there are some inconsistencies based on the different pieces I just pointed out. That's all.
DR. HOWELL: So Coleen has made some comments. There has been a move and a second and some comments. Any further?
(No response.)
DR. HOWELL: Those favoring the adoption of the minutes?
(Show of hands.)
DR. HOWELL: Thank you very much. And the minutes are under tab 5.
There are a few housekeeping things that I will go over at the current time before we move into the substance of the meeting. Breakfast on Thursday morning will be for committee members, speakers, and organizational representation, and that's in the Twiggs Restaurant which, as you come in the main door of the hotel, is off on the left. There is a large room there.
The New York Room has been set aside for committee members during the scheduled break on

the agenda, and Tamar and company will tell you where that is.
The subcommittee meetings will be tomorrow morning from 8:00 until 10:30 and they will be on the second floor, and there will be signs indicating which room your group will be meeting in. Laboratory Standards will be in the Ohio Room. Education and Training will be in the Federal A and B. It is located on the 12th floor of the hotel, not the second. And the Follow-Up and Treatment will be in the New York Room, which is on the second floor of the hotel. And the staff will be outside to help you if you get lost.
If any of the presenters has changed your presentation from what has been sent, be sure that those are made available to the laptop here.
Tonight there is a dinner in the Twiggs Restaurant. It is a very popular restaurant. We just had lunch there and there was a bird flying around. So the bird hopefully will not be on the menu tonight.
(Laughter.)
DR. HOWELL: But anyway, that is on the main floor, and there are some very specific recommendations about that. Number one, the restaurant has recommended that we bring cash instead of credit cards. I think they are worried about the vote in the Senate today, that the bank may close that has your card.
(Laughter.)
DR. HOWELL: And the other thing the restaurant has announced is that they will not reconcile a check with more than two credit cards. So that is another issue.
There are actually a series of choices for dinner. The dinner will cost 38 bucks plus gratuity and tax, and beer, wine, and liquor will be abundant, but at extra cost.
And the dinner is, again, for the committee members and speakers tonight down in the Twiggs, and we hope that many of the persons here will be able to attend.
Are there any other housekeeping things, Michele?
DR. LLOYD-PURYEAR: No.
DR. HOWELL: I think that we have had enough housekeeping.
We've got a really busy agenda over the next couple of days, and I'm going to urge everybody who is presenting to be as succinct as possible because there are many, many things that we need to do.
And having said that, we will go to our first speaker, who is Nancy Green, who I don't see, but she was certainly sitting at the computer. Here she is. She is gracefully going to present this afternoon for Ned Calonge who chairs this particular workgroup, and Ned is unable to be present. And Nancy is actually going to go through the process of creating recommendations based on the systematic evidence review. And members of the workgroup are Denise Dougherty, Piero, Coleen Boyle, Mike Watson, Tracy Trotter, and Sharon Terry. And Nancy is the liaison member from the external workgroup.
And then after Jim Perrin's presentation this afternoon, we will use the protocol that Nancy is currently discussing to look at the Pompe evidence review and determine the usefulness of this approach. If the committee finds this appropriate and workable, then we should consider adopting that as an operating procedure.
Nancy, let's roll.
DR. LLOYD-PURYEAR: Sorry. Nancy, Ned Calonge was able to call in at the last minute.
DR. HOWELL: And is he going to be able to I would assume that he is going to listen. Do we know when he is coming in?
DR. LLOYD-PURYEAR: Two seconds.

DR. HOWELL: Well, we can wait two seconds but not much more than that. Excellent. I am delighted that Ned will be able to listen.
+ DR. GREEN: Well, maybe while we are waiting for Ned, I just would like to say that this is really Ned's report and the workgroup. So certainly the more difficult, prickly questions should be addressed to Ned.
But on a serious note, I really would like to just thank him for a prodigious amount of consideration and work on this, despite not being here.
DR. CALONGE: So this is Ned, Nancy. Can you hear me?
DR. HOWELL: Yes, we can hear you well.
DR. CALONGE: So to save Nancy from having to answer prickly questions, I've left the EGAPP meeting and am happy to participate in this presentation.
DR. HOWELL: Thanks very much, Ned. So we will have Nancy go ahead and do the presentation, and we will save all the prickly questions for you.
DR. GREEN: So just as a reminder, the workgroup members, as Dr. Howell mentioned, are listed here and Michele Puryear and I have been involved with this as well.
So having had the advisory committee approve a process for nomination and a process for evidence-based review, we're now at the stage of designing a process for creating recommendations based on those two processes, the nomination and the review processes, and keeping in mind the overriding aspects that standard levels of evidence are unlikely to exist for certainly all of these conditions being nominated. And so thanks to the wisdom of the advisory committee and the workgroup and certainly Dr. Calonge, there is an adaptation of existing evidence review that we are proposing to apply to this process.
And, Ned, I will refer to you in the informal. You will forgive me. Ned has referred to this as the indirect chain of evidence for evaluating analytic validity, clinical validity, and clinical utility, and then with the expectation that the advisory committee would make recommendations based on the certainty of net benefit.
So as Dr. Calonge has steered us through this, there are steps in the process to define the question regarding testing for the specific question within an analytic framework that includes an overarching key question and then a chain of related key questions, again, the concept of indirect evidence.
This is the analytic framework which may initially look complicated but actually is pretty straightforward. If you just start on the left with the general population of newborns and the overriding question being will screening improve the outcomes of those newborns, that's sort of number 1, the overarching question. And then the questions 2 through 7 addressing the issues of testing, identification of condition, identification of any harms in testing or risks in testing, as well as any potential harms for treatment or other interventions. And I'll go through those in this presentation.
DR. CALONGE: Nancy, can I just make a couple comments on the analytic framework?
DR. GREEN: Please.
DR. CALONGE: So, first of all, I point out this is not a decision tree because there's not another arm saying screen versus not screen. This is really a framework that's designed to help frame the questions that we evaluate in the evidence review, and the framework, as you look at it, is used both, I would say, by three evidence-based groups in the United States. One is the U.S. Preventive Services Task Force. The other is the EGAPP Working Group, which is where I am today. So I apologize for not being there. And the third is the Community Guide to Preventive Services. So this is a pretty ubiquitous way of looking at screening for conditions.

DR. GREEN: Great. Thank you. Those are important points.
So, again, the key question 1, which is really the overriding question, is there direct evidence that screening for the condition at birth leads to improved health outcomes? And best evidence would be certainly randomized trials, large-scale population-based detection. But as I mentioned earlier, for many of these conditions, it's unlikely that that kind of direct evidence will exist, hence this modification.
So key question 2 is, what is known about the condition? Is the condition well defined and important? What is the incidence of the condition in the U.S. population, the target for screening? What's the spectrum of disease for the condition? And what's the natural history of the condition, including the impact of recognition and treatment?
I would like to just interject that as you hear these key questions that I'll present, these in fact are in parallel with the nomination form and the other steps that have preceded an evidence-based review so that there is nothing new here.
Key question 3. Is there a test for the condition with sufficient analytic utility and validity? And this refers to the laboratory performance of the test, both the analytic reliability and the assay robustness. that may include some aspect of pre- and post-analytic considerations.
Key question 4. Does the test accurately and reliably detect the condition and clinical disease? This is the clinical validity issue. Sensitivity, specificity, certainly prevalence of the condition, positive predictive value, and false positive rates. And the measures must relate to clinical and symptomatic disease, the phenotype. For example, what happens when you identify somebody with a disorder but who is clinically well?
Key question 5. Are there available treatments for the condition that improve important health outcomes? Does treatment of the condition detected through newborn screening improve important health outcomes when compared with waiting until clinical detection? Are there subsets of affected children more likely to benefit from treatment that can be identified through testing or clinical findings? Are there treatments for affected children standardized, widely available, and if appropriate, FDA-approved?
As part of key question 5, the advisory committee will need to determine which outcomes should be considered as important health outcomes, and these, I would say, are not necessarily of equal weight but for your consideration. Certainly patient outcomes, specifically morbidity and mortality; therapeutic and management decisions; diagnostic thinking and health information impact; as well as familial and societal impact.
DR. CALONGE: And Nancy, if I could interject here. In the longer document that this slide points to, there's a table taken from the Advisory Committee on Genetics, Health, and Society, the other genetic advisory committee. And I would refer folks to those tables because each one of these four areas is fleshed out in more detail.
DR. GREEN: Great. Thank you. I assume the committee members have that report. Okay. Thanks, Ned.
Key questions 6 and 7. Are there harms or risks identified for the identification of these children? That's 6. And then 7, are there harms or risks for treatment of affected children? These include the harms of screening, including ELSI issues, ethical, legal, social issues; harms of diagnostic workup for screen positives; harms of treatment, especially if there's no benefit or if
DR. CALONGE: Or if treatment is provided to false-positives.
DR. GREEN: Thanks, Ned.
Key question 8. What is the estimated cost-effectiveness of testing for the condition? And as we all, I think, recognize, there's unlikely to be empiric data on this point, but the question may be

addressed through decision modeling which could provide potentially estimates for the advisory committee to take into consideration when considering a recommendation.
So translating evidence into recommendations. Given those eight questions, the judgment regarding the magnitude of net benefit needs to be determined, and that's the net benefit minus the net harms. Also something that will be important, I think quite challenging for this committee, is the judgment of the adequacy of evidence in answering the key questions, especially as I mentioned since the more traditional evidence, randomized trials, et cetera, will likely be lacking, and the judgment of the certainty of net benefit.
DR. CALONGE: I would like to interject at this point. I very carefully, in making these slides, used the word "judgment." I think there's a great deal of the process that we use that is objective, but ultimately there are these three areas where we will have to make a judgment based on what's presented to us.
DR. GREEN: Thank you.
So how do we assess the magnitude of net benefit? Certainly if it's significant where the benefits clearly outweigh the harms, where there is zero net benefit or even some net harm, or that there may be a small net benefit. Again, I think underscoring Ned's points that he just made, that we have to carefully consider the level of certainty and other issues such as cost-effectiveness in the absence of, again, these more traditional studies and the likely absence.
So the adequacy of evidence. What I'm going to present, I think, is more thoroughly presented in the document that the committee members have, and I refer to the appendices which classify evidence in various gradations and I think that's important reading. But this is just really a synopsis of that.
The evidence should be classified as adequate or inadequate. Inadequate evidence for a key question represents a "break" in the evidence chain that would lead to a finding of insufficient certainty for net benefit. And the adequacy should be determined by applying a set of critical appraisal questions to each key question.
Ned, do you want to add anything at this point?
DR. CALONGE: No. I think that was great.
DR. GREEN: Critical appraisal questions.
Number 1, do the studies have the appropriate research design to answer the key question?
Two, to what extent are the studies of high quality, such as internal validity? Again, the issues of quality or laid out, I think, nicely in the appendices that Dr. Calonge provided.
Three, to what extent are the studies generalizable to the U.S. population? And Coleen, I think that touches on the point that you're addressing about whether non-U.S. data could or should be included in the consideration.
Four, how many studies and how large have been done to answer the key question, i.e., the precision of the evidence?
Five, how consistent are the studies?
And six, are there additional factors supporting conclusions?
DR. CALONGE: The epidemiologists in the room will recognize these as supporting when we use indirect evidence to support a conclusion. They are in place now for the Preventive Services guideline and published in our methods, and I just pulled them directly from there for consideration by the advisory committee.
DR. GREEN: Thanks.
Judging the certainty of net benefit. Based on the available evidence, estimate the magnitude of benefit or potential benefit. Based on the evidence, estimate the magnitude of harm or potential

harm. And then estimate the net benefit, benefits minus harms. Easier said than done. Base judgment of certainty of net benefit through applying critical appraisal questions across the chain of evidence. So while I say that this is hard, I would propose to the committee that the details included in the appendices help address making those judgments.
Certainty. So the evidence is sufficient or insufficient. So where evidence is sufficient to determine the effect on health outcomes with an acceptable risk or level of comfort of being wrong and thus a low susceptibility of being overturned or otherwise altered by additional research. I think I would just interject that things migrate over time and it may be that if a particular condition were added to the panel, I think the underlying assumption here is that there would be an ongoing evaluation of the impact of that addition on the evidence.
And the other alternative certainly being that the evidence is insufficient to assess the effects on health outcomes and that additional data or information from future studies would be useful or necessary.
And then there is kind of a gray area which is insufficient certainty but compelling contextual issues. I think this is worth thinking about in this committee's deliberations. There may be conditions where the evidence is inadequate to reach a conclusion, but contextual issues support a recommendation to add the condition with the commitment to fill in the gaps in evidence going forward. So a structured evaluation.
Contextual issues might include known benefits associated with testing and intervention for similar conditions. High incidence of the disorder that would translate to potential substantial net benefit. Availability of promising but yet unproven new therapies, and indirect evidence of perhaps less important health outcomes but with evidence of low potential harms.
DR. CALONGE: So I want to make sure the committee realizes this is not an all-inclusive list but trying to provide some examples of contextual issues that might lead us into this realm of compelling contextual issues.
PARTICIPANT: Are we holding comments until the end?
DR. GREEN: I'm almost finished.
So this is a recommendation matrix with four potential recommendations, although I would hasten to add that the third one is not necessarily an existing pathway at the moment, but I'll get to it.
So if you just look at the columns, recommendation, level of certainty, and magnitude of net benefit. So this largely is organized as, I think, what we've said, but the options being, number 1, recommending adding to the core set with a sufficient level of certainty and a magnitude of net benefit, but again, with the potential caveat that special considerations for net benefit is small. Again, this is this issue of the magnitude of potential benefits and harms.
Number 2, recommend not adding the condition because there's not a clear potential net benefit.
The third one, as I said, add with some provisional status where there's insufficient evidence to support screening for a particular condition, but there's compelling maybe indirect evidence for screening. I think this is something that the committee may need to discuss downstream.
And then lastly, recommend not adding the new condition now, but recommending some specific pilot studies that would be useful because existing data are not sufficient to make a decision.
Again, I'd like to thank Dr. Calonge for really doing the bulk of this work, as well as people listed here, Michele and Piero and other members of this workgroup. Ned had already acknowledged these other august groups. So thank you.
Ned, do you have any other comments? Again, thank you very much.
DR. CALONGE: I do want to, first, thank the people on the last slide who had a chance and

opportunity to review the second iteration of the draft and, at the same time, apologize to the rest of the subcommittee that I didn't get this to you in time to engage in a conversation. It was just a matter of my day job and other commitments. So I want both an apology and acknowledgement in place. And I am really excited to hear comments.
I guess the last thing I would add is that EGAPP is meeting today, and my direction to them they had considered whether or not their scope should expand to include newborn screening, and I said that would be totally redundant and we don't need to do that.
DR. HOWELL: Ned, let me thank you for this excellent report. And Nancy, thank you for presenting this in Ned's absence at the EGAPP.
Let's have some comments about this document. I might point out that later today we're going to review the recommendation for Pompe disease that has come from the evidence group, and this particular format will be used in that presentation. But some comments? Gerry?
DR. VOCKLEY: Obviously, this is difficult because we're dealing with conditions where we will probably never have the type of evidence that we want, and so I think we have to maintain flexibility. And this document does an excellent job with that. I think they almost did too good a job.
There are some areas there where it seems to me that the obvious response is it's not ready, get more information, and in particular, that last group where you say you've got a compelling reason for wanting to do it, the third one in there, but you just don't have enough data to really support it. I wouldn't call that provisional. I'd just put it in the last category and say we can't recommend it right now. I think that's maintaining too much flexibility. If we flat out say we don't have the information we need to make an intelligent decision and we're just going to go on potential or compelling net benefit, I don't think that's a good reason to put something in the standard panel. I think we ought to have a higher standard than that to the standard panel. The data should say that there's some reason to believe this is going to work as opposed to some reason for wanting it to work.
DR. CALONGE: Rod, can I answer that?
DR. HOWELL: By all means,
DR. CALONGE: So, Gerry, it's an excellent point and I think goes to the heart of something that the committee needs to decide. In the other evidence groups, everyone recognizes there's kind of this insufficient, optimistic category or I positive. And not only the other task forces, but the international work in *GRADE are wrestling with what to do with these I positives. And most of them are saying that's all they are. We can't make a recommendation. So this would be the first foray into doing something a little bit different with that I positive group.
And I agree with you, the cleaner approach from an evidence-based standpoint would be to say "not ready." So I have a hard time advocating for one side or the other, but I want you to know that there are a lot of groups wrestling with this specific question.
DR. HOWELL: Thank you very much.
Tracy, you had a comment?
DR. TROTTER: Yes. I was on this committee that Ned so ably chaired. We want to give him great kudos for putting a very difficult project together in a way that makes sense to me. And we wrestled a lot with this third possibility of provisional status. I think one of the points that should be brought up that was brought up frequently in our subcommittee meetings is how do you undo provisional. I think it would be difficult both realistically and politically and otherwise. Therein is another reason that maybe that category will take a lot of thought for something to fall into that category as to one of the other three out of four.

DR. HOWELL: Nancy?
DR. GREEN: Just to underscore what Dr. Trotter has said, that the states which really make these decisions don't have provisional as a category. It's a pilot or it's in. So I think that we've discussed it in the context of might this be another pathway, but absolutely it doesn't exist at this point.
DR. HOWELL: The third category is going to be arguably the most difficult that comes to the committee because there are going to be conditions that we know are extremely serious and that there are treatments that are effective and there are screening tests that probably work and have been demonstrated to work maybe somewhere else. And the question is that you have the situation of should that be given provisional status with specific notations about the fact that you need to do this, that, and the other thing or else say that it's not ready to be added and you should do these pilot studies or whatever you need to do and come back. I think that certainly, I'm sure, is the core of the discussion that this committee spent a lot of time on.
Coleen, do you have wisdom over there?
DR. BOYLE: I was just going to add the discussion we had on our phone call a couple months ago. We could recommend pilot studies. I understand the issue of trying to move it along outside the realm of research, but I guess I still feel like that informed consent issue is important, given the uncertainty that we have relative to the evidence.
DR. HOWELL: In view of those comments, how would you amplify this third category? I mean, you come down and you have recommended adding the condition with provisional status. How would that be tied up in your recommendation? What would you say about that?
DR. BOYLE: Well, I guess I would probably make the fourth category more tentative, you know, that it's clearly not ready for prime time yet. And I'd make the third category one that is provisional and the committee would strongly encourage pilot studies, you know, population-based studies that would be implemented within the context of a state screening program.
DR. HOWELL: So you would keep the provisional status in the third category and have very specific recommendations. The issue that's been raised by Ned is, if you have a provisional category, how do you stay in or out? In other words, how do you move from provisional to a less provisional? I think that would be relatively easy, but going the other way might be tough.
Gerry?
DR. CALONGE: Dr. Howell?
DR. HOWELL: Yes, Ned?
DR. CALONGE: I'm sorry. I need to sign off and go back to my other meeting. Nancy, I assume you'll brief me on what we decide?
DR. HOWELL: You're leaving us just when the stuff gets tough. But go back to EGAPP.
DR. CALONGE: I have to apologize.
DR. HOWELL: Thank you, Ned.
DR. CALONGE: Okay.
DR. VOCKLEY: When the going gets tough, the tough get going.
I agree with changing that last category to being very much more negative. Really, we have a category where you just didn't come close to the threshold and we're sending you back to the board. You do what you think you need to do based on the comments that you receive. That's fine. I think that's what number 4 should be.
And I think that what you say for number 4 right now really becomes number 3. That provisional status is not we'll accept it provisionally. It's send it back with some encouraging comments that say that we're very sympathetic to this. We have recognized that there are some special

circumstances here that might be in play, and here's what you would need to do to get it over the threshold.
But I would put an encouraging status somehow to it as opposed to a provisional accepted because I think going provisional accepted is going to just open it up to looser and looser guidelines that everyone is going to want to say, well, I want come in category 3. Don't reject me. Put me in category 3. I think we're asking for trouble with a provisional acceptance as opposed to an encouraging rejection.
DR. HOWELL: Any more specific comments from the members of the committee?
DR. LLOYD-PURYEAR: I have a question just to clarify for my notes. So the last category is really you're not even ready for pilot studies. There's a lot of research still needing to be done before you're even at the status of doing pilot studies. Is that what you're saying?
DR. VOCKLEY: Yes. I think we have to have a status for outright rejection, and then a status for we think you have something here, but here's what you need. The encouraging rejection, as opposed to the provisional acceptance, gives a little bit more latitude there because then you can tell people what it is you're thinking. And if it is one of these compelling stories where the committee may well be able to apply a slightly looser formal testing standard than some of the others, but then you at least get that message back to them and say, fill in the gaps, take six months, take a year, but do it as a pilot rather than trying to make a recommendation that we're going to implement it.
Because what does provisional implementation mean? I mean, you're going to tell states everybody is going to go ahead and start putting it in, and then you're going to turn around a year later and say never mind? Once the cat is out of the bag, it's very, very difficult to do that. So I just think we need to be a little bit tighter than that.
DR. HOWELL: It's my impression, having had an opportunity to review everything that's come to the committee and the cases are extremely compelling. And in a number of cases, there is clearly really compelling material and so forth. But there's one section that may not be ready to suggest. I would think if we do that, we should be highly specific about what the holes are. In other words, I don't think you'd just say come back later, but you'd say this is a wonderful condition to screen for, but we really need this information.
And then the bottom one, you would suggest to say recommend not adding the condition at the current time, and then take out pilot studies, block that out, and then insufficient, et cetera. You would not have enough information to make specific recommendations, but a more global requirement.
Is there some sense of that? Bennett?
DR. LAVENSTEIN: Well, I wonder. I think your point is a good one. There's got to be some time frame to this otherwise it seems to be very amorphous. So it seems that in a way we want to have conditions that are under study that will meet the criteria for consideration within 6 months to 12 months so people have an idea that they can move with the data within a time frame.
DR. HOWELL: I think that would be fine.
Any further comments from the committee?
DR. DOUGHERTY: Yes.
DR. HOWELL: Denise?
DR. DOUGHERTY: I guess in reading through all the materials together, including the Pompe material, and then looking at this starkly like this, the last item about pilot studies, what strikes me is that sometimes I think we always meant pilot studies of screening. But in some cases, we may want more evidence of the treatment benefit before making a decision. And I'm wondering

how that kind of situation would fit in this recommendation matrix. Rather than just using the term "pilot studies," we may want to unless that goes with the revised number 3. It would go with the revised number 3 that we need more evidence on the effectiveness of treatment?
DR. VOCKLEY: I agree. Don't say pilot studies. It could be anything. So the third category becomes the "you're close but" and we can tell them what the "but" means. And the last one is just you're not ready.
DR. HOWELL: And I would infer, Denise, that the evidence that is required would be specified. It might be treatment. It might be a test. It might be anything, but I think it would be specified. Mike, do you want to make a comment? I want to come back to Gerry's recommendation.
DR. SKEELS: I just want to agree from the point of view of a state screening program. As Nancy said, it's really a binary issue for us. Either we are or we aren't screening. We don't provisionally screen any babies.
I also want to add a couple of other people have said this, but you can't unring this bell. Once we establish a core set and states embrace it, there it is, and it will be pretty hard to go in and say we'd like to offer less service than we have been in the past.
So those are both valid points.
As I've been listening to this, it looks to me like the guiding philosophy was to make sure that we don't miss the opportunity to add disorders to the panel that we could possibly be screening for if there's any validity at all. And at the risk of sounding negative, I really think where we ought to be is we should not be screening for anything less there's compelling evidence to do so. I think this looks like we were just trying to get anything in there that could possibly have benefit. I really think that's the wrong starting point. I really think from the public accountability point of view, we should only be requiring mandatory screening and using the force of law to require parents to have children screened for the things that are unequivocally valuable to those children and beneficial.
DR. HOWELL: Thank you, Mike.
The sense I get is that the committee recognizes this as an outstanding bit of work here, and I see the committee being quite supportive.
And Gerry, I would like you to come up with a specific. You've had specific recommendations about number 3 and 4, and maybe we could have you suggest wording that you would suggest there. And maybe you can make a motion for that wording, and if we can get a second, we can actually vote on it.
DR. DOUGHERTY: Rod, can I ask a question? I guess when I was listening and reading this, there were a number of kind of semi-recommendations or suggestions that the committee needs to decide which outcomes it's going to look at. I'm sorry Nancy is leaving, but maybe Michele knows this. I'm wondering if we could get from Nancy and Ned or Michele what next steps the authors of this think the committee needs to take. Do we need to revise just this language and then accept it as a recommendation? What next steps is the committee supposed to take before just working with one part of the language?
DR. LLOYD-PURYEAR: Well, I'm just really staff, but the expectation is if this were without any changes, any concerns, that perhaps the committee would adopt it as their methodology. I don't know if you could adopt it provisionally
(Laughter.)
DR. LLOYD-PURYEAR: or not until our November call. But the point is to get the specific changes in there and get the decision process in place so that the committee can begin to use it. Rod had said that Mike Watson would be using this methodology to evaluate the Pompe

evidence review. So we might want to wait to see how the methodology works before
DR. HOWELL: Let me make one suggestion.
DR. DOUGHERTY: But this is not a definitive document. So what do we do? We can accept it provisionally and say that we will work on the things that the writing group suggested we work on.
DR. HOWELL: Denise, let's do the following. Let's have Gerry comment about the wording about 3 and 4. Let's then digest this a bit, and then let's see how it goes with Mike because Mike is going to use basically this same format for the Pompe. Maybe then we can come back about adoption.
And the other thing is that I also don't know whether the committee members have found significant issues within the text that they would like Coleen?
DR. BOYLE: I just wanted to mention one other thing, and it was exactly what you had said about putting into practice for Pompe disease. There was one piece for me missing between key question 4 and key question 5, and that was the issue about the confirmatory test. That seems to be missing from this entirely, whether or not a confirmatory test exists, whether it's reliable, that type of information. It's just not there. And obviously, that was an important issue for Pompe. So that's why it sort of jumped out at me. So I just wanted to make that to Ned, but he's not here, but Nancy can carry that back.
DR. HOWELL: Our person who is getting ready to make recommendations about the matrix has exited into the corridor to take a phone call. Are there any comments while we're waiting on Gerry to finish his phone call? Mike?
DR. WATSON: I am going to go over the set of questions and some of the input from Ned and Piero. But I don't think it has any implications actually for this. This is a recommendation you do or don't make.
DR. HOWELL: It does not have implications of this particular chart. Come up with some wording, Gerry, so that we can see whether or not there's consensus on that.
DR. VOCKLEY: I think probably the only thing that you need to change on line 3 is the first box, which is recommend adding with provisional status. I would say recommend something to the effect of
PARTICIPANT: The same words as in the first of number 4.
DR. VOCKLEY: Yes. Recommend not adding the condition now, but encourage additional specific studies.
DR. HOWELL: Right, and then on the fourth line, you would say recommend not adding the condition now. Period. Is that correct?
DR. VOCKLEY: Yes. What I want to do is distinguish the last box from number 2. Number 2 was saying there's compelling evidence that we shouldn't do this. Number 4 is saying we just don't have enough evidence one way or another.
DR. HOWELL: Okay. But basically you'd say recommend not adding the condition at the current time but encourage you to return the pilot studies. That would be number 3.
DR. VOCKLEY: With additional studies. Don't use the word "pilot."
DR. HOWELL: And the fourth one would be recommend not adding the condition now. Period.
DR. VOCKLEY: Right.
DR. HOWELL: Is there a sense that that fits with what the group around the table is thinking? Coleen, is that sensible with you?
DR. DOUGHERTY: *[1b flip] because why wouldn't people who get a 2 also go out and get more information

DR. VOCKLEY: Well, they could, but what number 2 is really is the committee is saying my interpretation is the committee is saying there really is actually evidence to not include this. You have a much higher barrier to overturn that one. Number 4 is simply saying we can't make a determination one way or another. I view number 1 as being positive, number 2 as being negative, number 3 as being you're close, and number 4 is we don't know.
DR. TROTTER: I agree. That's a perfect representation. I was on the committee. Number 2 really says the level of certainty is sufficient, but the magnitude of benefit has been shown to be zero or in some cases a net harm. And there is evidence available that you can assess it. Whereas, 3 and 4 were really saying we don't really have enough. So there is quite a difference between those.
DR. HOWELL: That's clear to me. Is it clear to everybody else at the current time?
Let's don't vote on this. We will have that as an operational definition. We'll look at it once we go through and see what other thing I think Coleen has had some significant questions about the confirmatory testing that might need to be added between 4 and 5 and so forth.
Nancy, thank you very much.
Tomorrow Nancy, we hope, will be in the morning. I understand that you will be, and one of the things that we will do tomorrow under Nancy's able leadership is to quickly go through the recommendation of the nomination review from the Prioritization Workgroup for Niemann-Pick, which has been handed out to you today.
Let's move along. We've got a lot of things on our agenda today, and we're now going to go the Evidence Review Workgroup report of the candidate nomination on Pompe disease, and we're going to ask Dr. Perrin to present the work of his group. This is an exciting day because this is the first formal report we've had from the Evidence Review Group. Of course, it's on Pompe disease.
And when Jim has finished with his discussion about how this proceeded, we're going to have Mike Watson work through the review for the committee. Piero Rinaldo, unfortunately, had to fly quite quickly to Italy because his dad is very sick. So he has prepared the slides and material that Mike will use later.
Jim?
+ DR. PERRIN: Thank you very much. I think I'm going to stand, if that's okay, Rod.
DR. HOWELL: Please do.
DR. PERRIN: First of all, I just want to say how much we appreciate the opportunity to work with the advisory committee. We have found this a fascinating experience, and we are very pleased to update you where we are.
I would start by saying that, indeed, we are presenting to you the review of Pompe disease. We are well along our review of severe combined immunodeficiency and we have just begun the review of Krabbe disease too.
For the Pompe disease review that we're presenting today, the key author is really Marsha Browning who is a metabolic geneticist at the Mass General, a member of our content team, and Alex Kemper, who is here today. And I may need to ask Alex to respond to questions that I really can't handle.
We have a really good staff of people who are part of this, and I want to acknowledge all of them, frankly. Anne Comeau is here not representing us but for other purposes. Nancy Green, whom you've just heard from. Alix Knapp, who is in the back of the room, is our project coordinator. Ellen Lipstein, who is a young pediatrician on our fellow group, who is, by the way, taking a major role with our SCID review. Lisa Prosser, who is not here, but who works a lot on

cost-effectiveness and related issues. And Denise Queally, who has substantial experience in the PKU community and represents consumer communities for us.
Now, I don't have a slide, but I'd like to sort of remind the advisory committee somewhat about the process that you folks went through in order to get us started on the Pompe review because some of you are new and may not remember that or may not know that.
So basically there is a nomination form that is available on the committee's website that is to be filled out by anyone who wishes to nominate a particular condition for review by the advisory committee. That is reviewed initially technically by the MCHB staff, through Michele Lloyd-Puryear's office, and then if it has all of the elements in it that are needed for further work, it goes to the advisory committee which then decides whether to send it to the Nominations Committee for review of whether this is a nomination that they would recommend back to the advisory committee should be sent out for external in-depth scientific review.
In that context then, it comes to us on referral from the advisory committee for us to carry out those reviews. And as I mentioned a couple moments ago, the three that have been recommended so far are Pompe, Krabbe, and SCID.
In our methods and I will tell you about them a little bit more in detail we have tried to be very clear about issues of conflict of interest relating to both our own staff and were there any possibilities of conflict of interest. Since I was born before Mendel, I have none whatsoever. (Laughter.)
DR. PERRIN: But we have dealt with that fairly actively and in some interesting ways in our group. And similarly, people we have worked with we have asked to fill out fairly substantial conflict of interest forms so that we know what they're doing and how that might influence the kind of information they provide us.
Now, Pompe disease, as I think many of you know, is a lysosomal storage disease. It's autosomal recessive with a number of described mutations so far in the GAA gene. In this disease, glycogen accumulates in several tissues, mainly in muscle and lung, and in infantile form in the heart as well, and it really relates to diminished or lack of enzyme activity.
There are two forms generally described, the early and late-onset forms, and I will talk about them in a little bit more detail a little bit later.
Now, why did this particular condition come for review to the advisory committee? What was on the nomination form and what did the Nominations Committee look at? There were probably these three primary aspects that led to the recommendation for further in-depth review. One is that methods for newborn screening for Pompe disease do exist, including two major forms, enzyme activity measures done a couple different ways and direct protein quantification.
There has been a recent population-based pilot study of newborn screening, and we will talk in a little more detail about that particular study.
And there is some evidence for effective treatment of early-onset disease by enzyme replacement.
The methods for review, in this particular case and this will differ for some of our future reviews. In this particular case, we had the advantage of a preceding systematic literature review that Alex Kemper had carried out and it was published in Pediatrics in 2007. We updated that review in a couple of different ways to make sure that we had more recent innovation and also looked back at some of the papers that were analyzed in that earlier review.
We also did some assessment of unpublished data from key investigators in the area of Pompe disease.
So what were our review questions? You'll see some real similarities to what Nancy presented a

few moments ago. Do current screening tests effectively and efficiently identify cases of Pompe disease that may benefit from early treatment? Sort of a critical question. Does early treatment improve outcomes? What is the cost-effectiveness of newborn screening for Pompe? And what critical information is still needed?

So the materials that either we provided to you so far or have available for you are, first, a draft review summary. And I believe the committee got a copy of that a week or so ago. I'm not sure. The procedures that we went through as we have an external review committee who works with us. That includes Harvey Cohen, Bob Davis, Jeanine Cody, and Celia Kay. And we sent it to them approximately a month or month and a half prior to this meeting that's our goal prior to the time it comes to this committee and ask for their reviews, which we then incorporate into our draft version, which were incorporated in the draft version that we sent to you. It then, a couple of weeks ago, went to review by the Nomination and Screening Committee, Ned's committee, and that will be presented a little bit later by Mike Watson. So again, there's a fairly systematic review of this review.

We provided this. And I really want to call this a draft, and I hope that will be allowable to the committee because we realized even in the last two or three weeks that there are things that we need to clean up and say a bit better. We've provided you an evidence table of the abstracted articles, really Alex's work. We have a bibliography we've not provided that to you, but we certainly can and will to the Bureau of all the identified articles. And we'll describe to you in a few minutes the interviewees whom we've talked to related to Pompe disease.

The systematic review of the literature was based on looking at articles from 1996 to 2008 in Medline. We looked at only English language articles and only ones in human studies, no animal studies. We also looked at references that came from the nomination form, in case they didn't show up in our systematic review, and we looked at the reference lists in key reviews relating to Pompe disease. That was the major methods of our identifying articles for review.

We did an initial review of the abstracts from all those articles and then an in-depth review of articles that were selected as meeting review criteria.

Now, we've talked with this committee before about the issues of quality measurement in these studies. As I think you will notice, we're providing almost no information about quality in this review. We will have more information about quality in the SCID review. But the reasons for that are that we are still struggling with the best of doing it. That's the simple way of saying that. Our sense is that most of the studies we have in most systematic reviews would be labeled as in the poorer level of quality. We recognize, as Gerry just mentioned, that we'd like to provide you with sort of more in-depth review of what that quality level is at that edge of the spectrum of quality. But that, in general, is what we're finding. I think what we have provided to you in the tables is a little bit of a commentary about the strengths and weaknesses of individual papers, but we'd like to be able to provide it to you more systematically as we move forward.

We also had, mainly under Marsha's direction, expert communication with people who represented a variety of the questions related to Pompe disease. This was determined, again, by literature review and by discussion with people who are particularly expert in the area of Pompe disease. We included experts representing, we think, all the major issues in Pompe disease. These are some of the people that we've had direct communication with and discussions.

And as I mentioned, again in each case, we've asked these people a couple things. One is to let us know if there is new information that they do not yet have published that might reflect on the key questions we're trying to answer about newborn screening for Pompe disease. So we're not asking them, for example, to say we have a draft or a review, what do you think about it? That is

absolutely not what people are asked to do in this context. The review remains with us. We are simply asking them, do you have new information that we should have that might benefit us in providing information for the benefit of the advisory committee? And in each case, that is exactly what we asked for rather than say what do you think we ought to do, what do you think the committee ought to recommend. Our job is really to gather the evidence, provide that evidence for the committee's decision-making. We're not making recommendations. We didn't have any recommendations, in fact, to share with these experts.

I've listed them here. There are a pretty wide-ranging number of people and wide-ranging sets of where they spend their time, but it includes people in the continental United States, as well as folks in Vienna and Adelaide in Australia and Taiwan, among other places.

Now, the natural history studies in Pompe disease typically show and this is, to a degree, in your Tables infantile forms, and there are more or less two forms of infantile Pompe disease, classic and non-classic. Simply, the non-classic version tends to appear somewhat later, not in the first few months of life, may not have cardiomegaly until after the first birthday, and does seem to be a somewhat different clinical version from the classic infantile version, although I would say there are not a lot of studies that really well document this. And then there's another form, which is late-onset.

Now, for the infantile version, symptoms usually exist by 2 months of age. Diagnosis is made on average at about 5 months of age. These are children who do have glycogen in their cardiovascular muscle and cardiomegaly is a very common presentation here. Without treatment, the natural history is that the median age of death is 9 months. Fewer than 10 percent of children with early-onset classic Pompe disease survive to 24 months.

As I mentioned a moment ago, the non-classic has a somewhat longer survival. Cardiomegaly which is found in the non-classic version typically is not present until about a year of age.

Late-onset Pompe disease is a very wide spectrum of conditions. Cardiomegaly is essentially not present in late-onset Pompe disease. There's a very wide range of age at diagnosis and severity. One paper was a retrospective review. Basically onset of symptoms in this particularly study was at about 8 years of age and the age of diagnosis was about 37 years. So this is a very different, palpably different condition from early-onset Pompe disease. The series that do exist of late-onset Pompe disease may, indeed, be biased toward more severe cases, i.e., ones that will be diagnosed. There may be other people with even less severe forms of Pompe disease in the community who aren't now and never will be diagnosed, at least by the current methods of diagnosis.

So this is based on Alex's work, but this is a series of studies of prevalence from a number of examples. I might say that these vary tremendously in the quality of the studies. So the third one down, for example, is a letter to the editor and really provides very little detail on the methodology behind how these numbers were arrived at. As you can see, the first and third are really based predominantly by inferences back from mutations that were determined here. And the second and fourth are more birth cohort prevalence. The Chien study in 2008 is the Taiwan study that was published in Pediatrics in June or July of 2008.

What is of interest is that the rates appear to be at least in total approximately the same general order of magnitude, something on the order of 1 in 40,000. It is not at all clear from these studies actually, though, what is the relative rate of early versus late-onset, and that probably reflects the real difficulties and real variations in these studies about really what late-onset consisted of in them. So I think we can say that the studies give us some general information about prevalence. They don't help us a great deal in distinguishing between the groups.

Let me move on to screening tests to talk about the fact that, as I mentioned, there are more or less two major ways of screening: the enzyme activity measures which are done in a couple of ways by mass spectrometry or by fluorometry, and then the other approach which is really looking at the protein directly and the amount of protein which really the group in Adelaide and elsewhere has been doing a substantial amount of that work.
I don't have here the Taiwan data. That will be on my next slide because the Taiwan data represent the only population-based survey so far in Pompe disease. Period.
So these are all basically selected or *convenience or other sample studies not in population-based studies in general. And you can see that, in general, the sensitivities of the strategies used vary from as low, in the paper in 2000, as 82 percent to, in the paper that was early this year by Dajnoki and others, 100 percent.
And the specificity varies again somewhat substantially from reports of 100 percent but based on very small numbers of controls. We want to stress that. For example, if you look at the last paper here, that's 150 controls in that particular paper, 195 in the one above. So the specificity seems to be high, but of course, with a condition of 1 in 40,000, we need to know more about the specificity than it seems to be in the 99 to 100 percent range.
The Taiwan screening experience is the one that I mentioned was published in Pediatrics around June or July, and this is an enzyme activity measured by fluorometry. This is actually a revision of the data presented in that paper again, Alex did this for us because the initial work, the original criteria row basically says that in the initial work, per 100,000 children tested, 6 would have been referred for diagnostic confirmation because of very, very low enzyme activity. And 800 or so were referred for a second blood spot. After the second blood spot, 80 or so would be referred for confirmation, and the total number of cases per 100,000 diagnosed was 3.
They found basically that by changing their criteria, that they could actually cut down on the false positive rate without changing the sensitivity essentially at all, presumably not at all. And thus, the bottom row represents using more specific criteria basically in order to figure out which children would be referred. So in that case, you have per 100,000 children about 6 referred initially, not quite 400 referred for a second blood spot, 40, not quite, referred for diagnostic confirmation, and again 3 cases per 100,000. So it gives you a sense you may not want to call this sensitivity and specificity, but this gives you a sense of what actually will happen in population-based screening based on these data.
Coleen, please.
DR. BOYLE: Should we hold our questions? I just need a clarification.
DR. HOWELL: If it's a question of clarification, I would go ahead and do that.
DR. BOYLE: So it was unclear to me, based on your previous slide and the little thing you had at the bottom, "no screening test"
DR. PERRIN: I'm sorry. I should have mentioned that.
DR. BOYLE: Yes. So in reading through the literature and reading some of the original papers, it was unclear to me whether the expectation would be that in a newborn screening program, you'd be able to distinguish late versus I mean, whether you'd even pick up late-onset from a theoretical standpoint.
DR. PERRIN: From a theoretical standpoint, you should be able to pick up late-onset, yes. But the analyses that we've done would indicate that there is no current newborn screening mechanism to distinguish late- versus early-onset at the point of screening.
DR. BOYLE: You would get.
DR. PERRIN: The answer is we believe on the theoretical basis, yes. I do think that's one of the

questions we will raise in a moment about the Taiwan data. But yes, thank you for pointing it out, Coleen, because I should have mentioned that while I was still on this slide. One cannot, by current methodology, distinguish early- versus late-onset by newborn screening.
DR. HOWELL: Let me ask one technical question. Recalled for a second blood spot means the patient is actually brought back for a second spot and not punched from the same original document.
DR. PERRIN: That is our understanding.
DR. KEMPER: Alex Kemper from the great State of North Carolina.
So what happens is in the Taiwan protocol, newborns get screened. If that screening test is abnormal, they are to rescreen with a second punch in the same dried blood spot, and if that's still persistently abnormal, then they're recalled for a second blood spot unless it's so abnormal that they're referred directly to diagnostic confirmation. So the second column there, "recalled for a second blood spot," are those children that are requested to come back for an actual second blood spot.
DR. HOWELL: So they physically have come back for a second spot and there's not a punch out of the first spot.
DR. KEMPER: Correct.
DR. HOWELL: Thanks very much, Alex. Good. Thank you.
DR. PERRIN: That is our understanding, including from some conversations with the Taiwan group.
Now, I'm going to present a little bit more data here. I really think we want advice from this committee as to whether you would like us to present these kinds of data. So I want to use this as a test opportunity for you people, among other things.
Let me go back one second and say we did gather from a number of these people, the Dajnoki group, for example, some of the primary data and basically we reran the analyses to see if they fit, but frankly, we found nothing new and different from what was already in the published findings.
In the case of Taiwan, we've had conversations with the Taiwan group, but we have absolutely not seen these data. They have not been shared with us to do any kind of primary analysis on our own basis.
But this is sort of an update on the publication from June or July, which is now up to over 200,000 children. The numbers are actually pretty much what we showed you on the previous slide with one important difference. .3 percent are recalled for a second double blood spot, about 600 cases out of 200,000. About .04 percent required confirmatory testing, about 82.
Now, in the original report in 2008, all of the cases diagnosed were labeled as being I'm sorry 3 of the cases diagnosed were labeled as being clearly early-onset, and 1 was probably early-onset. Is that right, Alex?
DR. KEMPER: Yes.
DR. PERRIN: Now, we've been told over the phone that they now have 11 cases, 6 of which are infantile and 5 of which are late-onset. We don't know the methodology of the distinction except we assume that these are in the 5 late-onset children who did not show symptomatology by 2 or 3 or 4 months of age after the screening. But we don't know more than that. We don't have the evidence to back up this information here. What is different is the fact that they do have some cases of late-onset identified here which were not in the 2008 paper.
Now, let me move from screening to treatment issues, and basically there are treatment trials, but they're quite limited. Basically all the treatment trials are entirely in clinically-identified children.

Now, as in other conditions, clinically-identified kids may be ones who are identified partly on the basis of family history and therefore are potentially identified shortly after birth. But in general, this is not from newborn screening. These are cases that were identified, again, clinically in traditional clinical ways. They're all from one center, and they are all infantile cases.
The evidence from the relatively short-term studies that exist is that mortality may be substantially improved, at least the 9 month mark. Morbidity may be improved, at least as measured by ventilator dependence. There are some patients who probably have vanishingly low or absolutely zero enzyme activity who seem to be producing some antibodies to the enzyme and who have fared less well. And we know essentially nothing about long-term outcomes from the current clinical treatment studies. Very limited information, but some.
DR. HOWELL: Why did you use the term "may" on the morbidity? Because the difference at 9 months in their published data is quite dramatic.
DR. PERRIN: Quite dramatic.
DR. HOWELL: I mean, it's not "may." It's quite striking. I mean, basically all the controls are dead and all their patients were alive, which is pretty dramatic.
DR. PERRIN: So one of the issues has to be, of course, any selection biases in the sample that might have affected those findings. So you're absolutely right. You're dealing here with a circumstance in which children typically die with this disease. So we're comparing this functionally with historical controls, but one question would be, are there important selection biases in the initial sample which are not easily identifiable from the study itself. Again, Alex, please jump in if I'm not saying this correctly.
Treatment for late-onset. We really don't have much evidence relating to treatment for late-onset, and particularly from the notion of newborn screening, we had no evidence, yea or nay, relating to whether there are benefits of early identification, i.e., in the newborn period, of people with late-onset Pompe disease. There's just no evidence in this area in one way or the other.
Now, let me go on to some of other areas and to really get down to the fact that we don't have data in many of these areas. These are all areas where evidence would be very beneficial for sure about harms and cost-effectiveness. In simple terms, we find almost no studies of harms and cost-effectiveness specifically related to Pompe disease, not at the level of screening, not at the level of diagnosis. I did mention the notion that patients who are enzyme-zero may develop antibodies that may limit effectiveness of treatment. So there may be at least some lack of benefit of treatment, if not harms of treatment. We were not able to identify any cost-effectiveness studies at all in the area of Pompe disease.
So to summarize, first of all, population screening in Taiwan does indicate feasibility. The false-positive rate, if you want to call it false-positive rate, the number of children who come back for a second screen and the number of children who are sent on for further diagnostic testing, is fairly substantial. The lack of identification of late-onset in the published report the reason for that is really not clear, why there aren't late-onset disease patients identified there. That's partly in response, Coleen, to your question.
The treatment of early-onset disease may be lifesaving, probably is lifesaving, but it's important to realize we have no studies of treatment of screen-positive newborns. By the way, that's one of the reasons we want to change our report. I believe the heading says treatment in screen-positive individuals. That was an error on our part.
There is certainly indirect evidence that earlier treatment has better outcomes, primarily from that single-center study.
As I said, no cost-effectiveness studies exist.

So I can go on at this point and tell you where we think there are some critical needs for evidence, and perhaps I should do that and then we can open it up for further discussion.
One, as became clear as we were really talking through the work here is we don't have a very clear standardized case definition or agreement for what we mean by infantile Pompe. In the printed report that you have, we have made what we would call the first draft attempt at a case definition. That needs to be vetted and thought through. We don't know if it's the right case definition, but at least it's an opportunity that might help future studies in what we mean by cases in the area of infantile Pompe disease.
We need to know more about the accuracy for screening for infantile-onset in population studies. We have the one population study so far.
We do not know about population-based screening using strategies other than enzyme activity. It could be that a protein quantity measurement might also have some substantial utility.
We have no information really about the feasibility of screening using current laboratory infrastructures.
Again, demonstrating the screening techniques in multiple laboratories would be helpful.
The diagnostic level. Again, a standardized case definition seems pretty critical. There should be some work done to differentiate classic and non-classic especially during the presymptomatic period, as well as distinguishing early-onset and late-onset. So there are two or two and a half categories, and it will be important to figure out how we can distinguish among them by newborn screening.
We need to know more about treatment for infantile Pompe, and I mentioned selection bias a moment ago. We need to know whether it's reproducible in a variety of treatment centers. We need to know more actually of what's going on with these children who are enzyme-negative who seem to be having less good responsiveness.
There are other issues that are needed here, improved strategies for determining the prevalence through systematic case finding, including the clarity of early- versus late-onset. Are there benefits to the identification of late-onset Pompe in newborns? We need to have information about the acceptability of screening, harms, and cost-effectiveness.
So thank you. I do want to say how much we've appreciated the opportunity to work on this particular review. We've taken many of our lessons so far and are applying them very actively to the SCID review that we're deeply involved with now.
DR. HOWELL: Jim, thank you very much.
Mike, you had a comment?
DR. SKEELS: Yes. Actually I just have a question. Back on the Taiwan data, I'm looking at the recall rate. As you said, it's very high. In fact, it's prohibitively high, I think, to be practical for a population-based newborn screening program.
But my question is, do you, or perhaps Dr. Kemper, have data that would show the range of results that were reported as positive? In other words, to what extent, just with the data that they already have, could they change their cutoff and eliminate false-positives while not removing any true-positives? I don't need an answer this second, but as a laboratorian, that's the first thing I'm going to ask, to what extent can you fix this problem by just changing the cutoff?
DR. LLOYD-PURYEAR: Alex, you can sit there. It might be easier.
DR. KEMPER: That's a great question.
When they first developed the protocol that they were using in Taiwan, they used a threshold that they knew ahead of time was going to cause a lot of false-positives in the hopes of not missing any true cases. But after having run through the first 100,000 children, they realized that they

were able to lower the threshold. So I can't tell you, without looking at the paper, exactly what it was that they were lowered. But that's how they were able to get from the 820 to the 370 per 100,000 children recalled for a second blood spot.
So those numbers on the second row, though, weren't published in the paper, but I just took what they thought by lowering the numbers they'd be able to lower the recall rate for a second blood spot through, and they said that by lowering that number, they weren't going to miss any true cases. So I just modeled the numbers and ran them through. But I can't tell you whether or not they can lower it below that 370.
And the other question I think you were getting to is if you look at the other studies of screening tests, if you applied those numbers, what kind of results would you get. And it's important to note that there are so relatively few cases, a few non-cases, a few controls, that it's hard to know exactly where between 99 and 100 percent specific they were. I guess one thing that we could look at is you know, it would be easy to generate 95 percent confidence intervals and get a sense of what the range would be, but I don't know if that would actually get to the question you're asking, which is how to redo the test to make it better.
DR. SKEELS: No. Actually that was very helpful. Thank you. I was just hoping that there might be in there some good segregation of true-positives and false-positives that they hadn't picked up, but it sounds like there really isn't. It sounds like they're smeared all over the place. So thanks.
DR. HOWELL: And I think the other thing that is in some of the appendices and so forth, some of the folks are working aggressively on the tandem mass spec assay that might have considerable advantages. It's not been done in a population study but it looks very promising. Gerry?
DR. VOCKLEY: Thank you, Rod.
This is a really great way to look at this information. I mean, this is what we need to be doing. So if we apply this rigor to all of our disorders, I think we'll be doing everybody a good service. Having said that, there are some really difficult aspects of this that make it hard to go forward. Mike just commented on the recall rate being prohibitive for real life. As someone who is on the other end of that and runs a newborn screening clinic that has to take the patients in, when you get to the point of being referred for a diagnosis after a second blood spot, if I had to take in one new patient every week for every disease that we add, which is basically what these numbers would do to my clinic, we would be overwhelmed with that clinical volume because the time involved in following up on one of these patients is really prohibitive.
So I think one of the things that we have to consider, as we start talking about adding something to the panel, is not just the front end numbers, but what they're doing to people downstream. So that was one comment that I had.
I wanted to follow up on your question about the morbidity. I think the issue there is not so much what's happening at a year, because you're right. I think in the published data and certainly what they've been presenting at meetings, the untreated babies die. The treated ones live. I think the real question is, for the longer-term outcome, are we really looking at improved outcome, or are we looking at delaying the morbidity? So if everybody survives for a year and they all die at 2, are we really accomplishing something?
DR. HOWELL: Yes. My question is actually on mortality on the slide and certainly not morbidity.
DR. VOCKLEY: I'm sorry. I did mean mortality.
So if everybody died by a year and you delayed that by a year, would we consider that an outcome that would push the committee to want to add this to the common panel? So that's

another issue that we have to address.
I had a couple of comments on just some of the specifics of the process. First of all, as we get the bibliographies in the back, there are a number of them where, after a while, you run out of authors and it just says "et al." And I'm sure that's because it's a multi-author study. I think we ought to see all the authors' names because there may be something that comes up in an obvious conflict that wouldn't otherwise be there.
And then when you presented your expert opinion, your list of experts that you got opinions from, the one thing that struck me there was that was truly expert because those are individuals who are all there in the trenches on the front lines working with this disease and these therapies. And so I wonder if we also ought not to incorporate some well, not quite dissenting opinions, but other individuals who may not have such a vested interest in getting something like this to screening, people who are taking care of the patients, recognizing that they may not have the information on the latest screening data, but they're still going to be able to tell you what they think about the therapy and the trials. So it might be nice to balance out the expert list a little bit. I'm going to stop there.
DR. HOWELL: Jim, why don't you make a comment and let me thank you? I think this is a great job. Again, I think that as we move ahead, Piero had prepared some material and it focuses very heavily on recall, not surprisingly, and you have numbers. And you would not get one patient a week. You'd get much more than that. So one a week would not be a problem.
But anyway, Jim, you had a comment before we move on to Mike?
DR. PERRIN: Just for Gerry, and I think it's a very helpful comment about experts. Again, we would be very much interested in the advice of the committee. Again, our interest in talking to the people we've talked with was primarily is there something out there that's not published yet that might influence the answers to the questions we're raising. So I would wonder whether this other group would help us or not.
The other thing you know, all of you have heard us speak about this before. We say there are several kinds of experts in this field of, say, Pompe disease. One is people who are working on it on a daily basis as clinicians or investigators. Another very important group is the parents who are taking care of children with Pompe disease or family members with Pompe disease. And we actually have done a little bit of work to interview people along that line, but we'd like some help on that question because we've asked fairly specific questions like do you have data that would help this committee know more about newborn screening. That's sort of what we were asking. And frankly, in most cases, the consumer groups or the consumers don't have those data either. So I think we would like some advice from you about what do we want to be asking, what would be helpful from your viewpoint as we move forward along that line.
DR. HOWELL: Thank you very much, Jim.
Mike, could we move ahead with you? And we will use this material and look at it. Again, Mike is speaking on behalf of the advisory committee this afternoon and its look at this data. Again, Piero and his group have worked extensively on this and have prepared the slides and so forth.
+ DR. WATSON: All right. Well, thank you. This is relatively short notice, so these slides are certainly very fresh in my memory of the last 10 hours.
So as we heard, Piero was not able to be with us.
The slides are laid out in a format, though, which is going to reflect those key questions that Nancy went through when she presented. And then you'll see some comments after each question, and those are based on a discussion that Ned Calonge and Piero had about what they felt this information from the evidence review was telling them. So don't interpret that as my

view of what this means. I'm going to try to go through this without reflecting my own views too strongly about what this all says, and I'll ask myself questions about that later I guess.
(Laughter.)
DR. WATSON: Yes?
DR. BOYLE: Can you tell us who is part of the Decision-Making Workgroup?
DR. LLOYD-PURYEAR: That was on the previous slides or Nancy's slides.
DR. WATSON: Nancy presented that.
DR. LLOYD-PURYEAR: Nancy presented that. But I can tell you.
DR. HOWELL: Tell us, please. Coleen's short-term memory is having a problem.
DR. LLOYD-PURYEAR: This is from memory. It's on the second slide of Nancy's presentation. But Mike is one of those people.
DR. WATSON: Yes.
DR. LLOYD-PURYEAR: You're one of those people.
DR. WATSON: You are one of those people. So no more pre-questions.
(Laughter.)
DR. LLOYD-PURYEAR: I did send this all out to you Friday night.
DR. DOUGHERTY: Yes, but we only had like two seconds to look at it.
DR. HOWELL: You'll all have an ample opportunity to comment. So we're looking forward to great wisdom from all of you folks.
Mike, move ahead.
DR. WATSON: Administratively, I'll say there are 21 slides, I believe, in this set, and there are 13 minutes.
DR. HOWELL: You'll have to go fast.
DR. WATSON: Not even at my typical pace could I make it through that in that amount of time. So tell me if you want to cut for a break and how you'd like to follow up later or tomorrow once we get to that point.
So key question 1. Is there direct evidence that screening for Pompe disease at birth leads to improved health outcomes?
The general consensus from Piero and Ned was that there were no studies of this overarching question currently available.
Comments? Disagreement? Agreement? Overwhelming consensus?
(No response.)
DR. WATSON: Key question 2. *[2a flip] condition, and it's been broken down into these subsets of questions under what is known about the condition. Is the condition well-defined and important? What is the incidence of the condition in the United States? What is the spectrum of disease for the condition? And what is the natural history of the condition, including the impact of recognition and treatment?
So we'll go through each one of those individually. Is the evidence adequate? Their feeling was that infantile Pompe is well-defined, classic versus non-classic, doesn't interfere with the importance of the condition nor raise concerns about the spectrum of the disease. And if you have comments on any of these views, as we go along, just speak up.
Late-onset raises issues and the body of evidence regarding detection and treatment around late-onset is less robust than it is for the infantile onset forms.
There is variation in prevalence with wide confidence intervals as is not unusual with rare conditions prior to having been part of newborn screening programs.
And the largest prevalence studies available are not in the United States. There's a large carrier

population in, I believe, New York that was presented in the evidence review.
So, on this particular question of is evidence adequate, we're not going to that judgment thing of how it fits into those four levels of recommendation or three or however many there are now. Any questions or comments? Denise?
DR. HOWELL: Barbara, do you want to make a comment now?
DR. BURTON: Well, Denise was first.
DR. DOUGHERTY: Go ahead.
DR. BURTON: Okay. You know, I guess I just wanted to go back a little to that key question 1 now that I thought about it a little bit. Does the unpublished data from Taiwan not address that issue directly?
DR. KEMPER: (Inaudible.)
DR. BURTON: Why not? I mean my understanding of that unpublished data is that the screened infants at the age at which they are now have a substantially better outcome.
DR. HOWELL: The screened infants have certainly been treated in Taiwan.
DR. WATSON: Yes, there are the 6 patients from the 138,000.
DR. BURTON: Right, and then they had an unscreened group. I mean, I know this is unpublished thus far, but my understanding was that they were showing a distinctly different outcome.
DR. KEMPER: Data from the Taiwan screening program regarding outcomes for the neonates that were detected early are not available yet.
DR. BURTON: Oh, he is not sharing that data. Is that what you're saying? They're not sharing it.
DR. KEMPER: They're not available to us right now. Yes.
DR. PERRIN: We only have data on outcomes from another U.S.-based clinical trial, none from the Taiwan.
DR. WATSON: That screening pilot, or whatever you want to call it, began about is it a year and a half ago?
DR. KEMPER: Yes, somewhere in there. That's correct.
DR. BURTON: Which is plenty of time to see a difference in the natural history of infantile Pompe disease. But if he's not sharing that, I mean, I guess my understanding of what's going on there comes from unpublished sources. So you're saying that he's not willing to share that information.
DR. KEMPER: Yes. I'm saying I can't comment on the outcomes of those infants.
DR. BURTON: Okay.
DR. WATSON: And the granularity of the data that you got I think you reflected on as being somewhat thin at least for the additional 70,000 or so.
Denise?
DR. DOUGHERTY: Okay. On the answer to key question 2 and maybe Jim and Alex can help with this by saying infantile Pompe is well-defined, my sense was that there are classic and non-classic and there may be some issue with something, that maybe there are one and a half types. So I'm not sure how that fits with saying that it's well-defined.
DR. WATSON: I think the issue is that there have been a range of stratification schemes for Pompe disease that once referred to an infantile onset, a juvenile onset, an adult onset, and I think as people have looked at this more recently, they've felt that there is an infantile onset but it is the cardiomyopathy that distinguishes the infantile form, whether it be classical or non-classical, where the cardiomyopathy is later onset, slightly later onset, from the adult onset forms that don't have the cardiomegaly.

DR. DOUGHERTY: So I guess what you really are saying or what the review is saying or what that sentence is saying is that it's classified well enough to not interfere with recognizing the importance of the condition or concerns about the spectrum, not about the treatment.
DR. WATSON: Yes. I think the consensus was that classical and non-classical infantile forms are bad.
DR. DOUGHERTY: But you're not saying anything there may be some issues about the treatment and the definition of the disease. Is that true? I know we didn't get to treatment yet.
DR. WATSON: Yes, we didn't get to treatment yet.
DR. DOUGHERTY: But the implications of the definition for treatment
DR. WATSON: This is purely for definition of disease, and the basis of the enzyme replacement therapy is such that I don't know that you would expect the organ specificity.
DR. DOUGHERTY: Okay.
DR. WATSON: Any other questions?
(No response.)
DR. WATSON: Moving on then, is there a test for the condition with sufficient analytical utility and validity? They felt that this was a gap that still needs to be filled. There are competing methodologies of tandem mass spectrometry just recently reported and the fluorometric-based assays used by the Taiwanese group. There is variation in how screening is done, and there's only one type of test that has been tested prospectively in a large-scale population study, that being the fluorometry in the Taiwanese study.
Comments? Yes?
DR. BOYLE: In Ned Calonge's appendices
DR. WATSON: I'm sorry?
DR. BOYLE: In Ned's decision document, there's an appendix, I think A and B, that talks about evaluating analytic utility and validity. So I'm not sure whether we were actually going to get to the point where we were going to apply those criteria because I thought they were terrific.
DR. WATSON: Analytical utility is a novel concept that isn't really one that you read about when you look at laboratory performance tests, but it presumably relates to availability of technology.
DR. BOYLE: I think Piero wrote the appendices.
DR. WATSON: Yes.
DR. BOYLE: And so actually I thought that was a great idea of trying to qualitate
DR. WATSON: Yes. I was operating on the assumption that we had all read the appendices and how utility and
DR. BOYLE: But this doesn't do that I guess is the point, Mike. I know you're just reporting back what Piero put together here, but I was just going to say I thought it was a great idea to have some metrics to actually evaluate analytic utility and validity.
DR. WATSON: Yes.
DR. BOYLE: We should use those as a
DR. WATSON: My sense of those criteria is that they're probably not easy to apply at this point in time because this is so early and there's only the one pilot that's been done in Taiwan.
Mike?
DR. SKEELS: If the phrase "analytic utility" is broad and means everything from defined performance parameters, sensitivity, specificity, predictive value, but also includes feasibility of use and operational capability and all that kind of stuff, then I agree completely that that's a gap because my understanding of the methods is that they are still very labor-intensive. There are a

lot of preparatory steps. They're not yet amenable to multiplex approaches, and although the very end of the MS/MS process is multi-flexible, the rest of it is not. So I just want to make that point, that the word "utility" is real important for those of us who would be operationalizing this.
DR. WATSON: Yes, Denise?
DR. DOUGHERTY: I guess I read Ned's first draft using his decision criteria, and now you're presenting something that other people have you have blended together or Piero did. And I'm wondering just because there's some confusion about who was actually on this group, if you could say if there are any areas here where Ned said one thing and maybe you or Piero disagreed and would change the
DR. WATSON: I was not involved in
DR. DOUGHERTY: Oh, you're just reading.
DR. WATSON: This is a consensus of Piero and Ned. They agreed on what is stated here.
DR. DOUGHERTY: Okay.
DR. LLOYD-PURYEAR: Dr. Buckley also commented on it.
DR. WATSON: Yes. There were some additional comments when it went out, and you were the only one fast enough to get something back. And I'm trying to reflect those as I recall them.
DR. DOUGHERTY: I'm just trying to get a sense of the certainty.
DR. HOWELL: But the document was written by Ned and Piero, and then it was sent around for comments. And I think that, indeed, Becky was the only one speedy enough to get anything back.
DR. LLOYD-PURYEAR: Do you not have Piero and Ned's document?
DR. WATSON: It's been converted into a slide format.
DR. HOWELL: Everybody has Piero and Ned's document, and this is a PowerPoint presentation from that document.
DR. WATSON: Theirs was written in a paragraph form that has been put into this bullet format.
DR. LLOYD-PURYEAR: It just seemed like people didn't have it. So I just wanted to make sure.
DR. WATSON: Any other comments or questions?
(No response.)
DR. WATSON: Okay, good.
DR. HOWELL: All that is accurate.
Number 4.
DR. WATSON: Key question number 4. Does the test accurately and reliably detect the condition and the clinical disease?
Evidence is adequate that available tests are able to discriminate between those with and without the condition, but at the cost of a high false-positive rate. In the Taiwan study, nearly all, 97 percent of cases, who tested abnormal twice had a false-positive outcome.
There is some question about separating out late-onset disease and related phenotype. The data supporting early detection and early treatment of late-onset disease is insufficient.
Comments, questions?
DR. BUCKLEY: Maybe Dr. Kemper could answer this, but I notice that there were 6 that were detected initially with the first screen, and then ultimately you ended up with only 3. So were those 3 from the initial 6 or did any come from the second screening?
DR. WATSON: That was normalized to 100,000. So they did 138,000-plus in that initial group. He's just normalized it to 100,000, which brought the number down.
DR. BUCKLEY: So you don't know whether they all came from the first group or not.

DR. KEMPER: I don't know what the ratio was between the ones who were flagged after the initial screen versus those who went through both steps. I think Dr. Browning might have that information, but I didn't speak to the investigator myself.
DR. WATSON: And it does track with the infantile going up by 2 with another 70,000 in their unreported data, but the 5 late-onsets are
DR. BUCKLEY: But the other possibility where the late-onset going up in the second data set is that they live long enough so they knew they didn't have the early-onset. Could that be the reason if their study has only been going on for a year and a half?
DR. WATSON: I hope not. I mean, I would hope that they found things like *DIVS8 mutation that is almost always associated with late-onset as being the mechanism by which they call that.
DR. BUCKLEY: Is there a genotype/phenotype correlation?
DR. WATSON: There are some mutations that are specific to the late-onset, but I think, by and large, there is poor genotype/phenotype specificity.
DR. KEMPER: Dr. Buckley, there are more than 250 mutations of the gene as well.
DR. WATSON: And I think that's one of the things that can be cleaned up somewhat in the evidence review. You talk about mutation severity and there's a whole mechanism by which one does interpret mutations that is not necessarily enzyme activity, which is not necessarily outcome, and that there are very separate things. And I think you should probably talk about them in separate ways of looking at severity.
No more questions, comments?
(No response.)
DR. WATSON: All right. Moving on, now we're going to look at some actual data that Piero prepared to break down the Taiwanese study. 132,538 newborns tested in the published report led to 1,101 newborns being retested where a second sample had to be obtained. Of those, 121 recalled for diagnostic confirmation, with 4 true-positives, no false-negatives.
This is a classic Piero slide. I could tell it the second I saw it.
(Laughter.)
DR. WATSON: But fundamentally, what it's doing is taking the data, calculating sensitivities and specificities and showing you the formulas by which those are done, walking through the data in that particular way. I don't know that it tells us a whole lot that we didn't see in the last slide, except it does pull in the true-negatives and the specificity questions that aren't as clear in the prior layout of this data.
Any comments, questions about this?
(No response.)
DR. WATSON: So given a false-positive rate of .83 percent in a real-life scenario, how does that translate into practice? A positive predictive value of 0.4 percent. If you look at the states these are the states from Region 4 in the regional collaboratives you'll see how many patients would come into testing on a weekly basis.
DR. WATSON: And those are weekly, Gerry.
DR. VOCKLEY: Ouch.
(Laughter.)
DR. WATSON: And we don't even have Pennsylvania here.
But I would argue that we need to separate out the manpower problem from the actual downstream effects of having all of these patients come into systems and that there are slightly different issues
DR. BURTON: You know what? That data does not look to me like it gibes with the flow chart

that you showed. That looks like it is calculated on the basis of the recall for a second blood spot, not going in for diagnostic
DR. WATSON: Yes. That was one of the reasons why I started asking questions earlier about the flow in the Taiwanese laboratory.
DR. BURTON: So that's not going to put 28 patients a week in Gerry's office. I mean, those are just second blood spots. That is not the patient that comes for diagnostic confirmation, 28 a week. No. Look back at the original flow chart where he has the 132,000. There were 121 recalled. So 121 out of 132,000. That means in our State of Illinois with 177, we're going to have maybe 50 or 60 a year coming for diagnostic confirmation. So that's 1 a week to some center, not necessarily my center.
So this is extremely misleading. Don't let people think these are the numbers that are going in to the geneticist, to the diagnostic center. No. These are just the ones where the pediatrician gets a call, send a repeat blood spot.
DR. HOWELL: To get a second blood spot.
DR. WATSON: I sent that question to him this morning to have him clarify this particular one because it was 10-fold out of the box.
DR. CHEN: Mike, those are the numbers, though, of the patients that would re-present to the primary care physicians' offices.
DR. WATSON: No, no.
DR. BURTON: Yes.
PARTICIPANT: Yes.
DR. CHEN: For their second blood spot, yes.
DR. BURTON: Yes.
DR. WATSON: Oh, yes, to have that blood spot obtained and returned.
DR. HOWELL: Because we did get clarification that this is a second blood spot that you have to obtain and not a punch out of the original. So you are correct. This is the number that would go to someone to collect a second blood spot.
PARTICIPANT: But just to side with Gerry, that means that many telephone calls to Gerry to tell me what to do with that second blood spot.
DR. VOCKLEY: I do think that this will and maybe we ought to get off this, but this will impact the treatment centers because while some pediatricians will be happy just poking the kid and getting the blood spot and sending it on, you make this phone call to the parents and you inevitably will generate the anxiety that is now going to make a call to the treatment center. So as you said, that's maybe a separate issue, but it's not quite as clean as
DR. WATSON: And it will be enormously variable from state to state because some states would take this straight to the metabolic specialist to deal with. Others would go through a primary care provider to sort it out at this level.
Yes, Jim?
DR. PERRIN: Just to make two comments. One is I actually don't think we know from Taiwan that there are no false-negatives. And I think the numbers here, if I read them from the Taiwan experience, would be about 150 per year in Illinois. So that makes 3 per week.
DR. WATSON: Yes, 138,000. Yes.
Moving on?
DR. HOWELL: Moving on.
DR. WATSON: Key question number 5 then. Are there available treatments for the condition that improve important health outcomes? Those have been broken down into these sub-

questions.
Does treatment of the condition detected through newborn screening improve health outcomes when compared with waiting until clinical detection?
Are these subsets of affected children more likely to benefit from treatment than can be identified through testing or clinical findings?
And are the treatments for affected children standardized, widely available and, if appropriate, FDA-approved?
This is now Ned and Piero's consensus view that there is adequate evidence that recombinant human acid alpha-glucosidase improves important health outcomes based on a sample of 18 affected infants, the Duke study.
Evidence of benefit is specific to infantile-onset Pompe disease compared to natural history, and lasts at least 52 weeks. No long-term health outcomes beyond 52 weeks of treatment or 18 months of age are available yet.
Small body of evidence suggesting that the CRIM-negative cases will not respond or will not respond well to the recombinant human enzyme. However, it is insufficient to conclude that cases should not be treated, and there's work in immunotherapy being done to see whether or not those CRIM-negatives can be managed in an alternative way that's unpublished.
Questions, comments? Denise?
DR. DOUGHERTY: I guess I had a question about the treatment study, and that was published in 2007. Right?
DR. WATSON: Myozyme has been approved by the FDA and is in phase IV surveillance. So there's ongoing
DR. DOUGHERTY: That was my question. Was there any investigation of the follow-up data after that study was published? I mean, those are the questions we have. How long do the children live?
DR. HOWELL: Alex, can you comment on that?
DR. KEMPER: From talking to the investigator, I've found out in general how they've done. There's still a large battery of tests that these kids are undergoing, but from what I understand, all the 18 children are still alive. I can't comment, though, on how they're doing other than that.
DR. WATSON: Moving on. Key question 5 continues. The view was that there was no description in the evidence review about how the 18 cases were detected. After conferring with the research team, only 2 cases were detected by screening at birth in families where there were other affected children, meaning they could be detected at birth. The other 16 were detected clinically following either respiratory or cardiac adverse events. It's a pretty straightforward statement.
Yes?
DR. BOYLE: I just have a question to you. For those 2 children who the sibs of an affected child, when was their treatment started? Did you get the information on that?
DR. KEMPER: Yes, I did, actually. I called yesterday. So those children were detected at birth, but because of the criteria that they had to meet for the trial and that sort of thing, the earliest that they were started on therapy was 10 weeks of life.
DR. WATSON: Any other questions?
(No response.)
DR. WATSON: Moving on, continuing with question 5. Treatment started prior to 27 weeks of life is effective. Gaps around this area of treatment included outcomes of treatment prior to 27 weeks of life is a gap in the information. The age at which treatment benefit decreases remains

unknown, and the proportion of cases of infantile Pompe disease that could be detected clinically versus only through screening remains to be determined.
Moving on. The evidence supporting early treatment of late-onset Pompe disease detected through screening is inadequate at the current time.
Questions, comments?
(No response.)
DR. WATSON: Key questions 6 and 7, the daily double. Are there harms or risks identified for the identification and/or treatment of affected children?
The views were that there were no studies reporting harms of screening, including anxiety associated with the need for second screens or diagnostic testing. The diagnostic testing for the screen-positive infants seems to carry little risk of harm. And the harms of treatment involve immune reactions to the recombinant enzyme, and that these harms relative to the benefits are small.
Comments? Mike?
DR. SKEELS: Yes, just quickly. If 99.6 percent of the positive results are false, it's hard for me to believe that there's no psychological implication for the families.
DR. WATSON: And whether it was actually tested remains to be seen. I didn't see anything in the references about surveys of those people. I think the literature suggests that they tend not to be.
DR. HOWELL: But there's no literature on that subject in this situation.
PARTICIPANT: There is for other newborn screening disorders.
DR. WATSON: That's right.
Other comments or questions? Yes, Denise?
DR. DOUGHERTY: I guess maybe harms relative to the benefits are small. Relative to death, most harms are small. But it would be good to know a little bit more information about what those harms really are and what an immune reaction is. So just for the future.
DR. WATSON: Okay. Moving on. Key question 8. What is the estimated cost-effectiveness of testing?
There are no studies or published models at this time.
The magnitude of net benefit, being benefit to harms, of treatment at least up to 18 months is significant for infantile Pompe disease.
Questions, comments?
(No response.)
DR. WATSON: Okay. Moving on. So overall adequacy of the evidence. If one feels that the lack of evidence regarding how newborn screening might better translate to treatment initiation prior to 27 weeks of life is a critical gap, the evidence, even for infantile Pompe, would be assessed as inadequate. If not, then one could conclude there is adequate evidence. This assumes that screening and diagnosis will, indeed, discriminate between infantile and late-onset Pompe, which genotype/phenotype correlations would suggest it will.
Comments, questions?
(No response.)
DR. WATSON: Certainty of net benefit. Again, certainty, measured as sufficient versus insufficient, here depends on the level of confidence that treatment benefits require screening for timely case detection and that clinical detection leads to much less benefit in terms of health outcome is important.
Questions, comments?

(No response.)
DR. WATSON: All right. Contextual issues. While the evidence of follow-up for treatment is short, treatment translates to survival and ventilator independence. This is a compelling potential net benefit.
No questions, no comments.
So in summary, based on what is presented in the report of the Evidence Review Workgroup, there are significant concerns with the specificity of testing, the comparative effectiveness of alternative testing algorithms, repeat specimens versus second tier tests, and the potential applicability of prognostic tools.
There's another summary slide which I'll hit next and we can come back to all of these.
The dramatic effectiveness of available treatment in infantile Pompe cases has been noted. However, better evidence is needed regarding the ability for screening to distinguish between infantile and late-onset disease, the efficacy of treatment in either presymptomatic or symptomatic cases.
Any comments on the summary views that were expressed?
DR. HOWELL: Ladies and gentlemen, we obviously did not allow near enough time in the agenda to do this adequately well beyond the time we're scheduled. Let me make the following suggestion and throw it out for you. If we have a chance to think about what Mike and Piero have presented today and so forth and kind of think of it this afternoon and over dinner, and in the morning if we allow two hours for the subgroups and get back 30 minutes early, then we can allocate a half an hour to kind of go through this and do that.
Does that make sense to the group? I hesitate to get dramatically further behind in the agenda today because, number one, to be specific, some of our presenters I know are having to leave at the end of the day, Sue Berry and so forth. If that's acceptable, why don't we plan to do that then? And then, more importantly, let's take a break and we'll return. Why don't we return in 15 minutes? Because we don't have a lot of public commenters, and we'll keep them to a rigid time frame and we'll get back on schedule.
Thank you very much, Mike, for that presentation. It was very well done.
(Recess.)
DR. HOWELL: We're now moving into a very important area of the program when we have public comments from folks in the audience.
And one important thing that I've just been reminded of by Michele is that we have never formally introduced Jane Getchell who is here representing APHL. Jane, welcome. We're delighted to have you representing APHL, which is obviously a very important partner in the newborn screening community, and we appreciate your efforts here.
We have two people to comment this afternoon. The first is Ron Bartek. Ron is President of the Friedreich's Ataxia Research Alliance. Ron?
+ MR. BARTEK: Thank you, Dr. Howell, and ladies and gentlemen of the committee, thank you very much for the opportunity to address you today. My name, as Dr. Howell said, is Ron Bartek. My 22-year-old stepson Keith has a neurodegenerative disorder called Friedreich's ataxia.
Keith was a beautiful, apparently healthy child at birth until about age 9, at which time he was doing well in school and was typically active. He was enjoying, for example, karate lessons and riding his bicycle with his brothers and friends.
Keith's world began to change rapidly and drastically, however, at that point, and by age 11, he was diagnosed with Friedreich's ataxia as his incoordination, cardiomyopathy, and scoliosis

became apparent. By age 16, he was unable to walk and his scoliosis required surgical implantation of metal rods along the length of his spine.

Now at 22, Keith has developed diabetes, is full-time in his wheelchair, and is dependent on others for most activities of daily living. Although his intellectual capabilities remain intact, he has significant communication difficulties due to vision and hearing loss, as well as slurred speech. He had to terminate his college education as a freshman due to difficulty overcoming all these challenges.

We estimate that there are 5,000 to 6,000 individuals like Keith living in the United States.

On the day in 1997 that my wife Rachel and I received Keith's diagnosis, we learned three things. First, Friedreich's ataxia has a horrific prognosis. Second, there was no organization focused entirely on supporting research and education in Friedreich's ataxia, though there were organizations like the Muscular Dystrophy Association, for example, that had Friedreich's ataxia in its 40-plus disease portfolio. And third, we learned that the disease gene and molecular defect in Friedreich's ataxia had just been identified in the previous year.

With the support and encouragement of Drs. Giovanna Spinella and Audrey Penn of the NIH's Neurological Institute, we decided to form an organization to support research and education in this disease. I am co-founder and President of that organization, the Friedreich's Ataxia Research Alliance, or FARA. On behalf of FARA and the patient and research community it represents, I would like to express our gratitude for the important service this committee provides in helping the most vulnerable members of our society.

Friedreich's ataxia is the most common form of inherited ataxia. About 1 in 50,000 people in the United States are born with this disease. Symptoms of Friedreich's ataxia include progressive loss of strength and coordination, known as ataxia, in all four extremities, leading to loss of ambulation within 6 to 10 years of symptom onset, life-shortening cardiomyopathy, severe scoliosis often requiring surgical intervention, and type 1 diabetes. Onset of symptoms can vary from childhood to adulthood. Childhood onset of Friedreich's ataxia is usually between the ages of 5 and 15 and tends to be associated with a more rapid progression and premature death.

Since the identification of the disease-associated gene and mutation in 1996, our scientific community has made tremendous progress in understanding the pathophysiology of the disease and the function of the protein called frataxin, which is dramatically reduced in our patients. The protein, frataxin, functions in the mitochondria and is critical for iron metabolism, antioxidant protection, and overall energy production.

A number of promising therapeutics are in clinical trials or in development. At present in the United States and Europe, for example, there are two ongoing phase III clinical trials of the antioxidant Idebenone. A phase II of the iron chelator, Deferiprone, is also underway in Europe. These trials will be completed in 2009, and data from previous studies of both drugs suggest improvements in both cardiac and neurological function that would, at a bare minimum, slow the progression of the disease significantly.

This past July, Canada granted conditional approval for use of Idebenone in Friedreich's ataxia, and our FDA filing for approval is anticipated late next year.

In addition, there is a phase I clinical trial now underway here in the United States of another novel antioxidant in Friedreich's ataxia. This and a number of other very promising drugs now in development with our pharmaceutical partners hold real promise for substantially greater benefit.

Due to the progressive nature of this disease and the strong likelihood that damage begins long before symptom onset, we believe that the earliest intervention with these treatments will be critical in reducing and preventing morbidity and mortality. Our organization is clearly not alone

in this conviction. For example, at our third international scientific conference on Friedreich's ataxia in November of 2006, Dr. Story Landis, Director of the NIH's Neurological Institute, told our organization that her institute was so encouraged by our progress and confident that we would achieve effective treatment soon, that we should begin working with her NIH colleagues and others on the development of a newborn screening test.

Since then, we have been working with a team of investigators at the Mayo Clinic in Minnesota, led by Drs. Devin Oglesbee and Grazia Isaya, to develop using dried blood spots, a newborn screening test that is protein-based and multiplexable. The goal is to validate this test analytically and clinically with a pilot study beginning in 2009 of approximately 70,000 newborns so as to meet the nomination standards set by this committee. We would welcome, of course, in this development process the involvement of other academic groups and industry as appropriate.

We understand the role of this committee in ensuring that suitable screening tests are developed and that safe, effective treatments are available for implementation in the newborn period. We also recognize the social, emotional, and ethical challenges of diagnosing presymptomatic individuals.

We look forward to the opportunity to keep you informed as we achieve critical milestones in test development and treatment outcomes. On behalf of Friedreich's ataxia patient families and our research community, thank you for your commitment to the health of newborns and children, for your attention, and for allowing me to make this presentation to you today. Thank you.

DR. HOWELL: Thank you very much, Mr. Bartek. I'm aware of some of these studies, the clinical trials, and they are, indeed, very exciting. The fact that you're working on a test and so forth and you can see the discussion this committee is dealing with about how to proceed and the kinds of things that one needs to do to accomplish these things. And so we'll look forward to your coming back with more data, more information, lots of pilot studies and so forth so that we can get along with this. Let's hope that the clinical trials that are underway will be effective. Thank you very much.

MR. BARTEK: Thank you, Dr. Howell.

DR. HOWELL: The only other person that we have scheduled this afternoon is John Adams. John, you had signed up to say a few very brief words. And you know what the rules are. We're tough. Four minutes.

+ MR. ADAMS: You're being generous today, Mr. Chairman. Thank you.

DR. HOWELL: I'm always generous.

(Laughter.)

MR. ADAMS: My name is John Adams. I'm from Toronto, Canada, and I happen to be a PKU dad. And I just wanted to take a moment to say thank you very much for everything you do and to share, from a personal basis, a case study of PKU treatment and long-term follow-up.

This Friday, two days from now, will be the one-year anniversary of my 21-year-old son being on the first-ever drug therapy for PKU. He is not a responder. He has turned out to be a super responder. He says he has two side effects. He's sharper and he's more clear-headed. He has been on it for an academic year and his marks have improved. He's now, in a very carefully and measured and thoughtful way, gradually increasing the whole protein load to the point where, since June, he has been on all whole protein and completely off formula.

So my real purpose of coming here today is thanks to the generosity of the taxpayers of the Province of Ontario, I have in my basement a two-year supply of Maximum XP amino acid formula for PKU therapy. If you know any American or any other person in the world who needs that, I'd be happy to donate that.

Thank you so much. My son has also had the pleasure of being an all-expense-paid guest of the Biotechnology Industry Association. He was the non-American case study, patient example, of the successes here of the 25 years of the Orphan Drug Act. So thank you for that. Although I was glad to hear from the previous speaker that we do get a few things right in Canada, the new drug therapy for PKU has not yet been applied for, is not yet available. My son is the first named patient to have access to it in Canada. I just want to work with people who want to work with me to make sure that when there is a breakthrough in treatment for whatever rare condition, the patients get to be early adopters and not late adopters of the new therapy. Thank you very much.
DR. HOWELL: Thank you very much, John. The neuromuscular group in Ottawa is very impressive, and you can learn some lessons.
Put your formula on eBay. I think that would be a good place to do that.
(Laughter.)
DR. HOWELL: One of the really important clinical issues that physicians who take care of the patients that are screened for have been dealing with a very, very long time is the provision of medical foods. So we now have some really important information that we're going to hear over the next period of time.
And our first speaker is Susan Berry. She's representing the Medical Foods Expert Workgroup, which is a subgroup of the Committee on Follow-Up and Treatment. And so, Sue will have a lot of good things to tell us this afternoon.
+ DR. BERRY: Well, thank you all for the opportunity to share some of the results of some work that we've been doing as a part of this subcommittee.
I'm going to lead off with this. I thought this was amongst the most compelling single description of why we might ask this question. John has just given us some information about this, but I'm just going to read this very briefly. This is a comment from a parent from one of our sample surveys.
And she said, "I do not think it is fair for children with medical problems and you do not get help to provide for your child. I have a child with LCHAD, and I am very short for money and unable to work do to my child's needs. I am getting help on medical bills but not for her MCT oil that she needs for the rest of her life or she may not survive. I currently have that medical in collection because I am unable to pay for. What I am suppose to do to pay for it and keep getting her meds. Also it is very expensive to buy the foods she requires. I do not get help for her fat free-low fat foods. Please help pass this on thru states and put yourself in our position. What do u do?"
Well, the first thing that we thought it was important for everybody to keep in mind when we were thinking about you've been hearing about ways to add new disorders to the things we screen for, but for many of the things we've already screened for, the real treatment is a medical food. And the FDA definition for that is "a food which is formulated to be consumed or administered enterally." It doesn't say through a G-tube. It doesn't say through an NG. It just says, "enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by a medical evaluation." That's the definition of a medical food.
Functionally this encompasses a little bit more than that. So what are those treatments that we use to manage children who have these rare inborn errors of metabolism? Of course, we have the medical foods. These are specially compounded formulas. In many cases, unless you can put them on eBay I don't think you can put them on eBay. They're available only by prescription

because they are supposed to provide a substantial portion of nutrition for the treatment.
There are also what has been termed nutriceuticals, which are pharmacological doses of cofactors or vitamins, or single amino acids that provide substrate or prevent specific deficiencies. There are other vitamin-like drugs like carnitine and then the MCT oil like our mother mentioned.
Now, both of these classes of agents require physician supervision and in most cases require a written prescription. You can't just go to the drugstore and buy a case of Maximum Aid XP or any other formula. It has to be ordered by a physician or by an appropriately licensed health care professional.
Now, both of these elements are required therapies for the treatment of inborn errors. In addition to that, there are also specially manufactured low-protein foods which are not necessarily requiring prescription but which are an important adjunctive aid in the care of these children.
So what's the problem? Well, it turns out, of course and there are good reasons why that was, but it's still a problem medical foods and the nutriceuticals aren't drugs. They're materials of nutritional value. That means that they don't have the same treatment in insurance plans as drugs.
Medical foods are more expensive than traditional foods. They have to be processed correctly and they're manufactured in small amounts. We all know about orphan drugs. So medical foods are expensive.
Now, everyone needs foods, but traditional foods, as we think of foods, stuff that was out on the table for all of us to take when we went out for a snack there, often may be harmful to persons with inborn errors of metabolism so that the medical foods that patients need aren't optional. They are the treatment, in some cases, the only treatment for these children.
Because they're foods, however, and not drugs, they're sometimes excluded by many insurers from the coverage of the medical treatments, and the costs of applying for these may be prohibitive. Coverage is at best variable.
The bottom line is that affected persons can't survive without them, but they can't afford to buy them. That's a real terrible catch 22.
So what are some of the barriers that impact this? Well, each insurer has its own practices. There are private insurers, moreover, and public practices that vary from state to state.
Every policy, even with the same company, may have different coverage I'll turn to this a little bit when we talk a little about some of the information we got from some of the insurers because they're written to each client's needs. So even the same company may have different coverage from client to client.
Every state has different rules or laws that cover the provision of medical foods, and we'll hear a little bit more about these in a subsequent presentation.
And even when the laws exist, they don't cover all insurance carriers.
And finally, even when they exist, they're subject to interpretation by the insurers and by the states.
So there are a lot of variables that are not under anyone's control.
So I'm just going to tell you how I got started on this to give it some personal context, and then tell you a little bit about what the workgroup has been doing to try and learn more about this.
In my own state, the State of Minnesota, you hear about it because Piero likes to talk about Minnesota, but those 11 patients. Those are me. Our law is really not my favorite law amongst all of them because our law says that you must provide coverage for special dietary treatment for phenylketonuria when recommended by a physician. Well, that's a very nice law, but it's specific to PKU. And of course, there are other diseases that are very important that use medical foods.

We went back in our own clinic and reviewed the denials from health insurance claims for reimbursement, first, for medical medications. I don't want to go through every number here, but the bottom line was about half of our these are just the appeals. Somebody asked me what the denominator for this was. I don't actually know that number. *[2b flip] taking care of an average number of metabolic patients. While many of these were ultimately approved, many were not.
In a similar fashion, for our medical foods, we had many denials. We didn't even see in our management group with our nurse practitioner, who did a lot of this work, any impact until the dietician had had the chance to have them, first, reviewed and then denied. And we in this particular time period had 17 appeals that had to be made. Four required reappeals, and even after that, although most of those were ultimately approved, many of them were not.
So what happens? What did we learn from this? And I think this is not just applicable to my own experience, but the group felt this was generalizable. That's why I present it here. We found that many nutriceuticals and medical foods were ultimately covered by insurance, but many only after repeated appeals. That takes a lot of time and effort and a lot of heartbreak for the families. The responses were not uniform and each one took its own strategy. I had to write a different letter to every company. In the meantime, some of our patients went without treatment. Some changed insurances or obtained Medicaid. We even found some charity groups who would pay for a month or two of formula.
But our problem came in that each year the process started over. Coverage is typically granted for a one-year period, and we questioned whether there was another way.
So fortunately, this committee, in its august wisdom, had already started working on these issues and had constituted a medical food expert workgroup, which I was able to begin participation in. This is a workgroup of the Follow-Up and Treatment Subcommittee of this committee, and its charge was to ensure that families of children with inborn errors of metabolism have coverage for medically necessary treatments, including their medical foods.
So this is a list of our workgroup. I want to thank everyone for their continued devotion to the many iterations of the work that we've been doing and to their ongoing support of this process. You can read all the folks here. I just offer my congratulations to all of them for their hard work on this project.
So we thought it would be important that we define the scope of the problem in a little more analytical way, and we thought that we would take two tactics to do this. The first would be to find out what families are really experiencing with regard to this. We have a lot of anecdotal evidence but there's no systematic assessment of it. And the second was we thought we should know what mandates and regulations govern public and private coverage.
I'm going to turn first to the experience of the families, and to do this, we elected to undertake a family survey to find out about coverage for medical foods, nutriceuticals, and feeding supplies. This is the sort of bare bones outline of the survey that we wanted to build. We wanted to know a little bit about the demographics. We wanted to know how old the person who was being evaluated was, what disorder they had, and what state they were from. We wanted to know what types of coverage they had and what financial burdens they were incurring even with coverage or without it. We wanted to know what success or not they had in coverage for their medical foods. The other term that is often applied to those is "formulas." We also wanted to know, in addition, about low-protein foods, if they were using them, about the nutriceuticals, and for the feeding supplies that some also require to take medical foods. We also wanted some room for free-text comments for the families to add information that we hadn't been able to capture from the bare bones of the survey, and that was where I got that comment.

Our first phase of our survey was to develop an instrument that we could use. And here's where we had a lot of true devotion to this. People met very regularly by phone and email so that we could define a good survey that would be of value.

We piloted the survey with two parent focus groups. I want to thank the parents group at Westchester Medical Center and Mount Sinai Medical Center. We did one pass and then from the parents' focus group, we made some additions, corrections, and alterations, and then ran it through another focus group. And they were extremely helpful in clarifying the nature of the survey.

We then undertook phase 2, which was a pilot test on a larger scale of the survey. This was designed to be a qualitative test to really look at the response patterns we had from families. We did this in three regions. This is a very small sample. We wanted to look at both children and young adults who filled it out. It allowed us to also test the feasibility of the product. It allowed us to get several centers through the IRB process. It turns out because of the nature of this survey, that it falls in an exempt status, but it still has to go through IRBs. And it allowed us to develop some products for performing this survey, protocols, response sheets, and some things like that. So it allowed us to really get at the heart of whether we would be able to do this with the anticipation for full survey implementation.

So let me tell you a little bit about what we've done so far. We've been able to do this full pilot process in Region 2, the NYMAC region. We asked for one center to do this, and they submitted eight surveys. The Southeast Region had one center that did 15 surveys. In my own region that was basically my clinic I asked for and received 21 surveys. So what we wanted to do was to analyze these for the utility of the survey. We're not trying to collect data about how people are getting their information back yet. This was really to see if we'd be able to do the survey, and we learned some important things from doing it.

First, we learned that we didn't ask the questions quite right. I don't think that's any surprise to anybody who does surveys that there were some things we needed to clean up. We ourselves have trouble, and we took some time to learn about this. And even then, we realized that there's a difference between state subsidized private insurance versus unsubsidized private insurance, but families mix those together because if they had a private company giving their state insurance, they would characterize that as private insurance. And we need to really be able to tell the difference between those things.

We realized, after we worked hard on it, we each loved every word in the survey, but it's too long and we need to condense, collapse, and reorganize it so that families who respond to it can record their responses more effectively and particularly really understand the distinction between medical foods and our dietary supplements or nutriceuticals.

We wanted to make sure that we had a chance for genetic center staff I in my own center, when I did it, I just took them raw and sent them in for people to look at. But in looking back at them, I realized it would have been probably helpful if I had looked at some of them just to make sure that the families knew exactly what they were filling out. And I did do that a little bit, but we need to have a good review of that.

We learned from this that we want to rebuild the survey to some extent and then replied in a very small sample to make sure we've corrected some of these problems. But I think we've had a very significant improvement potentially in our survey from this, and it's really very close now to final implementation.

So what will we be doing next? Well, obviously, we encountered some initial problems in the survey use, and so we're going to be revising that for full implementation.

At the suggestion of Coleen and I want to thank you for that it was suggested that we present this problem, this issue as a roundtable at the American Public Health Laboratories meeting upcoming in November. And so we'll look forward. We had that accepted and we're looking forward to sharing some of our thoughts and looking for some input from that group about this.
We hope to complete phase 3 by spring of 2009, with a full implementation of the survey, with a goal of about 200 surveys per three collaborating regions. We hope to be able to use this information to develop a manuscript but, more importantly I think, to identify potential actions.
So I just want to mention the three regions that are going to be doing the phase 3 implementation and thank them for their support. It's going to be folks in Region 2, the NYMAC Collaborative; Region 3, the Southeast Collaborative; and some other folks in my own group in Region 4.
Second, in terms of defining the scope of the problem, we hoped to be able to have a better handle on the mandates and regulations that govern public and private coverage. And to initiate some discussion about that, we had a group meeting with some invited participants from a wide variety of individuals that would be able to give us some more specific information so that we could truly understand what the barriers to reimbursement would be and to begin to develop some recommendations for potential action.
We had folks, of course, from our Medical Foods Workgroup. Everybody came for this one-day meeting. We had representatives from private industry, private insurance, and from industry from the Department of Labor and from the IRS. We had some folks from CMS. It was a very fruitful discussion. I think all of us were both a little overwhelmed and also surprised by how difficult the task was going to be based on just the expanse of different people that have input into this very complex process.
Some of the potential actions we identified that could impact financing of medical foods with regard to Medicaid were perhaps to be able to broaden some federal statutes to cover medical foods. That is not a simple but a potentially very fruitful avenue.
Perhaps more manageable, because each of these is rendered on a state-by-state basis so each state makes its own decision, and I think this is actually probably more doable. And the group is looking very hard at the next process for this would be to develop a model state policy for medical foods. If a model policy could be adopted by states, I don't know if you'd even need a federal statute. States would be doing the right thing on a one-by-one basis, and if we could do a really good state policy, that would be, I think, very potentially effective. So we liked that idea for Medicaid.
With regard to the private insurers, in a similar fashion, we thought a model state insurance law to minimize variation from state to state might also be very valuable, and those two projects I think would go hand in hand. They would be two halves of the same coin.
We also thought that ways to develop reimbursement codes that would facilitate billing would be effective and to work with insurers to recognize these would also help practitioners who were doing the work to try and get the medical foods covered. If you have the right codes, most of the time it's just a matter of the insurer, in many cases, just not understanding what the problem is.
So we thought if they had a better knowledge base for their staff and knew more about coding and billing for these rare instances, that we would have more effective appeals or even prevention of appeals, maybe coverage right away.
Finally, we know that despite all the work that you might have about public and private insurers, there are a tremendous number of employer-based health plans that are exempt from state statutes, and this is a very large group that we need to have some impact on. We can do all the federal and state laws we want, and if they do not impact a big fraction of insurers, then we are

not going to be very efficient.
We also wondered whether it might be worthwhile to be careful and to really be thoughtful about whether we're correctly defining medical foods. That might also improve our ability to have these be recognized as someplace in that gray zone between drugs and foods.
That completes the part of the report that I wanted to present to you, but I'm going to turn the podium over to Alissa Johnson who did a tremendous amount of work with our workgroup to begin to document just flat out so that we know what the mandates and regulations are in place in each state. So I'm going to let her now come on up here and tell us a little bit about her work in that area.
DR. HOWELL: Thank you, Sue.
Alissa has had a report that was commissioned by the Regional Collaborative National Coordinating Center to look at what the state policies are on payment for dietary treatment of disorders identified through newborn screening, and that information is under tab 9 of the committee's report. Alissa?
+ MS. JOHNSON: Thank you so much for having me here today.
I should tell all of you that may have previously known me in my other life, I no longer represent state legislators. I don't know if that may incline me to get in more or less trouble for what I say.
So this July I embarked on an analysis of state statutes and regulations pertaining to payment for dietary treatment of disorders identified through newborn screening, and it was on behalf of HRSA and ACMG and the National Coordinating Center. I'm here hopefully to present some helpful information for you all.
So today what I'm going to go over is just what we did to gather this information, some of the characteristics that we looked for in the statutes and regulations to kind of sort through the maze because it is a bit of a maze, tools that states are using either through legislation or regulations to provide for payment for medical foods and formula, and then also talk a little bit about some work that Mike Watson has done as a follow-up to this.
So what I did was search the 50 state and D.C. online statutes and regulations. I have up there the search terms that we used. So it captured different forms of the word "newborn," combined with "metabolic," "inherited," "heritable," "PKU," "genetic," and so forth. And I analyzed the results that addressed payment or services that allowed individuals to obtain free treatment and thereby avoid bearing the costs. So it's being paid for on their behalf. And also reimbursement.
I did not include any provisions that simply talked about referral or offering advice or counseling regarding medical foods or formula. There was one case, for example, I believe it was Alabama. I did include that because it specifically said this may include provision of treatment.
Yes?
DR. SKEELS: I'm sorry. Do you mean free treatment or do you mean mandated insurance coverage?
MS. JOHNSON: All of the above, and I will separate it out. I'm going to talk about the services the state provides, sort of directly providing people medical foods or formula, reimbursing them, insurance mandates, tax credits. All of the above is what I tried to capture.
Now, of course, there are limitations on the online search that you do based on the search terms that you're using and how well the database is functioning that you're searching.
Summary results. This is a long list of statutes, but basically I found 43 states and Washington, D.C. had some form of law that addressed payment for dietary treatment for these disorders, and then 31 states had regulations. I found four states that had no results. And just so you can add this all up nicely to 50, there were three states that actually only where I found regulations.

The key things that I looked at were the definitions of disorders and treatment that were being used in order to try to figure out what the scope of the law was, and then also the legislative and regulatory tools that were used. So that will get to what you were asking.

I don't want to go too much through this because I think you can get really bogged down, but mainly what I wanted to show here was that even in one state, there may be multiple definitions of disorders being used and treatment being used that may apply to different entities. For instance, the state, in offering assistance, may list PKU as the disorder for which they're supplying foods or formula. However, the insurance mandate may apply to PKU and other metabolic disorders. In some cases, there's a third statute or regulation.

So I found 26 states that had different definitions of disorders being applied to different entities, and the same for treatment. There was one state that was not on first list and two that were added. So there were 27. And these differences may be different statute sections. So it's something the legislature might have actually done or it might be in statutes versus the regulations the agency is interpreting or different agencies may be interpreting differently.

As far as disorders and how they were defined and only in six instances did I find that only PKU was covered, and those were actually all insurance mandates. So that wasn't in relation to state assistance 31 states and Washington, D.C. have statutes or regulations that define disorders such that disorders that are screened for under the newborn screening program are covered or define disorders broadly enough that it could potentially cover all metabolic disorders on the ACMG panel depending on what they're screening for. The remainder of the definitions may list specific disorders such as just PKU and maple syrup urine disease, but they aren't comprehensive as those 31 states, or they're open to interpretation such as "PKU and other preventable diseases" is used in Idaho. So it's really only by talking to the state that you're going to figure out what's going on.

Definitions of formula were pretty straightforward, medically necessary special formulas. And what I looked for food, in addition, was medically necessary low-protein modified food product formulated to have less than 1 gram of protein was used in about half of the states. And then in many cases, there were terms like "treatment services, dietary treatment therapy, formula, reimbursable treatment costs" that were not defined. So I think only really by talking to the states are we going to figure out what those entail.

And in addition to that, these statutes or regulations might authorize those actions, but it may not mean that they're happening.

Just to give you an example of how complex it might get, in Arkansas the statute pertaining to state responsibilities names PKU, galactosemia, and other metabolic conditions as recommended by consultants, and for that, food or formula may be supplied by the health department. But we don't know what the other conditions are that are being recommended.

Also, the state will reimburse treatment services provided by health care professionals, but reimbursable treatment services is not defined.

They have an additional statute requiring insurance coverage at least for the types of insurance the state can regulate, as Sue mentioned, and that actually refers to PKU, galactosemia, organic acid disorders, and amino acid disorders. And there you have the definition of treatment that's used. So it's actually more well-defined in that case.

As far as legislative and regulatory tools, insurance requirements for payment were found in 33 states. Now, as we discussed, states can only regulate certain types of insurance and can't regulate ERISA plans. Eight of those states only covered food, which I actually was surprised. I thought it would have been more. And 25 cover food and formula. Thirteen states within these

insurance mandates had caps, and they had a wide range, although by far the most frequent was $2,500 annually per person. But to give you an example, in Louisiana, it's $200 a month, and in Kentucky, it's $25,000 a year for formula and $4,000 for low protein modified foods. And that far exceeds actually most of them.

Four states, in addition for their insurance mandates, had age limits. In Colorado, it's 21 for men, 35 for women; in Florida, under 24; in Massachusetts, under 18 and also pregnant women; in Missouri, under 6.

So insurance mandates are one way in which states can take action, and it's important to note too that you have the insurance mandate, the statute from the legislature, but then you also have the insurance department and how they interpret it and whether there may or may not be an accompanying regulation.

One thing I want to point out, one of the states, actually Kentucky, I believe they have the large cap you'll see. They actually require insurers to report back the effects of the mandate. So if you could find out what information people are, indeed, reporting back and what it's costing insurers, I would think that that information would be available. But that's the only time that I did see that.

As far as state services, 40 states authorized the supply of medical foods and/or formula to eligible persons, but just because they authorize it does not necessarily mean it's happening. It depends on whether the funding is there and so forth.

If they are being supplied, I found and there was not always a clear explanation of how these things were being paid for. In fact, for the most part, there was not in the statutes or regulation, but what I did find, that states were using children's health insurance, Medicaid, WIC, the newborn screening program funds and fees for screening, birth record fees, children with special health care needs, Title V money. I had five states where I found that, in Georgia, Michigan, Nebraska, North Dakota, and Texas. A few states provided some reimbursement to providers, Alaska, Arkansas, and Massachusetts. And you'll see in the next point here, the reimbursement to individuals. That includes Kansas and Arkansas where you get some kind of reimbursement. In Arkansas, there is a reimbursement to providers and the tax credit. The tax credit I believe is $2,400. The reimbursement to providers is like $1,000 above the tax credit. So if you end up spending $3,400, you can get that. The $1,000 can go to the provider and the tax credit to the individual.

Now, following up on my search results, Mike conducted a survey of the states to see what they were reporting in practice. He did ask them, does your state guarantee or provide medical foods or formula for a subset of the population? And Mike and I talked about it.

And I should say too that there are five states, as of when I looked at the information, which was last night, because these things are still coming in, that hadn't reported yet when I was looking at it. But this was an open question to them as far as how they were interpreting it and what they wanted to report, whether they wanted to report state assistance that's provided or information about insurance mandates.

But he also asked if yes, if you are providing foods or formula, do you use Title V funds to do so? And 16 states actually reported that they were.

If we then look at the next slide, that will bring you to 11 more states reporting the use of Title V money than the initial search that I had done of the statutes or regulations.

If we go back to limitations as well that I initially discussed, there was an additional statute that was reported that didn't come up in our search, and that was in Oregon. So we'll need to add that. And I checked back. That was actually a function of the database. So that just didn't pick up the word "metabolism" which we searched for. So that can happen.

There were interestingly also several cases were statutes or regulations were unclear based on what I was reading, but then upon these responses, it was clear that the state actually was providing assistance. So it's definitely worthwhile to be communicating with people about what's really happening.
There were also several cases where the statute or regulation authorized treatment for assistance, but it wasn't happening. And to look at why that isn't happening like that was the case in Arkansas would be interesting.
I think it would be also helpful to talk to the states about clarifying what disorders are actually covered because that certainly seems to be open to interpretation in many cases, and treatment. And 12 states in Mike's survey also reported legislation that was being introduced or being considered.
And I think that pretty much sums it up. So if you have any questions, I'd be happy to try to answer.
DR. HOWELL: Thank you very much, Alissa.
Sue, do you want to come up front and maybe we can ask questions of the two of you.
I'm interested in kind of a where's up and how high is high question about looking all these data that Alissa has brought together, which is tremendous. Are there some immediate steps that you see that would be beneficial to consider in view of these findings and observations?
DR. BERRY: Well, I think when I commented that we thought that perhaps the most immediate strategy might be to develop some model state laws and to provide some very specific suggestions about how to make the processes more uniform because I think what we really found was that you can't fight a battle one state at a time if everyone has completely different rules. We also got the sense that there would be a fair amount of acceptance for the use of model legislation and/or regulations. And so we thought that would be a particularly fruitful use of the expertise of this group.
DR. HOWELL: What are some of the core things? Obviously, this would require a lot of thought, but what are some of the things if you were drafting a core thing, what are some of the things you would emphasize in there as far as what sorts of things would you want in that requirement?
I think one of the issues that will come up is one of the issues that comes up with nutritional supplements, that there are so many supplements around that it would be very important to really focus on the medically necessary things.
DR. BERRY: Exactly.
DR. HOWELL: I mean, there's a GNC store on every corner that's filled with people buying good things. So what are your basic thoughts about how
DR. BERRY: Yes. For this to be really viable in my view, we would have to be very careful about the definition of the kinds of disorders that be treated and the nature of the treatments that were applied. That I think was the point over which we had the most discussion when we talked about this. For example, I think it was New York that had a very expansive law that already covers a lot of these kinds of things, but it covers almost every disorder that has any kind of variant food you can imagine. And I don't think we'll have much headway in many places in promoting that kind of recommendation. So one of the things I think we'll have to be careful about is being explicit about what should be covered and why.
MS. JOHNSON: Can I make a comment really quick? You might want to think about whether this is something you want to do or whether it might be able to be done somewhere else. The National Conference of Commissioners on Uniform State Laws develops model legislation for

states. I mean, I had an instance where a consumer actually called me about one of her concerns and contacted them. They have periodic deadlines for when they consider new issues. But they took her very seriously. She was like two days before the deadline, and they worked with her to at least get her issue put out there. So you might want to see whether this is something that you want to promote or you could go through them. I don't know how much of the work they do versus what you do, but I think you might be able to unload some of the burden on someone else.
DR. HOWELL: Do we have a question?
DR. TROTTER: Susan, you sort of mentioned it I think in your discussion, but I'd like to amplify on it. Would part of the outcome of this be maybe providing providers with templates to use as well, like letter templates that would be helpful for writing the prescription the first time, for appealing? I realize each disorder certainly is different, and many times each patient is different, but probably 80 percent of it, you must have found some wording that works better than others. I don't know. I'm just asking.
DR. BERRY: We didn't really tackle that as a possibility. I think it would exist, but I think rather than writing better and more aggressive letters, we need to really tackle the fundamental issue of avoiding having to appeal. And I think that's an educational and policy set of decisions. We certainly could make that kind of thing available generally, but I think that's a band aid.
DR. TROTTER: Well, I agree.
DR. BERRY: In the meantime, yes, you're right.
DR. TROTTER: We're having a little trouble getting things passed here in the last week or so in the legislature.
(Laughter.)
DR. TROTTER: Just in case it took longer than a week or two, I thought maybe we could do that.
DR. BERRY: That's a good suggestion and we certainly could gather that. It wouldn't be that hard to gather that kind of material. So that's a really good suggestion.
DR. HOWELL: That could be valuable as an interim step.
DR. BERRY: It certainly could be.
DR. HOWELL: Dave?
DR. LOUDER: The focus of your look here, your study was catastrophic inherited diseases with very expensive medical foods. As a neonatologist, we tend to send home a lot of kids on very special diets that may not be super expensive, but nonetheless very complicated and very difficult to achieve.
As you were looking at state laws and regulations, did you see included in those provisions for nutritionals that you can't buy off the shelf at Safeway but are given to children who need those? They're medically necessary but don't fall into the same things that you use for inherited diseases.
DR. BERRY: We didn't specifically look for that. In fact, that's part of, I think, that fine line between what you want to ask for. I think all of us acknowledge that those specialized dietary needs for average preemies who are not average persons would certainly be complicated and necessary, but we really weren't trying to define somebody who didn't have an inborn error metabolism. We really were focusing very much on these medical foods as defined pretty close to the FDA definition.
But that's part of the problem because how do you draw the distinction between one set of medically necessary activities and another. It's a very hard problem.
DR. HOWELL: Joseph?

DR. TELFAIR: Thank you. Thank you both for that presentation.
I have a couple of questions, and two of them are for Ms. Johnson and the last one is for you, Dr. Berry.
Ms. Johnson, the two that I have because I really appreciate a lot of the information that you presented and how you presented it. But one of the concerns and it's only a "but" because I realize that we're in a tough time these days is the decision-making process that goes into this. So I was wondering in your research, did you get a sense of the time frame that was used from the first time the request went in for this legislation to the time the decisions were made? And the second part was did you discover in the work that you did that there were specific committees, individuals, or groups?
I understand that Title V was part of some of these decisions, but I also know and the reason why I asked that is because in a lot of this work, the sustainment question is what I actually have because the legislation could be passed but the continued support of that legislation in a substantive way has a lot to do with the other two questions that I asked.
MS. JOHNSON: Right. I didn't interview any legislators for doing this analysis, but based on my past experience working with them, I would say in the majority of cases it was probably a constituent that came to them. And newborn screening is a popular issue for legislators. So I think most of these, once they're introduce, probably wouldn't have that difficult of a time passing in that same year.
When I think of following this issue and watching legislative activity over the last seven/eight years, I mean, the momentum has definitely picked up, not to say that legislators aren't going to have concerns about how are we going to pay for it, but maybe, like you say, they're not necessarily addressing that because there was very little I could find in the statutes or regulations to say how it was going to be paid for. But there were clear instances where they were allowing for something to happen, but basically it's like if you can get the money.
So I don't know that that follow-through is necessarily happening, and the information that we found I think is like, you know, the statutes are the first layer and the regulations are the second layer in like a 10-layer cake, and we need to talk to the states and not just the newborn screening people but the WIC people, the Medicaid program, all of that to find out what's really happening in the first place and then figure out where the money is coming from that's there and what are the deficiencies and who do we need to be talking to because I definitely don't think there is necessarily a follow-up in the appropriations part.
DR. TELFAIR: Right.
DR. HOWELL: We have a comment from Frederick and then from Jana. Frederick?
DR. TELFAIR: I just had a part two.
DR. HOWELL: Oh, I'm sorry. You still are going?
DR. TELFAIR: Well, I had a part two, remember, my other point for Dr. Berry. But that's okay. I'll come back to it.
DR. HOWELL: Hold your second part and we'll go to Frederick and Jana, and then we'll come back to you.
DR. CHEN: So when you guys met with the insurers, I wonder how much you heard from them about inappropriate use of nutriceuticals, experimental use, investigational use, and how much they were really needing to sort of guard against inappropriate use and whether or not that wasn't sort of one of the motivating factors for them.
DR. BERRY: I think what we mostly heard about there was this distinction that we've sort of begun to touch upon, which is how rigidly do you draw the lines between what's a set of

treatments for a set of rare disorders and a more broad use of some of the same products overlapping for a much broader use. And what their fear is that if they open the door a crack, that people will push through and a great wall of water will come. And that will really make it impossible for them to be able to either estimate their costs or to control it. So we got the general sense of a sense of a real misgiving about how broad that crack in the door would be. Am I correctly representing that? I think that was part of their problem. They thought it could be very broadened perhaps to the detriment of the rare disease that you were trying to take care of.
DR. HOWELL: I'd make a quick comment about that. One of the potential mechanisms to accomplish that would be to say for conditions approved by this committee so that there would be a clear definition.
DR. BERRY: We would have to, I think, broaden the definition to ones that weren't screened for, though. I mean, you don't want to not feed an OTC kid because you didn't screen for it.
DR. HOWELL: But we're going to soon be screening for everything.
(Laughter.)
DR. BERRY: And the panel is great. Can I just add one other thing? I wanted to mention that Rani Singh you talked about a practical view of this. You had a view where we looked at the statutes. Rani has been systematically doing interviews to try and get a sense of what states really do as opposed to what their rules say they should do.
DR. HOWELL: Let's hear from Jana who has been patiently waiting down here.
MS. MONACO: Well, I pretty much had my question answered I think.
In that understanding where the insurance companies were coming from as far as why they chose not to cover these formulas, do you get a feel that if they were better educated on these disorders that they'd be more apt to reconsider?
DR. BERRY: I think there are two things. One is I think education would help a lot because sometimes it's just flat lack of knowledge on the part of the person who's getting the client, and if they had better training and better so codes, for example. They like numbers that match to numbers that they know. If you have that kind of information, you will get improvements.
But the other problem is that and this is what they've pointed out to us, and it makes me kind of uncomfortable but I think it's just part of the rules or how things happen, which is that they negotiate individually with clients, and if a client doesn't want something covered in their coverage, they don't cover it. And so they say we might offer the same package minus portion X to one company and plus portion X to another, and they don't have any control as a company about whether this is what they said. They don't have any control over what a given client decides to accept as part of their package in the negotiation.
MS. JOHNSON: Right. Also in the statutes, I mean, this is the basics I've presented of what's going on. Some of the more in-depth language is in the table, but it will also say deductibles, copayments may apply. You have to treat this disease how you would treat other like diseases. So when you really get down in there, what does this really mean?
And what I think is so interesting about what Sue looked at is it reminds me of questions I used to get when I was working or legislators. And a constituent would call us directly and ask me something like, can I be discriminated against? And they don't even know what kind of insurance they have. So it really depends on the individual knowing very well, even if there is a state law, what kind of insurance do they have to even figure out if it applies.
DR. BERRY: So we really did run up against some places where it was just the contract that the individual had and it just flat out said we don't cover it, and there was no provision to make any allowance for it at all.

DR. HOWELL: Joseph, part two.
DR. TELFAIR: Part two. Thank you, sir. Appreciate it.
Dr. Berry, I just have a few suggestions. Given the information that we received, the first one has to do with the work that you're doing with the convening of the groups, you and your colleagues and community groups. I would just wanted to add to that group a discussion with those who are responsible for the decision-making at the state level that you can have a chance to speak to as well.
I do think it's a good idea you consider a template for them as well because in terms of planning, particularly planning related to the financial aspects of this, given the ups and downs and given how priorities shift.
I understand that it's a popular issue, but also there are a lot of other popular issues in states. And this is a really critical piece. So I recommend that.
The second thing was with regard to the survey. It's going to be important in regard to the survey because one of the things you obviously ran into was the consistency in the asking of the questions, that you also include you may be already doing this. I just didn't hear it training for those who are asking the questions to make sure that that is going on because you are going to be changing the items somewhat and the format and those sort of things. So any kind of orientation, even if it's a written orientation, whatever, to those helping you with that will also help with the consistency issue and getting at the question as well, even if you have your second pilot going on.
DR. BERRY: Yes. We actually prepared a set of pilot materials for the centers that would be applying that, but some additional materials that would support that would be very wise I think.
DR. TELFAIR: Yes, and I'm happy to help you look at that, if you want to.
DR. BERRY: Thank you. That's very helpful.
DR. HOWELL: Duane?
DR. ALEXANDER: Susan, I was a little surprised how quickly you dismissed any kind of federal activity and went to 51 different places for the activity. Has your group given any thought to what kind of federal approach might be taken to try to address this?
DR. BERRY: We actually had a really, I think, very thoughtful discussion about that, and I probability shouldn't have been quite so flip about that because we really do think ultimately that's the correct answer.
There have been some model activities that were similar to the kinds of things we wanted to do, for example, provision of breast cancer supports. Maybe, Coleen, you want to mention that a little bit because you're sitting there looking like you wanted to
DR. BOYLE: Well, I was just going to say the feedback we got is it is very challenging. So for impacting ERISA-based plans, employer-based plans I'm recalling this now there are only three provisions. One was for reconstruction surgery following breast cancer. The other one was on the recent
DR. BERRY: GINA.
DR. BOYLE: GINA legislation, and there was one other. So there are really only three precedents to this. So we felt like that would be a real uphill battle.
DR. BERRY: But we were encouraged to consider it.
DR. BOYLE: Yes, we were encouraged.
DR. LLOYD-PURYEAR: But they all lacked this is what IRS said, if you remember the employers' sanctions. That's how you have force, and that's why you suggested, Coleen, looking at Title V.

DR. HOWELL: Yes. I was going to say, what sort of requirements, et cetera could be imposed in the Title V funds that might be beneficial across the states?
DR. BERRY: There was considerable interest in Title V as a mechanism for some of this as well.
DR. HOWELL: Title V funding would potentially impact a large number of the children that we deal with.
DR. BERRY: Oh, yes. It certainly would.
We're obviously not going to take only one approach to this. We'd like to encourage we just thought, in terms of things that could be done as a product relatively quickly, that model legislation at the state level could be accomplished relatively rapidly. But this federal approach would be more work but more complete.
DR. HOWELL: If there are requirements in Title V funding, how commonly do states then pick it up for their other programs in the state as far as requirements? I don't know. Is that a common pattern? If Title V requires something to be done, does the state insurance group say, well, gosh, that's a good idea, let's incorporate it?
DR. BERRY: Not as much as you might hope.
DR. van DYCK: Rod, Title V cannot impose any state to do anything.
DR. HOWELL: It cannot.
DR. van DYCK: It cannot.
DR. TELFAIR: They work in partnership.
DR. van DYCK: So states develop their own plan, have it approved by the federal government, but we cannot require any specific things except very broad, general guidelines.
DR. HOWELL: Mike?
DR. WATSON: *[3a flip] lines of attack on this. Actually the most successful for ERISA has been just raising awareness of the issue because there's a world of benefits consultants out there that work with these big companies. You know, they work with the employees of the company, and if the employees want something to be put into their plans, they actually drive through the benefits consultants to get them into the plan. So publishing this stuff and raising visibility of what is a well-recognized program and the fact that we're not succeeding and really accomplishing it at all because of some of these kinds of issues I think is very important. And that's not necessarily lobbying. It's just raising awareness through publishing
DR. BERRY: We thought that was one of the reasons that there was justification for going after publication because we do regard education of the industry as being critical to this.
MS. JOHNSON: There was one state that I know reported back in your survey, Mike, that 70 percent of ERISA plans were paying, even though they didn't have to. So I wonder in that state, if you talked to that person further, why is that happening?
DR. WATSON: Yes. I think, as you know, from looking at that data, they'll say they use Title V, but that's a recirculating fund so that insurance money that they can submit and get reimbursed on those that are insurable rolls back into that and replaces the Title V investment they made. So it's a real sort of money trail to figure out exactly what's covering what.
DR. HOWELL: Ladies, thank you very much. That's been very helpful.
I know that Rani has spent a huge amount of time. Do you have a brief comment you would like to make at this late hour?
DR. SINGH: I just wanted to respond to the request which had come up about the letters. The GMDI has already collected the letters and putting on the website from various clinics to help facilitate that. So that initiative has already been started.
And a lot of the insurance companies our effort has been they're looking for CPT codes to go

with it for billing. That was my biggest thing from private insurers when we go because we are using some codes right now which don't match in different states. So that's one effort for reimbursement I think they are looking for.
DR. HOWELL: Thank you very much.
Mike, you have a final comment?
DR. WATSON: Only one quick comment which is that it would be nice if we could think about all of the CPT HCPCs related issues that are coming down the trail because I'm already months into negotiations with the College of American Pathologists around newborn screening CPT codes just for the screening tests themselves, and that's an interesting negotiation in and of itself. But if we're going to go in for it might be easier to deal with many things in newborn screening all at once, be they for treatment or for testing, because it's a long educational haul through the CPT editorial panel, and you might as well educate them once in general and deal with all of these coding issues in one big package.
DR. HOWELL: Thank you for volunteering to host the CPT committee here.
(Laughter.)
DR. HOWELL: Ladies and gentlemen, I think we've had an incredibly productive day. So we'll reconvene in the morning.
I'd like to make one slight change in the agenda. In view of the fact that Jim Perrin has to get back to Boston early, I'm going to suggest that we start out the morning at 8 o'clock to discuss the Pompe review from 8:00 to 8:30, and then we will go into our subcommittee sessions. We won't change the amount of time allocated, but the order. So we'll all come back to this room first thing in the morning at 8 o'clock after breakfast, and then we'll go into subcommittee. Again, think about the Pompe review, the evidence-based review, and then come with some very concrete suggestions and thoughts because we should leave that discussion at 8:30 with a specific plan of action with regard to Pompe disease.
Thank you very much. We'll see you in the morning.
DR. LLOYD-PURYEAR: There was an error on the announcement for the subcommittee meetings because it said the 12th floor, but it's actually the second floor. Everything is here.
DR. HOWELL: And we'll repeat that in the morning. Thanks a lot.
(Whereupon, at 5:05 p.m., the meeting was recessed, to reconvene at 8:00 a.m. on Thursday, October 2, 2008.)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE ON HERITABLE DISORDERS
IN NEWBORNS AND CHILDREN

Thursday
October 2, 2008

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C O N T E N T S

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P R O C E E D I N G S (8:07 a.m.)

DR. HOWELL: We're here very much on time. Congratulations. It was a really tight morning. As you recall from our discussion yesterday, we had a wonderfully fruitful discussion with the Evidence Review Group about a rare disease, that is, Pompe disease. That's a world-breaking effort. It's the first time that there's really been a systematic look at a rare disease, and so we think this is important not only for our own parochial interests, but for the field in general.

My goal in this 30 minutes this morning is to review the efforts on Pompe disease. And again, talking with folks and so forth, I think that there's quite general agreement about the core issues that are at hand. At least I haven't heard any dramatic differences.

But what I thought we would do is we'll ask our evidence-based guru, Jim Perrin, and Mike Watson who had summarized for the committee yesterday to go through the key issues that we discussed and come up with a specific recommendation and also what we need to convey to the nominators of Pompe disease so that we will make a recommendation and we will say this is what the committee thinks, and then as a follow-up, in order to move the process ahead, if that indeed is the decision, these are the things that we find would be needed to move this further along.

So, Jim and Mike, this dynamic duo, let's get rolling.

DR. PERRIN: We're changing themes as we speak. No.

So this is probably the most important slide we'd like to focus on to begin with, which is the summary slide from our presentation yesterday, which talks about screening and treatment primarily. It notes that there is a population screening pilot that is in place at the moment. We have early data from that population pilot in Taiwan. It does have a fairly high false-positive rate. Again, we talked a bit about yesterday, what's really a false-positive versus recall, but I want you to just understand what we know about those data.

So far, we were surprised by the lack of identification of late-onset in the published data. It may represent an early phase of the results.

The second area is that there is some evidence that treatment of early-onset disease may be lifesaving, but it's really basically a single-series study, a very good single-series study, although we don't know such issues as selection biases in that.

And there are no studies, of course, at the moment of screen-positive newborns and no cost-effectiveness studies.

I think those were the three elements that are probably most important to summarize from our work so far.

Now, we've also got a variety of recommendations that are in the slides, which are some of the things that are needed to improve screening, some of the things that are needed in diagnosis and treatment in order to understand more about the kind of evidence that's necessary, and some other needed information about determining prevalence, for example, and so forth.

Rather than go through these one by one, they are available to you, some of our sense of what are the critical elements missing in literature in this area, but I think probably these three items are

the ones most important to focus on in our summary.
Michael?
+ DR. WATSON: All right. So to try to facilitate a discussion, as Jim said, rather than going through every question, we thought we'd just break it out into four main categories: what we know about the condition, what we know about the screening tests, what we know about the treatment and management issues, and the cost-effectiveness side of this, which I think are captured within these three areas on the slide.
So if we start with the condition then and the issues around what we know about it and don't know about it, it seemed that the question of early- versus late-onset was the biggie, with late-onset being the one less clear.
Questions or comments about where we are with our understanding of the condition and the adequacy of that information?
DR. HOWELL: Gerry?
DR. VOCKLEY: That bothers me the least of any of the things we discussed. I think we have a severe early-onset condition. It has a few flavors in the early period. We're used to that. That's standard in genetic disease. More will come out of what to do with the really late-onset, the adult or later childhood-onset stuff, as we screen positive. So I'm not so much worried that we have to deal with that latter group in advance. First of all, I don't think it's possible.
So we would come back to what's knowable and what's not known. I think that's not knowable right now. And so I would take it out of the equation and concentrate on the early-onset disease and say we're pretty good there. I think we know what we need to know.
DR. WATSON: Freddy?
DR. CHEN: One thing that I am concerned about, though, is the substantial false-positive rate. Given that there may be another technique, like tandem mass spec, which will reduce that, although that seems to be in the future and not really on the table for now, my main point about the false-positive rate, since we did have a substantial discussion about it, was if we look at the key question 6 about the sort of harms or risks of screening, even though there is no specific data of Pompe disease and the risk of a false-positive, I would point, however to the significant literature on the harms of false-positive screening for any other disease and just posit that the mother whose child has a positive test for cystic fibrosis or for maple syrup urine or any of the other diseases most likely suffers the same amount of stress and anxiety and harm that a false-positive for Pompe disease would have. So I do think that there's a literature there and some known sort of measurement of harm and risk that we can call upon for trying to quantify the harmful effect of the false-positive rate.
DR. HOWELL: I think there's considerable concern about the test and so forth. Let's go back and focus at the current time on the disease itself. Gerry has said that he's not concerned about that issue because we know a great deal about the infantile form and we will learn more about some of the variants after screening is underway, et cetera. Is that what I heard you say, Gerry?
DR. VOCKLEY: Yes, although I would add that I'm a little worried about the population of the screening data that we have, and we're going to need to come to a fundamental decision. You know, we had a lot of talk about the Italian Fabry study and said, well, we need to repeat that in the United States before we're going to do anything. We can't have it both ways. And so I'm not worried about the patients that we're identifying, assuming that we overcome the technical hurdles, but I do think we have to decide fundamentally either we accept non-U.S. screening studies or we don't.
DR. HOWELL: It seems like the discussion is moving rapidly to the screening test, regardless of

what we say. So we're going to put the clinical thing aside.
What's your next point?
DR. WATSON: I have one question on the condition, and that is, you say you understand early-onset, but if you're identifying patients in newborn screening that can be early or late, then you actually can't predict which. You may be able to predict some of the late-onsets based on one mutation, which are a lot of the late-onsets.
DR. PERRIN: May I make one comment?
DR. WATSON: Please.
DR. PERRIN: So I think one issue also you may want to think about is that there isn't a very clear definition of what we mean by a case of positive Pompe's in the presymptomatic phase. That is partly again an early/late-onset distinction, but we need to do some work to develop that definition.
DR. HOWELL: Coleen, would you like to comment on that? I know you've been concerned about that specific issue.
DR. BOYLE: Sure, and actually I was going to refer to the Taiwan study we spoke about this during breakfast this morning because there were a number of children who actually were considered false-positives that may, under a screening program, be considered presumptive cases. And that was a point that didn't come up yesterday. So I know screening programs have at least in epidemiology, we have various definitions, a confirmed case, presumptive case, and there clearly were children who, from a laboratory perspective, would be considered a case, but from a clinical definition, they didn't have the classic symptomatology. So I think we need to keep that in mind.
DR. WATSON: Yes. I actually think that's how we'd like to get to some resolution of this. We've discussed each of these areas in fair detail. If we can get to those things that we would say need to be really focused on in a pilot or in other data collection, pre-pilot or whatever, presuming that we don't say just go do it, which is not decided yet. But I think getting those gaps down and really what we need to capture is
DR. HOWELL: Gerry, you had a comment?
DR. VOCKLEY: Well, just to get back to Jim's comment, I agree we don't know the difference between the early- and the late-onsets in the screening, but I wasn't dealing with that. I was just saying that we have enough to know about the the most positive thing I'm going to say about this application is that I think we know we should treat the early-onset, seriously affected.
Now, what we don't know which of those screen-positives those kids are. What we don't know is does actually treating them at 2 weeks of age make a difference compared to when they first become symptomatic at 4 weeks of age. There's lots of stuff we don't know, but I think we should give them that the infantile form deserves early treatment. Now we have to define that better.
DR. WATSON: I think we have one question back here.
DR. HOWELL: We'll take a brief comment. Anne is burning up to say something, but we're not going to typically take comments from the audience, but we'll hear from Anne. She was on the Evidence Committee.
DR. COMEAU: Thank you. I think the one other concern about not having a very clear case definition at about 2 weeks of age is the issue of possible false-negatives because if screening identifies these babies and there is not a diagnostic test that can identify them at 2 weeks of age, we might be thinking that these babies are false-positives, not treating them, and then throwing away all of the work of screenings. I just wanted to bring that up.

DR. HOWELL: So what would you like to say about the case definition before we move on?
DR. WATSON: Well, it sounds like that seems to be the major issue. It's sort of the bridge between the condition and the screen itself, which is what is a screen-positive case definition.
DR. HOWELL: Becky?
DR. BUCKLEY: Yes. Does a confirmatory testing for the condition include mutation analysis?
DR. HOWELL: I don't know.
DR. BUCKLEY: Because you would think that if mutation analysis is done routinely, that you should be able to tell whether it's a true case or not.
DR. HOWELL: The typical confirmatory test that's done in Pompe's is an enzyme analysis at the current time.
DR. BUCKLEY: But a mutation analysis is not always done?
DR. HOWELL: I don't think so, but I don't know the answer to that. There are a large number of mutations known. There are hundreds that are known, and as far as a confirmatory thing Barbara?
DR. BURTON: Well, I think mutation analysis is now commonly done, and I think certainly in the newborn screening setting, it absolutely would be. We can rely on an enzyme assay if you have a patient with clinical symptomatology, but otherwise, yes. And I think in the paper it quoted the rate of detection of two mutations was close to 90 percent. Is that correct, Alex?
DR. KEMPER: I can't remember the exact percentage, but it's right around there. There are more than 250 mutations of the gene, and there's some genotype/phenotype correlation, but not very much. So there are some specific sets of genes that are associated, for example, with the late-onset.
In the very early newborn period when children are detected through a series of positive screens, the hallmark of the early infantile form is cardiomyopathy. So ECHOs-defined cardiac dysfunction is what institutes treatment.
DR. BUCKLEY: Well, the reason I raised the question was because in the case that Anne brings up of the 2-week-old infant who you don't know really whether the test was false-positive or not, you would think that mutation analysis should be included in cases like that.
DR. KEMPER: As Dr. Burton said, the mutation analysis is done, but it just takes so long for all that stuff to come back.
DR. HOWELL: Well, I think what we're hearing is confirmatory follow-up diagnostic tests, that as they're appropriate, they would include perhaps mutation analysis, enzyme analysis on leukocytes, which is another thing.
So how would you summarize this discussion, Mike, for this point before we move on to the next one?
DR. WATSON: How would I summarize it. I think it goes back one step, which is what is the best screening algorithm. Are there second-tier things that can be done in the screening lab to reduce the number of false-positives that we see in the fluorometry-based assays? Tandem mass spec has a long way to go until we have data to talk about it and its performance.
So you want it as what is the gap that we're going to say? How would you characterize it? It's around that case definition.
DR. PERRIN: Well, I think that there is a real need to develop a stronger understanding of the implications of positives and negatives in the newborn period and what are the strategies for the next steps in that.
I think Gerry sort of said it, though, pretty clearly. We do have a clinical case, not a screen-positive case, where there are children who are clearly very severely affected by early-onset

disease. There's no question about that. This is a very, very serious disease with extremely high mortality. So I think one can say that and then perhaps move on. There are things that need to be worked out in this, but I think the level of severity of disease, importance of natural history of disease, early-onset disease is a very serious problem.
DR. WATSON: And then I think we get to maybe not a secondary issue but an associated issue which Coleen raised yesterday, which is do we think all of these gaps and answers that we're going to ask for need to be done in the context of a U.S.-based pilot.
DR. HOWELL: Can we have a few comments about the U.S.-based pilot study? That's been discussed extensively in the past. Any comments? It's a fundamental question. Is this committee going to recommend the adoption of a newborn screening test if it is not accompanied with a pilot study that has been done in the United States? That's the question.
DR. WATSON: Sharon?
MS. TERRY: So that question very much interests me because if we're going to look at eventually, in the history of man, 7,000 rare diseases, the U.S. government is not going to have the money to support those studies, nor will private industry. And the idea that we would put boundaries around these diseases and not do this in a global way, since the cases are so rare and so limited, would be troubling.
I also understand, however, that in cases like this, if this had happened in the United States, I think we'd have a whole lot more data. I'm disappointed that we can't get the scientists here to tell us a little more about the background or even give the data to a committee that would keep it confidential and look at it.
So I get those two things, but I think we'd be severely limiting ourselves to say we should just look at U.S. pilot studies.
DR. HOWELL: So your answer is no, it should not be just in the U.S.
Any further comments? What is the potential value? Duane?
DR. ALEXANDER: Yes. I'm going to have to leave in a few minutes, but I did want to contribute some information to this part of the discussion.
In making a decision, people should be aware of the capacity that is being developed to do pilot studies like this in the United States, and it seems that the Pompe disease model is one that could fit very readily into the concepts that we're developing. We are planning to establish a network of the sites around the country that already exist in the regional collaboratives for conduct of studies like this. We've already funded a coordinating center to put these together to collect a central repository for the data and following up on outcomes and so forth, as well as to take the lead in working with the NICHD and CDC and the Maternal and Child Health Bureau in developing the protocol for such study. We then would provide assistance to the regional collaboratives for conducting that protocol and gathering the data and following up the treated patients so that we would have the data collected in a coordinated way as rapidly as possible with as large a population base as we could assemble.
So the mechanism for doing a pilot study like this is under development and almost ready. It seems to me that the Pompe's case is a perfect pilot kind of a situation for using in a network like this, probably using some different methodologies, certainly looking at the tandem mass spectrometry and seeing whether that helps to reduce the false-positive rate, and some other issues that could be addressed in a study like this. So the mechanism is going to be available very shortly to do this kind of a pilot study.
DR. HOWELL: Thank you very much, Duane. For those of you who don't follow the federal stuff, the program that Dr. Alexander mentioned, the new Translational Research Network,

funded by his institute was announced yesterday in the Federal Biz Ops. So if you want to read about it, that's where you can go read about it.
Any further comments about it? I think that there's a considerable sense of material there. Coleen?
DR. GETCHELL: I just wanted to make the comment on U.S. data or not. I see real difficulty in states adopting screening for Pompe in this case without having U.S. data.
DR. HOWELL: So you would echo Sharon's thing, that we should not be as restrictive as requiring U.S. data.
DR. GETCHELL: No, no, just the opposite. No. I'm saying we need U.S. data.
DR. HOWELL: Oh, I'm sorry. I misunderstood you. All right. So you would feel that U.S. data would be essential for you to adopt a test in Delaware.
DR. GETCHELL: Right, and I think our advisory committee would look for that and need that information to see how it applies to our population.
DR. HOWELL: I might put in one thing. As you recall, this group reviewed Fabry disease briefly. There were a number of situations, but one of the reasons that we did not recommend Fabry is there were no U.S. pilot data in the nomination. Just an historical perspective.
DR. BOYLE: I feel like this needs to have more discussion because I guess I'm feeling similar to Sharon that because these are very rare conditions, I think all data should be on the table. If a well-done study is conducted in Taiwan, which having read the Taiwanese study, I feel like I'm not a laboratorian. I'm an epidemiologist, but from an epidemiologic perspective, it's a very well-done study. That's in progress. So there will be subsequent publications from it.
But to not include that as very robust evidence in this context of very rare diseases I think would be sort of a disadvantage to this field. There may be an issue of pilot testing for the laboratory component of it, integrating that from a laboratory perspective. I guess I think we need to be a little bit open on that issue.
DR. HOWELL: Tracy has a comment.
DR. TROTTER: And I think we should maybe try to clarify the difference between utilizing data from a well-done study in this case from Taiwan versus there's not a population-based study that has been done in the United States. If there were one, would we then use that data as well? I think yes. Without one, it's a little more difficult for us to look at our much more heterogeneous population and maybe draw the same conclusions. So I don't look at it as excluding data that's not done here. I would look at it more as at least one population-based study that we felt was a reasonable study should be done here.
DR. VOCKLEY: I think that's right. How does the experience in a much more homogenous population translate into the U.S. population? And that's what we don't know and we don't know how all these false-positives and negatives and predictive values and everything else that we like to calculate translate into the U.S. population.
And so while I think if there were an absolutely compelling study that were not done in the U.S., a consortium of other countries that we could sort of extrapolate a little bit better to us, it might be acceptable. So I'm not saying we have to demand a U.S. study, but in almost any situation I can come up with, we would have significant enough questions surrounding a study done somewhere else that it would, in essence, end up mandating a U.S. study. So I don't know that we want it as an absolute policy, but the reality of it is it's going to be hard to get by without one.
DR. HOWELL: Coleen, you had something else.
DR. BOYLE: I was just going to say that I would compare a study done in Taiwan to one done in Iowa as being very comparable in terms of the heterogeneity of the population and the

diversity issues and whatever the issues are that we are addressing. I do feel like we just we have to take this on a case-by-case basis.
DR. HOWELL: It seemed to me that the other thing I must recognize, one of the most ardent supporters of requiring a U.S. study is Piero, who unfortunately isn't here. But it seems to me we don't need to decide this with regard to this recommendation. Let's keep this in the wind. Jane has some very good points from the state laboratory viewpoint. Others are speaking fervently about international studies. So let's continue to discuss that and let's move on because we're going to finish this promptly.
DR. WATSON: Good attitude. So you want to move on to treatment and management issues or continue on?
DR. HOWELL: I would continue.
DR. WATSON: Continue on the screening test?
DR. HOWELL: Yes.
DR. WATSON: Any other comments on the screening test?
You know, I think it boils down to two competing things. One is that the lab will do a pilot of some form regardless. They have to bring up the test even if they accepted everything in an international study. I think the issue of international studies boils down to the quality of the data and the transparency of the data, and we had some issues with some of the data that we didn't have access to that made us qualify it a little less than we might have desired. So I don't think it necessarily has to be all of one or the other. There are different things that will be piloted in different ways, as you bring a test on board.
Any additional? Mike?
DR. SKEELS: Sure. I'm going to repeat myself from yesterday, but why not?
I think we're going to be screening for lysosomal storage disorders sometime in the next couple of years, but the technology hasn't progressed to the point where we can do it in an efficient and replicable way. I'm not an expert on this, but my reading makes me think that right now there are a lot of preparatory steps, and hand steps, and things that are not amenable to automation at all, and a lot of basics in the way of sources of false positivity, both biological and analytical, that need to be worked out. And I think we're going to end up with a cocktail of different substrates, tandem mass spectrometry to identify the analytes, that is, the enzymatic products that are of interest, and we're going to be multiplexing against several different lysosomal storage disorders at once rather than starting with one and working our way through. I could be wrong about this. I often am.
But my guess is that we'll be ready to do this in a couple of years, and it will probably be driven by industry. Somebody I won't name the names of any big companies will come up with a kit that can be used, and I think that's where we're headed.
I can't imagine how we could possibly put something into production now that's so labor-intensive and has such an extraordinarily high false-positive rate. I mean, whether you want to call it a biological false-positive or we were talking about at breakfast whether it's a true false-positive or a false false-positive, I just don't feel like state screening programs are probably ready to put this technology into practice.
DR. HOWELL: I think there's been great concern about the test for a variety of reasons. It's clear that additional work needs to be done on a test that is more appropriate, shall we say, for newborn screening, and at the same time, the exact definition of the cases need to be defined.
Can we move along then? I think that again, obviously, we have experience in one state that has been screening for quite a long time with a large number of patients with one lysosomal disease,

that will come before us soon, which is, of course, New York State and Krabbe.
Again, it's very clear that commercial folks will have these tests on the street before you can bat an eye. I can assure you. As a matter of fact, they're on the way right now. They probably are advertising in the corridor as we go out.
(Laughter.)
DR. HOWELL: But anyway, Mike, let's move along.
DR. WATSON: Okay. Moving on then to treatment and management. I think clearly there is an available therapy, the enzyme replacement therapy. The big questions seem to be longer-term outcomes in those who were treated were only out to 52 months, which is not that bad, given a disease, at least in the infantile form, is usually lethal between 12 and 24 months, and then the question of the whole adult-onset side of this. When would you begin treatment if you knew it was an adult-onset form? And the fact that they picked up five adult-onset in the second 70,000 or the next 70,000 and none in the first 130,000 made me I couldn't understand that data particularly well from the Taiwan study.
So comments, questions around the treatment, what we know about it, what we would say needs to be known about it that we don't know?
DR. HOWELL: I think that that information will come out in the carefully controlled study that's done in an environment where you follow these people and you will never know the answer to that until you screen and follow them and see what happens and see how your treatment goes. Again, that needs to be done in a research environment that Duane has described once you start screening. But I think we can comment about that, but that will come with screening.
DR. WATSON: Any other comments, questions?
DR. HOWELL: Are we ready to look at the blocks that you had yesterday?
DR. WATSON: Well, I think as long as we have a general consensus on the cost-effectiveness studies, that we need to do those and that they're best done in the context of that pilot. Is that consensus there? Okay.
DR. HOWELL: Cost-effectiveness studies will be very difficult to do in Pompe disease because the patients who are untreated die, and that's not very expensive for the public. But I think that we don't think that that's a good way to go. So the value of an infant is extraordinary. So I think it's a tough thing.
I think one of the advantages is although treatment is expensive, the condition is rare so that the impact on the health department is not
Thank you, Dr. Alexander.
DR. ALEXANDER: See you later. I'll be back.
DR. WATSON: So we talked about these extensively yesterday. The major issues seemed to be around the category of provisional status and whether we modify that.
DR. LLOYD-PURYEAR: It's in the book under tab 6 at the end.
DR. WATSON: So first talk about that category of provisional and pilot and how they either relate or integrate.
DR. HOWELL: Let's have a suggestion from the gathered group around the table about into which of these holes you would put this. Gerry?
DR. VOCKLEY: Well, if we modify the third category to be promising but needs additional specific types of data, in this case a U.S. pilot with longer-term follow-up and better evaluation of the technology, so it's promising but needs some specific work. Not provisional.
DR. HOWELL: We're going to do away with provisional because we discussed that that's not an issue.

How would you word the recommendation succinctly to fit in the box? It can't go beyond the box.
DR. VOCKLEY: I'm always beyond the box, Rod. You know that.
DR. HOWELL: I'm talking about that little box.
PARTICIPANT: With just a couple of words changed.
DR. HOWELL: That's correct, a couple of word changes. What would you suggest?
PARTICIPANT: Box 4.
DR. VOCKLEY: We were going to put recommend not adding the condition now but pilot studies. We were going to move that up. It was going to be the first box, the left-most box on the third line. And then I think that everything else so if you take that and put it up in the third one instead and then that fits perfectly I think where we are with Pompe. We're not going to recommend adding the condition but it's sufficiently promising to suggest additional studies.
DR. DOUGHERTY: I would just say "additional studies" instead of "pilot studies."
DR. VOCKLEY: Yes.
DR. DOUGHERTY: Yes.
DR. HOWELL: Let's actually get the wording just the way we would like to have it.
DR. VOCKLEY: So change "pilot" to "additional." But then in the next box
DR. WATSON: I think the problem is that when you say "promising," I mean, there are some things you can learn outside of a pilot. You know, extending that long-term data collection on the treated patient doesn't necessarily require the pilot, but there are population-based things that do require the pilot.
DR. VOCKLEY: That's why I would leave it as "additional," and then you're going to have to come back with specific recommendations for this disorder, and those can highlight where we thought the holes were. And that gives you the flexibility there.
Now you have to get rid of, in the next column over, "insufficient, but potential net benefit is compelling." "Collect additional data and re-evaluate." You've got to get rid of the "add" because we're not adding it.
That's where I think Pompe fits. We're not ready to add it, but it's got a compelling story. It's close.
DR. WATSON: It's an interesting problem because it's a mix of some things that you have to do the pilot for in the newborn screening environment to get the information and things that can be gotten outside of that.
DR. VOCKLEY: Some of those questions can be answered by cajoling the Taiwanese to give us more of their data or having them publish it. Some of it can't.
DR. BURTON: Can I just ask a quick question about process since it looks like the committee is going to act on this nomination? And I think that's a hugely significant event in that this is the first one to come before the committee. Was the nominator of the application notified that this was going to be acted on at this meeting so that he or she or they would have the opportunity to hear the discussion? Because I think that would be an extraordinarily important thing to have happen.
DR. HOWELL: Do you want to repeat the question?
DR. BURTON: Was the nominator of Pompe disease notified that there would be discussion and action on the application at this meeting?
DR. LLOYD-PURYEAR: It's public record.
DR. BURTON: Well, the agenda, though I mean, it wasn't clear to me from the agenda that there was going to be action. There's a mention of the Evidence Review Workgroup report, but that's

not saying the same thing as what's actually happening here.
DR. WATSON: So the question is around what is the process.
DR. LLOYD-PURYEAR: So the direct answer to you is, no, the nominator wasn't specifically notified we'd be discussing Pompe disease. But it is a matter of public record, and most of the groups generally follow what the advisory committee is doing.
DR. BURTON: So in other words, we'd be relying on them to see that Pompe disease is on here and then call and say is this just going to be an interim progress report or is this going to be the final discussion and debate.
DR. LLOYD-PURYEAR: Well, I'm not sure everybody here, including me, anticipated there would be a final action on this because I think the committee opinion is quite divided on whether or not there should be a final action or at least was coming into this meeting.
DR. BURTON: Well, I would just like to offer my opinion that there should not be, particularly without the nominator not being aware that that's going to be taking place so that they could hear the discussion.
And I also feel like having heard what went on yesterday, to a certain extent, that this all happened very rapidly. I know I heard one of the committee members who was targeted with reviewing the external workgroup report say that the summary slide she had not had the opportunity to see. So it seems like this all has evolved very rapidly.
DR. HOWELL: What's the sense of the committee as far as what you would like to do with this? We will certainly move as the committee would like to do, et cetera. I think it would be advantageous for the nominator to be here. However, it's a public record and the nominator, seeing that we were going to discuss it, I would think would have come frankly, because the discussion is clearly on the agenda.
Gerry?
DR. VOCKLEY: Yes. I think the item was on the agenda. If there is a clear intent to vote on something, then I think it makes perfect sense to notify the group or the proponents. However, the fact that there isn't an intent to vote doesn't mean we won't. We may be able to resolve more than is anticipated. And in that case, if the committee is ready to make a recommendation, I wouldn't hold it back because we were more efficient than we thought we would be. So it happens so rarely
(Laughter.)
DR. VOCKLEY: we shouldn't hold ourselves back.
So in theory, I agree with Barbara, but I don't see that we can limit our action in any one meeting based on what we thought we were going to get to.
DR. HOWELL: I might point out that we obviously and Barbara, obviously, understands this as well as anybody would not have a nominator speak or anything at this meeting because the evidence review will be dependent on the
Let me hear from the group. What do you want to do with this? It seems to me that there is some concern, but on the other hand, I sense that there's a general agreement that this is an important condition and these are the things that we need to do to get that. Maybe my perception is not correct. Can we hear from some of the silent group to my left? Tracy?
DR. TROTTER: Move forward. Let's vote.
DR. HOWELL: Let's hear from everybody. Should we go ahead and get this off the agenda, or should we come back and talk about it next month in February?
MS. MONACO: I think we should move forward because we've clearly made some changes to the recommendations, the different columns, that might help us in moving forward.

DR. HOWELL: Denise?
DR. DOUGHERTY: I agree. We should move forward. I don't think there's anything between now and the next meeting. We're not going to redo the discussion, and I don't think there's anything that would change this.
MS. TERRY: Remember, my vote doesn't count.
I'm uncomfortable moving quickly on something so serious and particularly the first one.
DR. HOWELL: I'm interested in hearing from everybody, including those persons that don't vote.
DR. GELESKE: Well, I agree with what Barbara says. I think the nominator should it would be important for them to be here, but given that it seems like the group is coming to a consensus, then I agree that you move on as well.
DR. HOWELL: Fred?
DR. CHEN: Yes, I'm quite comfortable with moving forward too.
DR. HOWELL: And let's welcome Dr. Musci today, who was not here yesterday.
DR. MUSCI: Hello. I've had a chance to review the written materials and listen to this discussion this morning. I think given where I think the recommendation is going at the moment, the issue is still alive. So I would favor moving forward.
DR. HOWELL: Thank you.
Jane?
DR. GETCHELL: I agree. I favor moving forward. I think we've had an excellent, thorough discussion and have reached a consensus.
DR. HOWELL: Dave?
DR. LOUDER: The process seems to be working. So move forward.
DR. HOWELL: And we've heard from Barbara. Joseph?
DR. TELFAIR: I agree. Move forward.
DR. HOWELL: Coleen?
DR. BOYLE: Oh, I would agree. Move forward.
DR. HOWELL: Becky?
DR. BUCKLEY: I think we should move forward.
DR. HOWELL: And Gerry and Michael?
DR. SKEELS: I think we should move forward, but I think the next time we're going to make a decision on one of these, we should be sure it's in the agenda as a decision point rather than just a report.
DR. HOWELL: Let's go.
So the sense of the group is that the third box down is what we'll recommend to the nominator and recommend not adding the condition at the current time but asking them to conduct additional studies and present additional studies.
Anything else in the other boxes you want to add?
DR. WATSON: I think the problem with having those two they're not independent categories because it sounded as if some of the additional we need will only come from a pilot, and some of the additional can be gotten in or outside of a pilot.
DR. HOWELL: Well, collecting compelling data would potentially include a pilot.
DR. VOCKLEY: Are you questioning the difference between the third and the fourth categories or what we're recommending in the third category?
DR. WATSON: I just think they're not mutually independent.
DR. VOCKLEY: No, they're not, but my intent in suggesting the wording on the third and the

fourth is that in the third category we have definite yes. We have definite no. We have this is pretty close, but we need more. And then number 4 in my view was we're not saying yes or no. We don't have enough information. Period. So 3 is we're giving them the feedback that the committee thinks this looks pretty good right now, but we need you to seal the deal with some very, very specific suggestions about what's necessary to do that.
DR. WATSON: And I'm only trying to be pragmatic in looking at it. I mean, certainly some of the biggest issues are only going to be answered in a pilot. That's going to be, if it parallels SCID, a $2 million investment in a pilot study.
DR. HOWELL: Mike?
DR. SKEELS: Do you want a motion?
DR. HOWELL: If you're ready to make a motion, I'm ready to hear it.
DR. SKEELS: I feel one bubbling up.
(Laughter.)
DR. SKEELS: I'd like to move that Pompe disorder be reported out as category 3, recommended but additional studies are requested.
PARTICIPANT: Recommended not.
DR. SKEELS: Excuse me. Recommended not adding the condition now, but additional studies.
DR. BUCKLEY: Second.
DR. HOWELL: Dr. Buckley has seconded it.
Is there any discussion before we vote on that?
MS. MONACO: I have a quick question.
DR. HOWELL: Jana?
MS. MONACO: We brought up briefly yesterday about the idea of time frames. Is that something to consider in recommending for the additional studies? Is there a place to suggest a time frame that would be indicative of maybe going back to it?
DR. HOWELL: Michael, do you want to comment about that?
DR. SKEELS: Well, we certainly should consider that I think as a committee, but I'm not sure that I'd like to amend my motion to include it.
MS. MONACO: Not for the purpose of amending, just as part of the recommendation, putting in a time frame.
DR. SKEELS: Right now, we're not voting on recommendations. We've got a motion that's been made and seconded, and we need to decide whether to amend the motion or not. And if we want to amend the motion, then we need to go back and do that. Otherwise, we can then talk about what to include in our report in terms of recommendations.
DR. DOUGHERTY: Well, we can't really predict *[1b flip] data will be available. So as soon as it's available, we would reconsider.
DR. WATSON: Nor can we predict how long it will take for somebody to invest that $2 million in a pilot study if that is what was needed.
DR. HOWELL: Dr. Skeels has made a motion, seconded by Dr. Buckley for block number 3. Is there further discussion on that motion?
(No response.)
DR. HOWELL: Those in favor of the motion, please raise your hands and we'll count them. The voting persons.
(Show of hands.)
DR. LLOYD-PURYEAR: Oh, it's unanimous.
DR. HOWELL: And those opposed?

(No response.)
DR. HOWELL: Thank you very much. That passes.
Now, we should come up with a fairly clear list of things that we would like this group to do. Number one, I would suggest, Jana, that when we write to them, we would say this is a very important disease and we would hope that this would get done promptly. I'm not sure what the wording would be, but I would like to encourage them. But I don't think we can give them a deadline. If they decide to do a pilot study or there will be pilot studies going, I think they will be done, and then they will have to report them.
DR. TROTTER: I think they're going to have quite a vested interest in making that time line as short as they can.
DR. HOWELL: I would hope so.
MS. MONACO: Would something like this encourage the Taiwan group in releasing their information that has not been published yet? Would that prompt them more knowing that this has been addressed?
DR. HOWELL: Coleen?
DR. BOYLE: I have a question relating to this and Dr. Alexander's description of the research network he's building. So in terms of the priorities, the topics that are handled by that research network and I guess I'm addressing this to you, Rod, since you know more about that. Could the committee somehow recommend some of these conditions that are in this provisional category be priorities to be considered for that network? I don't know how it works.
DR. HOWELL: Well, I think that the bottom line is that the network will be accessible to those people who have projects and they will come to the network and say, we would like to use the network to do this and so forth. And I would certainly hope that the things that are recommended by this committee would come fairly close to the front of the line, and I think there's a good chance that that will happen because of the fact that the network is really established to deal with some of the problems that we're dealing with here. And hopefully, the Newborn Screening Saves Lives Act, which we've not discussed here, will have some funding.
What are we going to tell them that they need to do? We've got to be clear that these are the issues that came up that they would need to respond to.
DR. PERRIN: I think that's actually the question I wanted to ask, which is what procedure do you want to put into place. We could come, based on our work, with an initial set of potential needed information for the committee then to review and for the committee then to send on to the nominator. You could, obviously, revise and change that, but we'd be glad to take the first step if you think that's the wise way to go.
DR. HOWELL: Michele, what do you think would work?
DR. LLOYD-PURYEAR: It's up to the committee. That's fine with me.
DR. GREEN: I think this is very exciting to go this far in the nomination process. I would ask if the committee would like to formally consider accepting the Perrin's group report on Pompe perhaps with some modification and similarly the matrix that I'll call the Calonge report as well as a procedural aspect because I think without doing that, then there's some question about order.
DR. HOWELL: Gerry?
DR. VOCKLEY: I think that's a good way to proceed. We're using them now. We should have them as part of our formal bag of tricks.
But then I'd like to accept what Jim has offered, that we get something in writing that we can review as a group. I would recommend that we do that electronically so that we ask for a report in a couple of weeks. We give the panel another week to review it and get back comments. And

whether we need a phone conference or not or can then just consent by email, I don't know what the procedure would be, but we can move this a lot faster that way.
DR. HOWELL: I'm asking a FACA question.
DR. LLOYD-PURYEAR: You don't need a formal vote if you're approving a letter. If you're making a recommendation, then we do need
DR. HOWELL: I think your offer is good, Gerry. What I would suggest is that you come up with a list of things that can be sent to the committee electronically because I don't think that we should wait weeks or months to do this. It should go out. And then based on your work and the feedback from the committee, then we can send a formal letter to the nominator about what our recommendation is. Is that good? That is just basically an action matter. Is that good with the committee?
DR. DOUGHERTY: I would suggest I know it would take time, so maybe not for this time, but we're going to send the Perrin report with the letter is that right so that the nominating group understands the evidence review and the reason for the gaps that are going to be laid out.
DR. HOWELL: The evidence review will be posted on the website in detail.
DR. PERRIN: So we have asked and I think have been allowed information to call what is currently available a draft report. We have every intention of changing it and proving it based on a series of conversations we've had in the last 2 weeks, getting that back as the final report quite quickly. This is all a matter of public record. Our report is a matter of public record. So it is available. I would see no reason why it should not accompany a letter in that sense, but it's certainly publicly available.
DR. HOWELL: Well, it certainly is available and whether they refer to the website or it goes I think is secondary.
So, okay. We've made a decision about this. Now, the thing is that I also had on my thing is that we have discussed at great length the Ned Calonge report yesterday about the procedures and so forth. And we really should have a formal motion to adopt that. We've been using it, needless to say, but as a matter of record, we should indeed do that.
DR. TROTTER: I'd like to formally recommend adoption of the Calonge matrix with the Vockley revision as we see it in front of us right now.
DR. HOWELL: Is there a second to that?
DR. DOUGHERTY: Second.
DR. CHEN: I have a comment.
DR. HOWELL: Yes?
DR. CHEN: I think the academy is comfortable with this matrix. We're used to seeing it in many other venues, including EGAPP and the Preventive Services Task Force.
I would say, however, the fact that you've got two categories for insufficient and I understand. I think Ned alluded to this yesterday with the I positive and I negative. At least when these kinds of recommendations are put out for, say, primary care physicians, an I is an I, and you're lucky for most of them to even get past reading that letter. But the discussion and the recommendations in there really reflect sort of the discussion and recommendations that happened at this committee.
So even though I think there's a lot of interest in trying to make that a formal categorization of where you stand on an I, I think the question really might be for the public health laboratories that are going to be acting on these recommendations whether or not two categories of I would be, in fact helpful or whether or not that nuance really needs you have one I, one insufficient data recommendation, and then you really bring out the nuance in the discussion and

recommendations. That seems to be the way the task force has done it in the past.
DR. HOWELL: Any comments about that? Denise?
DR. DOUGHERTY: Yes. I agree with that actually because I don't think the ordinary person is going to see the distinction between these two categories, and there really is no distinction.
DR. CHEN: Granted, though it's not really for the ordinary person. Our audience is essentially public health laboratories I believe.
DR. HOWELL: Denise, do you have a specific wording recommendation?
DR. DOUGHERTY: Well, no, because right now we have this I with all the stuff about the potential really being compelling, and we intended the fourth one to say it's not that compelling. But it doesn't really say that explicitly. It's not that compelling. I'm not sure how you make that distinction, which is why either softening the thing about being compelling and just having it insufficient, one insufficient but that's difficult because we do want to send an encouraging message. So I don't know what the language for the fourth category should be.
DR. HOWELL: We have comments from the head table.
DR. WATSON: I'll go first. Then you can go.
I think if it's to integrate them, I think it's just bringing the word "pilot" up into that third one as one of the kinds of additional data that's needed, and then as Fred said, capture it in the specifics of what's needed, in which case you only need one insufficient. And if it's a decision that the population-based information is the critical thing needed, then it's in a pilot context, and if it's that plus other things about the length of outcome benefit after treatment, then it's not necessarily in a pilot that that's necessary.
DR. HOWELL: Jim, you wanted to comment?
DR. PERRIN: Just a comment that these are really two levels of evidence needed. It's not as if they're very substantially different.
Level 3 now is basically a lot of the stuff is in place. We specifically need X, Y, and Z.
Level 4 is it may be really compelling. If you look at Pompe, for example, in the report a couple years ago, it was at the very tail end of the report because it was a very important condition for which nothing really seemed to be in place to argue for it. So I think the last category really is we don't know much at all except it's a compelling problem.
So you could put them in a single box and sort of talk about levels of evidence needed. That would be another way of doing it.
DR. HOWELL: Mike?
DR. SKEELS: I appreciate Dr. Chen's comments, and I think I agree with him if I understood correctly. But at the risk of being the parliamentarian, we have a motion that was made and seconded that's I think now in the discussion phase. And we seemed to have drifted back to talking about what's on this matrix. I wonder if you could rein in the discussion and we could vote on this motion.
DR. HOWELL: Well, I think the question is that the motion is discussing some of the material that the motion is about.
DR. SKEELS: I thought the motion was that we vote to accept these reports. Wasn't that the motion? Could somebody read back the motion?
DR. HOWELL: Ned Calonge's matrix, and this is the matrix.
DR. SKEELS: As written. Right?
DR. HOWELL: No.
DR. SKEELS: Would somebody just read the motion please so I know what it is we're voting on as soon as we start voting?

DR. LLOYD-PURYEAR: The person who's taking notes back there? Yes, read it.
MS. KEMP: The adoption of Dr. Calonge's recommendation matrix with the Vockley revision
DR. SKEELS: Okay. So the motion was to accept it with Gerry's proposed changes.
DR. VOCKLEY: Right. What's up there now.
DR. SKEELS: Right, which is what's up there now. So I would just suggest that if amendments to that motion are being offered, that the person who made the motion be asked whether he's willing to accept those amendments, and then we proceed to vote on the amended motion rather than sort of getting into this cycle where we do group editing of this thing and we're here all morning.
DR. HINMAN: The mover does not have the power to accept the amendment. The amendment is an independent action.
DR. SKEELS: Okay, thank you, Dr. Hinman. That's a great point. But whatever the right parliamentary procedure is, we need to be careful that we get back to the actual motion itself.
DR. HOWELL: What would you like to do, ladies and gentlemen, for this? I mean, the bottom line, there's been a motion to accept Ned's thing with the modifications that Gerry made that are up there and so forth. Would you like to vote on that motion, or would you like to amend it? Would you like to vote on the motion?
DR. SKEELS: Yes. I'd like to call the question.
DR. HOWELL: All right. The question has been called. So those favoring that, raise their hands.
(Show of hands.)
DR. HOWELL: Those opposed?
(No response.)
DR. HOWELL: It passed. Now we have that.
Does anyone want to make any changes to the thing now that we've voted on that? Coleen?
DR. BOYLE: I just want to clarify that we were just voting on the matrix because I did have issues with the whole document, and I thought there was one issue that was missing there, which was the issue of confirmatory diagnosis, which I think is missing between key question 4 and 5, or whatever it was.
DR. SKEELS: Actually I think we just voted to accept the document. So it has been accepted by the committee by unanimous vote.
DR. LOUDER: I thought you voted to call the question.
DR. SKEELS: No.
DR. LOUDER: Right. So now you've gotten to the point where you have to vote on the matrix.
DR. HINMAN: Parliamentarially speaking, that's correct. You were voting on whether you were ready to vote, and you agreed that you were ready to vote.
DR. LLOYD-PURYEAR: We're voting on the matrix as revised.
DR. HOWELL: The motion was on the matrix I believe. Is that correct? So we were voting on the matrix, et cetera.
And our parliamentarian I think we're going to die of old age here
(Laughter.)
DR. HOWELL: Our parliamentarian had suggested that we are now
DR. LLOYD-PURYEAR: Could you read the motion again please?
MS. KEMP: Recommend adoption of the Calonge matrix with the Vockley revision.
DR. HOWELL: We were voting on the matrix, that thing up there, and nothing else. So would anybody else like to comment further about that? Dave?
DR. LOUDER: Well, since we're at the point of voting, a vote in the negative would be an

opportunity to further amend this.
DR. HOWELL: That's correct. So the bottom line is if you would like to make some amendments to this, you would vote not to accept it, and then you can make some modifications. Then we'll vote again. Any further comments?
(No response.)
DR. HOWELL: The motion is and we have approval from our parliamentarian in the back there to vote on this particular document as it stands.
DR. HOWELL: The document or the matrix?
DR. HOWELL: The matrix. That document up there is the matrix. Can we have a motion for that?
DR. HINMAN: You are actually beyond the point of discussion. You should be voting.
DR. HOWELL: All right. Let's vote. Those favoring that, raise your hands. As it is. Okay. Those favoring it as it is.
(Show of hands.)
DR. HOWELL: Those who oppose it as it is?
(Show of hands.)
DR. HOWELL: It's accepted as it is.
DR. LLOYD-PURYEAR: No. It was 3 to 3.
DR. HOWELL: Was it?
Those who favor adopting this matrix as it is, raise your hands please again.
(Show of hands.)
DR. HOWELL: There are 4 or there are 5.
Those who would not accept this matrix as it is, raise your hands.
(Show of hands.)
DR. HOWELL: Five to 2. It's accepted.
DR. LLOYD-PURYEAR: Three. Peter.
DR. HOWELL: Oh, Peter, okay.
PARTICIPANT: Four.
DR. LLOYD-PURYEAR: Four? Who's voting against? Jana. Oh, okay, four.
DR. HOWELL: It passes as it is.
What about the document?
DR. BOYLE: I would just like to see a modification between steps I think it's key step 4 and key step 5, which was the confirmatory diagnosis. It could be incorporated into key question 5.
DR. SKEELS: Mr. Chairman?
DR. HOWELL: Yes?
DR. SKEELS: I'm sorry to interrupt, Coleen, but could you just remind of who votes. Is it committee members or is it
DR. LLOYD-PURYEAR: Committee members only.
DR. HOWELL: Committee members only.
DR. SKEELS: In which case there are only nine committee members listed, of whom seven are present. Yet, we seemed to have just recorded nine votes somehow.
PARTICIPANT: It's Chicago.
(Laughter.)
DR. SKEELS: Yes, that's right. Vote early and vote often.
Not to be overly picky, but if it's just the nine people that are listed on page 1 of the committee and Dr. Calonge is gone

DR. LLOYD-PURYEAR: No, all the ex officios.
DR. HOWELL: All the ex officio members.
DR. SKEELS: Okay, so the ex officios and the liaisons vote as well?
DR. HOWELL: Liaisons do not vote.
DR. SKEELS: So ex officios. So there are 11 people present who are eligible to vote. No. Actually there are now 10 since Duane left. Okay, thanks.
DR. HOWELL: I don't think anybody was voting, I don't believe, who is not supposed to.
You want to make a modification.
MS. TERRY: Again, as just a nonvoting person observing the procedure, I would just say I get Roberts Rules and the legality of what you've just done, but this was a workgroup product. The workgroup had 24 hours to see the final. So we never really got to look at it. And a 5 to 4 vote for this being the thing to go forward with doesn't feel terribly solid to me as just a member of the public. So I understand that it's legal and you did a good job legally, but in terms of the spirit of the law, I think maybe there needs to be some consideration of amendments to this. And I'm not sure everybody understood that process that you just went through.
DR. HOWELL: Thank you very much. I think that these documents will be a work in progress, and I'm sure we'll modify them as time goes along.
I think that we need to go back and discuss what Coleen wanted to bring up.
DR. BOYLE: Actually I don't know where it belongs. It's either in key question 4 or 5, and I would like a question addressing the adequacy of the confirmatory diagnosis.
DR. HOWELL: And you would like to insert that. Can we do that?
DR. LLOYD-PURYEAR: No. I think something needs to be written in the document. I can pass this back out to the working group.
DR. HOWELL: So that will be added to the thing. It will be passed back out to the working group and the committee.
Is there any further discussion? Is there anything else that needs to come up before we go to our workgroups at the current time? Michele? Anything on here?
DR. DOUGHERTY: So do we have a plan to discuss further the entire Calonge report and decide what else we need to vote on?
DR. LLOYD-PURYEAR: I thought that was what Coleen was addressing.
DR. HOWELL: Would you repeat, Coleen, what you suggested?
DR. BOYLE: Sure. I said that we should insert evidence related to the adequacy of the confirmatory diagnosis, but there may be other questions in addition to that.
DR. DOUGHERTY: There are other questions that are raised in the document that we need to address. So just by adding that, I don't think I mean, what is the process for looking at the entire report and discussing its adequacy?
DR. HOWELL: I think we need to go back to the working group to add things. And so if you have suggestions that you want to add, it should go back to the working group to add those.
DR. BOYLE: Can I make a suggestion?
DR. HOWELL: Yes.
DR. BOYLE: We didn't get the report until just a day or two before the meeting.
DR. HOWELL: That's correct.
DR. LLOYD-PURYEAR: Can I just clarify that? You guys have had a version of this report and offered no suggestions in that interim period except for Piero Rinaldo.
DR. BOYLE: That's correct.
What I would suggest is that the full committee look at the report and that next time not the

report. I'm sorry. Ned Calonge's guidance for the process and that we have a discussion next time.
DR. HOWELL: I think that's logical, but I think on the other hand, is to submit any comments you'd have so that they can be incorporated because, as Michele pointed out, the comments did not come back.
DR. LLOYD-PURYEAR: And we do have a call-in on November 24th. Would you like to have a final product by then and the working group members promise they will get written comments to us? Thank you.
DR. HOWELL: We have workgroup meetings this morning, subcommittee meetings. Do you have the list of the rooms?
DR. LLOYD-PURYEAR: Yes.
DR. HOWELL: We have used much of the time allocated to this.
DR. LLOYD-PURYEAR: They are all on this floor.
DR. HOWELL: The Laboratory Standards is in the Ohio Room on the second floor. The Education and Training is in Federal A and B, also on this floor. And Follow-Up and Treatment is in the New York Room on the second floor.
Let's look at the agenda as far as timing is concerned. What do you think about when we should come back?
We'll be back here at 11 o'clock, and we'll have a brief committee meeting. We'll come back here and be back at 11:00 and have a report on the Personalized Healthcare Workgroup. Thank you very much.
(Recess.)
DR. HOWELL: Ladies and gentlemen, we're going to resume. A few folks are still en route here, but we have a busy calendar before lunch.
We're very pleased today to have Steve Downs and Alan Zuckerman here, and they are going to provide with an update on the Secretary's Subgroup on Newborn Screening and talk about the newborn screening health information technology standards and use case recommendations.
I know that Alan is going to be particularly interested in comments from the committee, and he's going to include a lot of stuff in his presentation.
So let's get started. Steve, you're first on the agenda to talk about newborn screening health information technology standards and the use case recommendations. Steve is co-chair of this subgroup, and he's Associate Professor and Director of the Children's Health Services Research Program at Indiana University. Thank you, Steve.
+ DR. DOWNS: Great. Thank you very much, Rod.
I'm going to start real quickly by acknowledging that there are a large number of people who put a lot of work into the information that I'm going to present to you, and rather than taking the risk of leaving anybody out, because there are several people right here at the table who contributed, I'm going to forego that. I do want to mention my co-chair, though, who is Dr. van Dyck.
The overview of what we're going to do this morning is that I'm going to talk briefly about the information technology in newborn screening in general and sort of motivate the case for it. And then Dr. Zuckerman is going to talk about the newborn screening draft detailed use case, which I had mentioned was in merely the proposal form the last time I talked to this group, and it has now been approved as a use case for AHIC and is moving forward. He's also going to talk about the next steps in completing the newborn screening use case and supporting the implementation of the use case and deployment of standards in the state of newborn screening programs.

And then I'm going to commandeer the microphone again and talk about a companion document that our committee worked on called The Research Guide for Newborn Screening Draft Detailed Use case and the issue of maintaining the research guide for the newborn screening use case. And then we're going to show you an application along the way for viewing both the newborn screening Resource Guide and the use case itself.

So the new roles for HIT in newborn screening. I think I'm speaking a little bit to the converted already, but I wanted to take a little time to motivate the case for what we're doing here. As you know, the advisory committee recommended 29 disorders be included on the standard newborn screening panel, and of course, that number is expected to grow as this committee reviews candidate conditions.

The CDC recently published an analysis suggesting that if all of the U.S. adopted these 29 disorders, it would increase the number of children identified by only 32 percent, that is, from a little over 4,000 to a little over 6,000 nationally. It doesn't take complex math to point out that what that means is that these are rare disorders, and if we want to improve the quality by improving the efficiency of identifying cases, we need to develop expertise in all of these rare disorders.

And because they're rare, this is likely to require regional expertise and some sort of coordination within larger geographic regions than programs have generally thought about for screening, diagnosis, and management. HRSA already has the structure of the regional network of technical centers which provides sort of a structural infrastructure for this, but not the information exchange that's needed to really coordinate. So that's along the dimension of rareness of disorders.

Along the dimension of time, there's a long-term role for newborn screening programs. As everyone here I think will attest, newborn programs are not just about screening and not just about screening and diagnosis, but also involve surveillance and tracking. And this kind of ensuring of screening and follow-up has to cover these many rare disorders, and we have to ensure clinical care and management of complex disorders not only the rare ones, but also some of the more common ones such as cystic fibrosis. And it requires many, many different types of specialists, and somehow coordination and communication of information has to take place among them. And lifelong clinical management over time is key.

So that's the argument for the need for some unified IT infrastructure for clinical care. It's also important for quality control and research. As I mentioned, these are extremely rare conditions. The natural history of these things is poorly understood. So therapeutic trials are going to require multiple centers. Natural history studies are going to be challenging because case definitions may vary from state to state and program to program. Optimal screening cutoffs in many of these unusual conditions have still not been established and are certainly not uniform.

Uniform and consistent coding of electronic exchange of data is going to be critical, and the exchange of data is going to have to take place in several different areas. From public health laboratory to a health department is an obvious one. From health departments or the laboratories to the clinician is also an obvious one. But also health department to health department when a birth takes place across state lines from a state of residence, for example, or when an individual with a condition moves from one locale to another. Health department to investigators, if we're going to assemble registries or combine data to look at optimal screening techniques such as what Dr. Rinaldo has been doing. And also from health department to government agencies for quality control, quality improvement, and so forth.

So how does this kind of exchange happen? Well, this is an example that I stole from a different

talk about immunization data, but you'll immediately see the parallels here. If you have an electronic medical record system and you have an immunization registry, you could substitute here public health laboratory. You need to have some way to talk about the same individuals in both systems. As you probably well know, patient identification may look different in two different systems. And so there has to be some mechanism, a global patient index that will tie these things together if we're going to be able to meaningfully exchange data from one individual to the next. And what that means is that a global patient index has to take those medical record numbers from those different systems and link them together.

There's also the notion of a concept dictionary because in this case in the immunization world, two completely different sets of vocabularies may be used to describe the same immunizations. Likewise, for newborn screening, completely different coding systems can be used to describe newborn screening processes. What's needed is some sort of a concept dictionary that links the concepts to specific codes. Then the codes can be linked to each of those systems, mapped to each of those systems so that everybody is speaking the same language.

If you have those two things together, a global patient index and, more to the point for today, a concept dictionary, then you can consolidate different information systems together and they can exchange data among them. And that forms what people refer to now as a health information exchange.

This is the standard by which people exchange information in something like a health information exchange. This is a small segment of what's called an HL7 coding message. There will be a quiz later. This is a little piece of it, and I just want to show you what the content looks like in these and why the use case and the standards are important.

This OBX at the beginning means that this is a clinical observation that's about to follow.

This piece in the middle here says that there's an observation name that's called endocrine disorders, and the L after the caret there means that it's some local code that somebody invented. In fact, this is a code that is used in the health information exchange in Indianapolis which until very recently was without national standards for representing these things.

Another term for the result of this endocrine disorder screen is that there was a borderline result that's coded OH-C-03-002. Again, this is just a local code that our own newborn screening laboratory came up with to describe this particular result, and then they have some text describing what it means. It has to do with a screen for adrenal hyperplasia.

Obviously, if I sent this message to any of your laboratories or any of your hospitals, you'd have no idea what this meant because all the coding is local. Most clinical labs use this kind of HL7 coding, but they use idiosyncratic codes for the tests.

Now, LOINC codes are a universal identifiers for laboratory and other clinical observations. And they facilitate the exchange and pooling of results because they represent that concept dictionary that I was pointing out before. The definition of a LOINC code includes things like a component, which is the name of an analyte like potassium or hemoglobin; a property, which is like a mass concentration or an enzyme activity, the property that you're measuring about the component; the timing, whether it's a point in time or something measured over a period of time; what the sample is, urine, blood, or in newborn screening a blood spot; a scale, that is, is it quantitative, is it ordinal, and so forth; and a method, what was the specific method that was used to carry out the observation. So one code can define all of those concepts.

That's an introduction to the reasons that we want to come up with a use case and standards for transmitting newborn screening. The process for moving forward with that is to start with a use case, which Dr. Zuckerman is going to talk about now.

DR. ZUCKERMAN: Again, it's a pleasure to be back here again talking to you. We were here last in January when the use case was just a dream. And now you have copies of it under tab 12 in your binders. And it's important to realize that this is the only use case which is being proposed in 2009, along with a number of extensions and gaps to other use cases that have been developed over the last three years.

The purpose of the use case is to describe high-level needs for health information exchange as it occurs between systems, various stakeholders, and individuals, and based on the various priorities and recommendations of the AHIC workgroup, they will describe information flows grouped into scenarios between different actors or different perspectives on who is sending and receiving information. And the details of that are in the events and actions that are part of the document that you have in front of you.

But in addition to that, we need to work carefully to define the basic needs and principles and the barriers to getting the use case implemented. And in addition to that, we have to be able to present the sample data sets that will need to flow between the different participants in implementation of the use case.

In terms of the scope of the use case, it's important to think about four major areas that have been proposed. And I think one of the most significant is the concept of integrating all of the clinical domains, including hearing screening, into a single comprehensive report of newborn screening results.

When we speak about health information technology, health information exchange, we try to address the needs of both health care providers, consumers, and also population health. So in terms of facilitating the provider, there's a goal of developing a consultation referral document that will integrate together all of the initial screening result and track the confirmatory process and all of the relevant referrals and encounters that follow.

In terms of population health, we want to provide a basis for sharing deidentified data from the initial screening and subsequent workup with public health and with the clinical research community so that this can add to what's happening in addition to identifying individual cases and making sure they are entered into registries and receive appropriate local services.

But the consumer also hasn't been neglected through the inclusion of distribution of educational materials and other support information to make sure that the screening process and follow-up is completed.

The perspectives that I talked about are basically all the individuals who will participate in health information exchange. In many ways, the use case is now a simplification of many of the things we had discussed within the workgroup, and we want to review it carefully at this time to make sure that we're not ignoring or lumping together the variety of data users and service providers that need to be involved in newborn screening.

But again, one of the unique features is the separation of the ordering clinician who attends the infant at the time of birth usually in the hospital and the pediatric clinician who will be working with the child later on during their infant period to provide ambulatory services and become a medical home.

The use case now has only two scenarios, the first of which deals with the initial screening, both the newborn dried blood spot and the early hearing detection and intervention, and it ends with the reporting of the results and notification of the need for testing or confirming that the results have been normal. It includes prescreening education, data collection at the time the specimens are obtained, and decisions as to whether subsequent screening is needed.

One of the greatest challenges is routing information to the clinician caring for the child and

closing the orders loop to make sure that results have been acknowledged and the process is complete. In graphic form, you see each of the individual flows numbered. The squares represent the contextual areas that are common to all children, and the circles represent individual child-specific flows of information. And there are many alternate pathways to deal with different arrangements for use of different testing laboratories or different arrangements for getting hearing testing results back to health departments.

In scenario 2, we deal with what happens when some of the results are abnormal or out of range, and this includes the confirmatory testing. Already there are many things which need to be reviewed for their accuracy because confirmation normally does not involve repeating the dried blood spot, but moving on to different modes of testing. There's collection of family history, and we may want to comment on whether this precedes or follows the establishment of a diagnosis. There's more in-depth evaluation of hearing loss. There may be needs for emergency treatment. There's case reporting to the health department. There are referrals to specialists, and there are also referrals for various dietary and early intervention support programs.

We also want this section of the use case to cover the sharing of deidentified data and we want all aspects of the use case to include bidirectional communication, something which is not commonly happening today, and also the distribution of educational materials to accompany provision of reports.

Again, one of the areas of potential oversimplification that requires review and comment is how information gets to other data users and to make sure that all appropriate information flows that will require health information exchange standards are adequately identified.

We also need to look carefully at data set considerations, both in terms of dates and information collected initially, and we'll begin to explain the role of the Resource Guide in helping to standardize the terminology and coding so that we can address the recommendation of the workgroup that we report both the conditions that are screened for, positive or negative, and also the quantitative analytes that have been measured.

You have instructions for filing feedback. We look forward to extensive discussion this morning but hope that you will also submit all of your comments in writing to the use case team and even offer your services to confer and meet with them particularly if there are areas in the current draft use case that you think need to be strengthened or improved in their accuracy.

Once the use case process is complete, there will be a detailed use case in December that we pass on to the Health Information Standards Panel that will begin their work in 2009 to develop an interoperability specification.

A good part of that will probably be based on an implementation guide for newborn screening laboratory results that is being developed at HL7.

We also have the evolving Resource Guide that Dr. Downs will talk about that's going to provide a resource for terminology and coding.

And finally, we anticipate that the standards emerging from HITSP will be accepted and recognized by the Secretary of HHS, but at that point, they still need to be implemented by screening programs. And it is essential for us to begin thinking now about generating interest in implementing this use case nationwide because the use case will only enable this direct reporting of results into electronic health records if the individual health departments and laboratories make the software enhancements to implement the standards that are selected.

But we also must be aware that because of limited rates of EHR adoption, we need to be sure that web access to these reports are an integral part of the use case so that newborn screening results can get into the medical records of every newborn and not just those whose physicians are using

EHR.
The deidentified data available for program monitoring, national reporting, and research will be another important feature that will require more than just selection of standards.
And finally, we need to think of this use case as a work order or statement of requirements for standards. It is the beginning of a process. We need to get as much into it now but we need to come back and work with the staff at HITSP to be sure they have the appropriate expertise to complete the standard selection process.
DR. DOWNS: *[2a flip] the committee that proposed the use case to begin with developed a subgroup to look at what we now call a Resource Guide for the Newborn Screening Draft Detailed Use Case. And I'm going to talk a little bit about that. A printout of this Resource Guide is contained in your notebook.
Basically the Resource Guide consists of a listing of codes and coding standards that would be appropriate for the entities that are important in newborn screening, specifically the conditions that are the targets of newborn screening and coding systems that are appropriate for representing those. In particular for conditions, we have looked at the Mendelian Inheritance in Man codes, the MIM codes; SNOMED, which is Systematized Nomenclature of Medicine; the EC, or Enzyme Commission codes that come from the International Union of Biochemistry and Molecular Biology; and the American College of Medical Genetics codes.
We also have assembled a list of analytes and clinical screening results, for example, the early hearing detection and follow-up codes or entities using LOINC coding, which I described to you earlier. And in addition to LOINC codes for specific analytes or results, we've included LOINC codes for sums and ratios that are frequently and commonly used in newborn screening.
And then finally, the Resource Guide includes mappings between analytes and conditions and symmetrically between conditions and analytes. I should say we've included this as a resource that may be helpful to folks who want to study the Resource Guide, although if you go from laboratory to laboratory, there's not complete consistency in the way analytes are linked to conditions. So this is not the be all and end all of that relationship. It's just a starting point.
So I'm going to show you a couple of screen shots to sort of give you an idea of what's in there, and then we'll take a quick look at where those exist on the web, and you can browse them yourself.
This is an example of a listing of tandem mass spectrometry detectable conditions, and this is just starting with the A's. So argininosuccinic aciduria is listed first. There's the ACMG code, ASA. There's the MIM code. There's the enzyme code and then there's SNOMED code. This proceeds down the list, and you can find this document in your notebooks as well.
This is an example of the way the analytes have been listed and coded. The top one on this slide is a ratio actually. If you look at the second one, it's hydroxylinoleoylcarnitine, and it's in the fatty acid oxidase category. So we have a classification of these. And then there's the short name for it, which is the carbon chain descriptor. And then we have a LOINC code. And most of these LOINC codes for newborn screening have been newly developed specifically for this effort. And you'll also see included here the units which are micromoles per liter. The ratios that are shown in there are referred to as molar ratios.
This is an example of the hearing loss clinical findings. There are basically two of them: auditory evoked potentials for screening and evoked otoacoustic emissions for screening. The LOINC codes have not been assigned for these yet, but basically have values of pass or refer.
This is just a quick example of the mapping, in this case from condition to analytes, in which we have MCAD listed as a condition and the list of coded analytes and ratios that would typically be

used in making this identification.
So I'm going to do a quick demonstration of the website as it currently exists, and this was developed under Dr. Zuckerman's guidance, and he assures me that while it works, it's brand-spanking new, and there are some features that have yet to be added to it. The website is here, and you can also find it in your book.
So this is what the website looks like. This is the home page. There are a number of places you can go with these buttons. I will point out that there's a fair amount of brief text bits here to help you find your way around it and to explain what the different parts are.
If we go to the analyte detail, we basically get a listing of all of the analytes that are there. If you want to look at analytes that are specific to tandem mass spectrometry or ones that are specific to non-tandem mass spectrometry, you can apply these filters, and it will change. These are just the non-tandem mass spectrometry filters. You can select one and look at it individually and see the LOINC codes and units that have been applied. Or if you want to look at all of them, you can select the full report and get something that looks like what you have in your book with the full report of all of the analytes and their respective codes.
Let me go back to the home page. Similarly, we can look at the conditions, and you can look at specific areas of conditions. So your primary targets identified by the expert panel from tandem mass spectrometry, and again, we can pick a specific one and see the corresponding codes. Or, again, if we go back, you can again pull up a full report to look at all of the conditions in that category.
And finally, I'll just show you quickly an example of the condition mapping in tandem mass spectrometry if we wanted to know, for example, what conditions argininosuccinate might be applied to. Well, that's not a particularly good example.
Why don't we look, for example, at medium-chain acylcarnitine deficiency? And here you can see the condition here and then a list of analytes that might be applied to its use.
The last thing that I want to point out about this is that there's an opportunity to email comments about the overall website and, in particular, about these mappings and codings as they currently exist. But at any point along the way, if you select one of these conditions, there's an opportunity for you to enter any comments about that and email your comments and those will be taken into consideration as this progresses. Obviously, the more input we get from the newborn screening community, the more effective this Resource Guide is going to be.
So finally, in terms of maintaining this newborn Resource Guide, the Resource Guide for the Newborn Screening Use Case is definitely a work in progress, and it would require a great deal of additional work to complete and, probably more importantly, ongoing work to maintain a current and complete set of codes. A revised version will be prepared to accompany the final detailed use case that is scheduled to be published in December, but obviously, as new tests and new methods of screening are developed and new codes are created, they have to be added to the Resource Guide.
Web access to the Resource Guide presumably will facilitate collection of comments and use by laboratories and other experts in the field.
And the scope of the Resource Guide could and I will predict will expand to include more information, for example, genetic data as genetic screening begins to move forward, and perhaps to link to other databases of coding systems as well.
So we need to find a home for the Resource Guide as the AHIC workgroups are completing their work, and that's one of our areas of interest in presenting this to you. On the technical side, we think an agency such as the National Library of Medicine is likely to actually maintain these

things from a technical perspective. But to maintain the clinical and laboratory content of these standards is going to require input from this community.
So we wanted at this point to bring out any comments or discussion. We are interested in getting affirmation from this group about the need for the new roles of health information technology in the newborn screening enterprise. We want any comments that you have about the draft detailed use case now or later, the stakeholders involved, any barriers that you see, for example, in terms of privacy issues, any comments you have about scenario 1 regarding initial screening or scenario 2 regarding confirmatory screening, any comments on the Newborn Screening Resource Guide or other data set issues and plans for assisting implementation of the newborn screening use case, and what might the role of this advisory committee and others in the room be for that, and similarly, plans for maintaining and distributing the Resource Guide and the role for this committee in that as well.
So with that, I'll close and open it up for any comments people have regarding any of that. So any comments or input from the committee?
DR. HOWELL: Comments or input from the group? I know that some of the subcommittees were discussing this briefly today. I know Coleen's committee was.
DR. BOYLE: Denise, do you want to comment? Okay.
Well, we did talk about this in the Follow-Up and Treatment Subcommittee, and we're encouraging our subcommittee members, not as a formal subcommittee or even a full committee because it's too late for that, to provide comments back to you. So we are going to put it on our agenda for the next two weeks.
DR. HOWELL: Mike?
DR. WATSON: It's actually something that wasn't said, which is always the place where we seem to hit the wall when were developing this thing, which is that even though Steve presented very granular kinds of data about analytes and levels and things like that, that was a very intentional decision to get to that level of granularity, realizing that the way these are structured is very tiered levels of information so that if the newborn screening program chose to tell the provider that there was too much of something, too little of something, that that's at a different level at which they can communicate that, the raw data, let you get through quality assurance kinds of activities at the laboratory level. But it was only by getting that level of granularity that let you communicate at any of a number of different levels to different people depending on what their interest in the data is.
DR. DOWNS: Thank you for making that comment. I think that's a really good point. There was a fair amount of discussion by the workgroup around that particular issue, the importance of having the capacity to drill to that level of detail, even though for certain functions that level of detail may not be necessary.
DR. ZUCKERMAN: And not overburden clinicians. We'd still have this available when needed for individual cases or for population planning.
DR. HOWELL: What comments do we have about the implementation? Does this group have wisdom on that subject?
DR. DOUGHERTY: We were wondering about the money and the resources. During our subcommittee meeting, I think there was a question about how this could possibly be implemented without some resources.
DR. HOWELL: Do you have some comments? Obviously, that's one of the early questions about a plan for maintaining and distributing. All of those things have significant resource questions tied to them.

DR. DOWNS: Well, let me make a few comments, and the Alan may have some more learned comments to make.
To start with, the concept behind the use cases and the whole AHIC process in general is that by establishing at a national level a standard set of codes, a standard set of communication protocols, it creates the opportunity for the software development community, software vending community to produce software that adheres to all of these standards. And it's a little bit like the notion of 110 volt electricity being in everyone's home or everybody's cell phone plugging into the same network of satellites.
If the standards are sufficiently spelled out and the recognition of the importance of adhering to the standards is sufficiently distributed, then it becomes part of the way people do their information technology business to create exchangeable data. So in that sense, much of the cost happens through routine information systems that laboratories and hospitals and public health departments are going to have to assemble anyway. But people have to be aware and adherent to these standards.
That's not to downplay the expense of maintaining these things, and that is going to have to be taken care of, but that's minimal compared to what folks normally think of as trying to implement whole new systems across the country.
Does that get at your question?
DR. HOWELL: I think that certainly moves it along.
I guess there are a couple questions. Mike has another comment.
DR. WATSON: As you look at it, it's going to be a lot of distributed money. The interoperability part may or may not happen in my lifetime which allows the pipelines by which all providers and hospitals and everybody else to talk to each other.
But the standardization of languages is one that we're going to use in the Translational Research Network right from the get-go as we establish a specific disease in which we want to do long-term follow-up or a disease that's not in newborn screening but for which we want to evolve a clinical and laboratory evidence base. The first step will be defining these so data is going to be compatible, and those feed straight back to the National Library of Medicine where they essentially fund the LOINC activities.
The cancer community has used this within their IT systems. Every time a group addresses a disease, they develop this language stuff through the experts that know the disease, and then that goes into the national system. So it's how the whole system evolves really around these expert groups that know the diseases once you've got sort of the infrastructure for the system built.
DR. HOWELL: Alan has a comment.
DR. HINMAN: Alan Hinman.
I wonder because in our subcommittee meeting, folks weren't entirely clear on this whole cycle of why you go about doing this. There's clout at the end of this. It's not just building standards and everybody agreeing that it's a good idea. There is then a process by which standards would be developed, passed by what's called HITSP, the Health Information Technology Standards Panel, and then presented to the Certification Commission for Health Information Technology, which if it then accepts them, means that essentially, as I understand it, federal funds will not be used to support health information systems that do not follow these standards.
So this is a lengthy and complex process, but it is leading to an enforceable set of standards. Since federal funds are the largest purchasers of health care in the United States, this will have a substantial impact on what health information systems look like.
I think I've said it correctly. Is that right, Alan?

DR. ZUCKERMAN: Yes. And again, one of the activities of the Personalized Healthcare Workgroup has been to set up a workgroup in implementation. CCHIT works primarily on the EHR side, and there are a lot of programs that require that part. On the public health side, however, we've begun to explore other opportunities within the Medicaid system and the MITA architecture, this Medicaid Information Technology Architecture. CDC is also interested in working to expand the adoption of standards and increase the public health informatics workforce.

So once the end product of the use case is out there in the form of recognized standards, there will be many touch points for implementation both within health departments and within the offices of practicing physicians and hospitals.

DR. HINMAN: And just if I might add one small note both of self-promotion and of promotion of the Genetic Services Branch, with their support we're involved in developing this HL7 implementation guide for newborn screening, and Steve is a member of that workgroup.

DR. HOWELL: Clarify for me exactly where you are in this cycle of approvals and so forth that Alan mentioned as far as getting to the point of having federal clout, shall we say.

DR. ZUCKERMAN: Again, HITSP normally works on an annual cycle. So they will begin developing an interoperability specification in January 2009 to complete within 2009, and knowing that it's coming, knowing the guides are ready, in July of 2010 it would be possible to have EHR vendors required to begin including this. And it's already on the road map for certification of EHR. The challenge will be to be sure that laboratories are ready to begin producing these electronic reports around that point in time and to see if we may have to delay an additional year.

DR. HOWELL: Sharon and then Jane.

MS. TERRY: Thanks very much. This is really well done.

We have some substantive comments that are fairly minor, and we'll send them in writing.

One maybe trivial question I have is I think the name Newborn Screening Resource Guide is going to be confusing in the consumer community, and while that's not your primary audience, it would probably be good not to confuse at least them. And I understand that that's paralleling some other guides, but there might be a consideration made here.

DR. ZUCKERMAN: We would very much appreciate any suggestions that any of you have to offer on the details of both the language in the use case, as well as other stakeholders that need to be considered adequately. It's extremely important that we get all stakeholders comfortable and participating and realize how this will be used for their benefit.

DR. HOWELL: And Jane?

DR. GETCHELL: I just wanted to mention a project that APHL is a part of. It's PHLIP, Public Health Lab Interoperability Project, which is very much like this only it is directed right now at influenza, reporting from state labs to CDC, from CDC to state labs. So it's something that state labs, I can tell you, are very eager to embrace, but we are, as you mentioned, sort of at the mercy of the software manufacturers that we utilize. But we are doing it with flu data right now.

DR. DOWNS: Well, thank you for that comment. We're aware of PHLIP. In fact, Alan and I are going to be talking to the APHL in San Antonio so that we can continue to keep the awareness of this undertaking. The last thing we need to have is different segments of the community reinventing the wheel. Otherwise, we'll end up with VHS and Betamax and that won't be good. (Laughter.)

DR. GETCHELL: The other thing I wanted to mention about PHLIP, it really was at the direction of the leadership of CDC that we embarked on this project. So they're very much

behind it.
DR. HOWELL: We've heard a lot of comments about the input and so forth from individual members and commentaries and so forth. Could we have any further comments about the role of this committee, both in assisting the implementation, more than what we've heard, and in maintaining and distributing? Does anybody have any specific additional comments on that?
DR. DOUGHERTY: I actually have a question about that. Now that the AHIC is a nongovernmental entity, is that who this committee, if they have comments or suggestions or find that things are lagging, should go to? Or what's the contact point for the committee if it wants to see implementation happen?
DR. DOWNS: Well, at this point, I think the contact point is probably Dr. Zuckerman, but that may evolve once the final use case comes out. I don't know the answer to that. Do you know who will be the contact point once it's published?
DR. ZUCKERMAN: Well, again, the AHIC initiates recommendations as to what our national priorities should be. The implementation falls to places like the Office of the National Coordinator for Health Information Technology, and I think the HRSA resource program for newborn screening will be another very important group involved in that. As I said, we do have an implementation group and a number of individuals are working to plan for implementation.
DR. HOWELL: We've heard Mike in his commentary that this will be helpful useable as he embarks on the Translational Research Network. So that will be helpful.
What additional comments would you like from this committee that you've not heard? Did you have any specific questions that you would like to address?
DR. DOWNS: Well, one thing that would be helpful to our group would be to have some formal endorsement from the committee.
And the other is I'd like the committee or subgroups of the committee, if it's your decision, to consider a formal role in reviewing new versions of the Resource Guide and the use case.
DR. HOWELL: The next question I had on my list was would you like a formal endorsement of this committee, and I guess the answer to that is yes. Obviously, it's your report and we can't vote to approve the report or anything else, but I guess the committee could certainly say that they feel that this effort is worthwhile and going in the right way and we could come up with a formal endorsement of that, if the committee so desires.
Do we have any sense of that around the table? The group has rarely been so quiet. Would the voting members of the committee like to recommend that we endorse this effort?
PARTICIPANT: I move to endorse it.
DR. BUCKLEY: Second.
DR. HOWELL: You move to endorse it. And Becky you seconded it, and we have another second.
So that's to say that we endorse this. This is a good effort, et cetera. So we had a motion and a second. Any further discussion?
(No response.)
DR. HOWELL: The voting members and there are nine voting members since Mike is very careful to keep our numbers right. Those favoring that, raise your hands.
(Show of hands.)
DR. HOWELL: Any opposition?
(No response.)
DR. HOWELL: It's unanimous so that the committee has formally endorsed the effort.
I would think with the question of could the subcommittees and so forth have a more active and

formal role, I think, Coleen, that's something you and your committee Coleen's committee is clearly the one that is focusing in this area, and it seems to me that's the discussion that you could have in your committee. Is that right?
DR. BOYLE: That sounds fine.
DR. DOUGHERTY: But we can't provide comments as a subcommittee because there's not enough time.
DR. HOWELL: That's right. The individual persons will comment to you, but then as they move along, they can consider what sort of a formal thing they could do.
DR. ZUCKERMAN: It is very important to remember that this is not really the only opportunity to comment. It is on the use case itself, but comments can go forward. But when HITSP begins work on this next year, they will be sending out a requirements design, a standards specification document. They'll be sending out draft versions of their interoperability specifications. So there will be other comment cycles in the future which we should plan for in greater detail.
DR. HOWELL: And I would urge you to have additional dialogue outside this committee with Mike and others about potentially becoming involved in some of the long-term activities in this effort.
DR. ZUCKERMAN: Of course, HITSP will also need volunteers, as will the HL7 effort, to complete the work of bringing the use case into an interoperability specification that can be recognized.
DR. HOWELL: Well, these are very impressive documents, and I congratulate you and your committee. It's been a tremendous amount of work in moving this forward.
Any further parting comments, gentlemen?
DR. ZUCKERMAN: Well, the other issue is whether the committee would like to review the status of the Resource Guide as it progresses. Is this something you would want to review at your next meeting?
DR. HOWELL: Yes, absolutely. Our next meeting will be a telephone call in November, and probably the most logical time to review something will be at our face-to-face meeting in February, which is the 25th and 26th I believe, or something like that, but in February I think will be the time.
Are there any further comments?
(No response.)
DR. HOWELL: Thank you for not only being thoughtful but prompt.
The committee has lunch in the York Room, which is around the corner, and so we will resume promptly at 1 o'clock. Thank you very much.
(Whereupon, at 11:57 a.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:04 p.m.)
DR. HOWELL: Ladies and gentlemen, we need to reconvene so we can finish promptly on time today.
We have a number of things to wrap up here this afternoon, and the first thing on the program is the emergency preparedness and contingency planning for newborn screening. We have two persons working on that. We have Susan McClure, who is Associate Director of Program and Partnership Development at the National Center for Environmental Health at the Centers for Disease Control and Prevention, and Mark Austin, who is again from the Division of Emergency Operations at the National Center for Environmental Health at the Centers for Disease Control and Prevention. And I assume that Susan McClure is going to be our first one.

MS. McCLURE: It will be Mark first.
DR. HOWELL: Okay. Mark will be first. Okay, great.
+ MR. AUSTIN: As was stated, my name is Mark Austin. I'm with the CDC COTPER, which is the Coordinating Office for Terrorism Preparedness and Emergency Response, and I'm the planning section lead. And it is my august pleasure to be working with subject matter experts such as yourselves on this very important project, newborn screening contingency plan, and helping to take the products of individuals such as Dr. Lloyd-Puryear and Dr. Watson and Susan McClure and putting it into a plans format.
The purpose of our briefing today is to review the Newborn Screening Saves Lives Act and also to discuss the progress to date on developing the aforementioned contingency plan.
For those of you that are not familiar with the Newborn Screening Saves Lives Act, just a quick review of the eight strategic objectives that were provided by the act. We have the collection and transport of specimens and the shipment of those specimens to newborn screening laboratories within the states, the processing of those specimens, and then the reporting of the screening results to physicians and families, providing diagnostic confirmation of the positive screening results, followed by the availability of treatment and management resources, and educating families about newborn screening, and then one of my personal favorites, which is carry out other activities determined appropriate by the Secretary. It's kind of like many job descriptions I've had where the last item is performs all other duties as assigned. So trying to figure out what that one means is a good one.
The contingency plan is going to address newborn screening for use by states, regions, or consortia of states in a public health emergency.
One of the things that's very interesting about this plan that we're facing is that contingency plans or national contingency plans are usually created at the department level. They are very rarely developed at the OPDIV level. However, Congress did in the act direct CDC to work in consultation with HRSA and state health departments to develop this contingency plan. A few months ago, I did contact HHS to make them aware of the project that we were working on, and at this point in time, they are not involved in the development of this contingency plan. We do expect that they will become involved in the future.
A contingency plan, for those that aren't familiar with it, is an operational plan that is devised for a specific situation during an emergency or when things go wrong. It typically includes specific strategies and actions to deal with variances to assumptions, and it monitors process and triggers for initiating those planned actions.
On this slide, you see some of the stakeholders that have been identified. A great many of these we've been in contact with either in person as various members of the working group at CDC have traveled up to D.C. to meet with, for instance, NACCHO and APHL. I came up a couple of months ago to meet with representatives from those organizations. And a number of these organizations also were present during the workshop that we had last week that was hosted by NCEH.
In disaster planning, you have both strategic plans and operational plans. This national contingency plan is going to be a strategic plan in the fact that it is broad and general, and it describes what actions are to be performed. What will need to be done in the future is to operationalize that plan and to get into the details which, of course, that's where all of hard work is, and that's one of the things that Susan will refer to when she talks about the hard work that was done at the workshop last week because trying to decide how, across the United States, the various entities perform those actions is where the important work is going to lie.

So we're going to need to describe how the actions will be performed, of course, who is going to perform them, certainly when those are going to be performed, and in some cases where those are going to be performed. And especially in an emergency situation, when you may not be performing your normal actions in your normal way in your normal location, that's where the crux of the problem lies.

And with that, I'll turn it over to Susan McClure.

MS. McCLURE: Good afternoon. I'm Susan McClure. I work in the National Center for Environmental Health in the Division of Laboratory Sciences, and I am a policy person. I'm not a subject matter expert on newborn screening. I do work with the newborn screening quality assurance program on policy issues.

So what I'm going to do today is talk to you a little bit about the workshop we had last week. CDC and HRSA hosted this workshop in Atlanta to receive advice from various partners about developing the national contingency plan. Participants included federal partners, state public health programs, newborn screening programs, state labs, maternal and child health programs, state emergency preparedness programs, and clinicians.

So at this meeting, we decided to take the eight elements that Mark described earlier from the act and use those elements as the framework of the national contingency plan. These elements really became objectives for us. We decided that we could add other objectives, if it's needed, as we walk through the plan, but we wanted to make sure that at least those elements that Congress directed us to touch on were really included.

So to do this, we used something called the SOARS method for objective based planning. And this is where you have a strategic objective and that really is one of those eight elements that Mark mentioned. And we then create an operational objective or a goal, and we identify the activities necessary in order to accomplish the operational objective. We identify the responsible party for accomplishing each activity, and ultimately the responsible party will develop a standard operating procedure for those activities.

So let me give you an example of how that might work. One of our strategic objectives is collect and transport specimens. So at the workshop, one of the operational objectives that we came up with was that there would be newborn screening quality assurance-program certified blood spot collection cards with the ability to capture appropriate demographics that also allow for follow-up available for use by any U.S. newborn screening program.

Now, from there, this became the operational objective. We then identified the steps that were needed in order to accomplish this operational objective, and that was the activities. We then identified who was responsible for these activities under the objectives. In order to meet the strategic objective, there could be multiple operational objectives. We went through this process. It took us quite a while. And I know some of you who are on the committee were actually in the room. There were about 40 people in the room, and to be quite frank, it was a challenging process I think would be the most kind way to talk about it. I think that it took us some time to wrap our heads around the fact that we're talking about response with regard to this contingency plan as opposed to preparedness. And once everyone in the room understood that, I think that we were able to move much more quickly.

However, one of the things that came out of this workshop is the fact that there needs to be preparedness plans. So while we're developing this contingency plan, we certainly are going to make a recommendation to the Department that preparedness plans are also needed at every level.

At the end of the day, I think we received some good input from the partners who attended.

However, there's a lot of work ahead of us in order to refine this plan and get it to the point where it can be shared more broadly.
Let's talk a little bit about where we're going to go with next steps. As I mentioned, we hosted the workshop and there were three centers involved at CDC with that, in addition to HRSA, and the three centers are the National Center for Environmental Health, the National Center for Birth Defects and Developmental Disabilities, and the Coordinating Center for Terrorism Preparedness and Emergency Response. So we're doing this in consultation with HRSA.
I have to say that one of the next steps would be to follow up with additional key partners. Unfortunately, because of some unforeseen circumstances, HRSA couldn't participate completely in the workshop, and so next steps would, obviously, be to share the framework with HRSA, as well as some of those partners who weren't able to attend. And that would be CMS, some hospital organizations, and I think some family organizations and groups as well.
After receiving this input, we will discuss the progress with CDC and HHS and complete a draft of the plan, brief congressional staffers about the plan, and after all these steps, the plan will be shared more broadly. Like most plans, we think it will be refined over time.
So I know everyone wants to know, well, when can I see it. While I can't give you an exact time frame on when we will have the document, I can tell you that we're working on a really compressed time frame. The act says that within 180 days of enactment, that Congress wants to see a plan, and that's October 21st. And so we are barreling toward that and trying to get a lot done before October 21st.
I would say that even with the limitations of time, that we are pleased that Congress has recognized this need in emergency planning in newborn screening, and we readily accept this challenge, and hopefully we'll have something for them very, very soon.
And at this time, I'd be happy to take any questions Mark or I.
DR. HOWELL: Any questions? We're going to continue to discuss the subject with other persons, but are there specific questions of Mark and Susan?
DR. LOUDER: Were there specific contingencies that you used as a framework for doing your analysis?
MS. McCLURE: Specific contingencies? No. We used those eight that were listed.
You know, whenever we tended to get off track, I think the way we brought it back is to say imagine you were standing knee-deep in water and you have to respond to one of these eight. How would you get that done, and what's the response to that? And then we tried to identify, well, what is the activity and who would be responsible. I think that doing that, we're then going to follow up with that person who's responsible or group that's responsible and develop standard operating procedures beyond that.
DR. ALEXANDER: Have you gotten input from the people who dealt with this during the hurricanes last year?
MS. McCLURE: Yes, we did. We had some of the states that were impacted. Mississippi was there. I think that we've gotten input from Louisiana as well, and Texas was there this time as well.
DR. ALEXANDER: Do they have any models for how your contingency plan might be developed and used based on their experiences?
MS. McCLURE: Yes. I think that they certainly had experiences within each of these areas about what worked and what didn't work, and that's what came up during the discussion for each of these activities.
DR. BOYLE: Can you clarify preparedness versus a response plan?

MS. McCLURE: Sure.
MR. AUSTIN: The difference between a and a response plan a preparedness plan would be something that you would have as a method of addressing how you do business day to day. A response plan is how do you respond when things go wrong. That's just a very quick thumbnail sketch of the difference. Does that answer your question? Okay.
MS. McCLURE: I have a problem with it too because emergency preparedness is not my background either, and so the whole knee-deep in water thing kind of helped me. It's like, okay, if I am knee-deep in water, then what am I doing at this point? If I have to accomplish these things, what am I doing?
PARTICIPANT: What's the preparedness analogy that goes with that?
MR. AUSTIN: Well, if there's a preparedness plan for newborn screening, which we all agree or Susan and I certainly agree that there probably will be need to be one in the future it will address how do you do newborn screening across the nation on a day-to-day basis. That is going to be different than how you do it whenever there is a disaster such as, like she said, when you're standing knee-deep in water. With a contingency plan or a response plan, you have to address how you're going to do what you normally do on a day-to-day basis, but when you can't do it the way you normally do it because everything has gone wrong.
PARTICIPANT: So preparedness is newborn screening without the water?
MS. McCLURE: That's it. You're right.
DR. HOWELL: Mark and Susan, thank you very much. We're going to continue with this discussion.
Before we proceed, let me introduce our recently arrived leadership from HRSA and welcome Mr. Stephen Smith here who is the Senior Advisor to Dr. Betty Duke, who is the Director of HRSA. Would you like to make any comments, Steve? We welcome your being here.
MR. SMITH: Well, thank you. Just to say thanks to everybody for the work they're doing and to let you know that HRSA leadership, especially since the passage of the Newborn Screening Saves Lives Act, has really tried to be involved in a way that's appropriate to work with our department and our other operating divisions within HHS. We are working hard to give the Secretary the materials he needs to make the decisions required by the act by October 21st and we'll continue to work with you. Again, thank you for all your efforts here.
DR. HOWELL: Well, thank you very much for being here.
Our next presentation is the Newborn Screening Preparedness/Contingency Plan Framework, a white paper by the Association of Public Health Laboratories. APHL has been in the business of addressing emergency preparedness for newborn screening. Jane Getchell, who is the APHL representative to this committee and is also Director of the Delaware Public Health Laboratory, will present APHL's contingency planning framework. Jane?
DR. GETCHELL: I just want to make a comment about when you're standing knee-deep in water. I think you'll do a lot better if you have a contingency plan in place already. Really, that I think is or I'm going to focus my comments on what the framework is designed to do to kind of help you in planning ahead.
A little bit about why APHL developed this framework. There have been a number of incidents over the past years that have shut down newborn screening programs: natural disasters, such as the flooding in the Midwest in '93; an electrical fire in the New York State laboratory; and of course, we all remember most recently Hurricane Katrina. Little did we know that two years after the hurricane, Iowa would still be doing Louisiana's newborn screening.
Terrorism is also a threat to newborn screening programs. We know that it shut down the New

York City laboratory in 2001. And we've also had supply chain issues where the kits, the reagents, the materials that we needed to do the testing simply were not available, and our testing ability was threatened by that.
So APHL's response has been to act as a central point of contact, connecting states that need help with those that can provide it, manufacturers with states that need supplies, reagents, and connecting states also with their federal partners.
APHL's other response was to develop this framework for a contingency planning. There's another term that I'd like to throw out and that's "continuity of operations plan," a COOP plan, which is actually what we've been calling it in Delaware and I think is called COOP planning in a number of other environments.
Back to Hurricane Katrina, this is the levee breaking. This is a slide of the Louisiana public health the laboratory is actually on one of the upper floors here, and I don't think the laboratory itself was flooded, but nonetheless, the equipment, the instruments were totally ruined. If I'm not mistaken, the laboratory, the building was condemned ultimately, and it was out of operations for two years for newborn screening.
I don't think I really need to stress why maintaining newborn screening laboratory testing is so important to this group. You all know that we're here to get the results out quickly so that we can lessen the devastating effects of these disorders.
What the framework developed by APHL provides for is assistance to newborn screening both programs and laboratories in preparing for disasters. It identifies partners. It addresses emergency laboratory testing, the procurement of testing materials, communication, and finally MOUs, memoranda of understanding.
When we talk about partners, looking first at local partners, they would include the hospitals where the babies are born, the clinics that provide care for those infants, physicians, medical association, hospital associations, case managers, and homeland security agency. City and state agencies are also our partners. Emergency response centers are important, as well as press offices, and I do want to stress the public health press office. The public health information officer can be invaluable in sort of quelling the panic and the fear.
National partners include APHL, CDC, HRSA, National Newborn Screening and Genetic Resource Center, ASTHO, parent advocacy groups, manufacturers, and of course, regional disaster organizations.
So we do have a checklist that laboratories can use to be sure that they are, in fact, prepared for an emergency and have addressed all the items that need to be addressed.
First on our list would be electrical power. Have you considered backup emergency power? Do you have a generator? Do you have fuel for that generator? Does the generator work?
Specimen acquisition. How will you get specimens to the laboratory if the roads are shut down, if planes can't fly? Do you have alternate means in place? Have you thought about that?
Case management. Can you get in touch with the case managers? Can they get access to newborn screening information?
Instruments are really critical to think about. Do you have backup instruments? Do you have alternate methods in place?
And what about your lab information management system? Is it duplicated in another location so that if your laboratory goes down, you can still have access to all the data that you need and the follow-up staff can also access that data?
Think about refrigeration in the laboratory environment. How are you going to keep your test kits, supplies refrigerated so they are still usable? And of course, then there's the laboratory

environment. Our instruments are all so terribly sensitive to temperature variations, humidity variations, and in fact, can only operate under a very narrow range. So it's important to think about how you're going to keep your laboratory cool or hot as the case may be.
Do you have a three-month supply of testing materials on hand? And water is critical to a lot of the laboratory testing that we do, and it can't be just drinking water. It's got to be filtered. It's got to be purified. It's got to be deionized. So how are you going to do that? Store it in carboys or whatever.
Can you prioritize certain tests to report first to do first?
Are there states that use the same methods that you do, might have the same screening materials on hand, so you could call upon them should you run out, should you need to access other materials?
We mentioned the contacts. Contacts from all those partners need to be identified. Their current contact information needs to be maintained, and quite frankly, it's ideal if you have a face-to-face relationship with those partners. It's much easier to work with somebody you know and have seen and kind of have an understanding of.
MOUs should be established with partners, particularly with other laboratories to provide testing in the event your lab goes down.
Do you have plans in place for compensating laboratory workers, for example, if they have to come in after hours, on weekends? Can you even compensate them?
Alternate plans for specimen transport, alternate plans for reporting of test results. If your LIMS is down, can you use a hard copy report, check boxes, that kind of thing? And what about data entry? Can you enter data from off-site? Can you access that data off-site?
Think about planning for temporarily relocating staff, which I think was one of the things that happened when the Missouri laboratory went down in '93 because of the flooding there. They sent staff to the State of Texas to help out with the testing down there. If you relocate staff, how can you reimburse them for their travel and for their housing? These are all kinds of sticky problems.
Testing materials procurement. Obviously, manufacturers and suppliers have some responsibilities in emergencies. They need to have adequate stock to be able to provide laboratories with the testing materials that they need, and they need to have a plan to provide those materials, whether it be equipment, test kits to a different site should the laboratory establish an alternate site for the testing that it does.
By the same token, laboratories have responsibilities. They do need to have backup testing plans in mind, alternate methods if a piece of equipment is down. Do you have another method that you could use to do that same testing? Has it been validated?
And laboratories also have an obligation to obtain documentation from suppliers that, yes, they do have an adequate forward stocking plan and that they can deliver the materials to the laboratories by some alternate manner than their usual means. Normally they probably fly the materials. Can they truck them? Can they send them by train or deliver them?
Emergency communications. I think we're all familiar with the incident command system. It's one certainly in Delaware we have exercised a fair amount. What it provides for is a single person in charge. And something to think about is if you're a 24-hour operation, you can't get away with just one person. You need to identify backup people to be in charge. You also need a record keeper who will keep track of important communications, decisions that are made, and other important information.
I talked already about contacts identified, suppliers, APHL, and other states.

In terms of communications, do you have a call-back system for in-house staff. If you need to get them back to the lab to start working quickly, how are you going to do that? Do you have current phone numbers, current email addresses, and can you call them in quickly? Have you tested that system? This says annually. We do it twice a year to be sure that people's addresses and contact information haven't changed, that the staff haven't changed as well. Review that communications plan regularly to be sure all the information that it contains is updated.
Think about communication modes. A telephone would include land lines, cell phones, and satellite phones. Communication might be through a courier system if you don't have access to phone lines. And of course, there are computer-controlled systems. Email comes to mind. And there are other alternate systems. In Delaware, we have a radio communications system for emergencies that we test out actually on a monthly basis.
Let me talk about MOUs for newborn screening emergencies. And you see in the framework, we recommend MOUs to formalize the mutual assistance agreements between states. In fact, APHL has developed a model MOU that states can use to tailor for their own use.
The elements in the MOU include identifying the contact people. The MOUs address liability, which for us at least has proved to be a very sticky problem and one that has tabled some of our MOU agreements, getting the liability issue through the state's Attorney General is a problem. MOUs address terms and termination particularly. In other words, how is this MOU going to be terminated, 30 days written notice, whatever. And of course, it identifies the signatories on the MOUs.
Importantly, the MOU forces us to think ahead of time about the specific services that are going to be provided and how they're going to be provided. It forces us to think about funding and reimbursement for the services that are provided. It forces us to think about specimen transport, contingency planning for that transport, and also very importantly, chain of custody and how that will be maintained.
This is a slide of a disk that APHL has prepared. And you see it's dated June 2007. The information on this disk is actually available on the APHL website, and if you want this disk, see Jillily who is in the back of the room from APHL. On the disk, there are a number of helpful checklists, kind of guides to use in developing what I'm going to call a COOP plan.
And let me conclude with three recommendations. Every newborn screening program should prepare for a disaster, should have a written continuity of operations plan, and should review that plan and update it on a regular basis. We encourage you to use the framework that we presented for preparing newborn screening program contingency plans and also encourage you to modify this framework for use with other laboratory testing programs.
DR. HOWELL: Thank you very much, Jane, for reviewing that white paper. A very thoughtful presentation.
I think that in view of the fact that we're going to try to stay on schedule some of the committee members have early flights we'll go ahead and ask Mike Watson to comment about the emergency preparedness for newborn screening, a report that involves the Regional Collaborative National Coordinating Center. Dr. Watson is Executive Director of that center.
+ DR. WATSON: Just the Director, not so executive.
I think what we've heard is a lot about what happens at the level of the newborn screening laboratory itself, and I think what you get from the newborn screening laboratory is protection of the testing and making sure everybody has gotten tested and some continuity into the diagnostic part of the program.
But because, as we saw yesterday, we're putting 6,000 to 10,000 kids a year out into chronic

disease management, many of whom are on highly critical therapeutics that they have to be maintained on, our issues were both what happens from the point of an infant being screened on, but what also happens to all those patients who are already out in the private sector in care who need to maintain access to their medical foods and formulas and therapeutics. So we had a slightly different perspective.

I'm going to skip over some of these slides to avoid repetition with the newborn screening laboratory component that we've heard about.

I'll skip the disasters except to say that they come in many varieties. Katrina and Rita were events that at least had some forewarning that they were coming. Terrorism events don't give you that advance notice to get some level of preparation in place. And certainly places like California that have extensive plans in place for earthquake types of disasters don't get much of a warning either and have to be much more prepared on a moment's notice than might be the case in an environment where you have a slower developing, anticipated sort of disaster.

So about a year and a half ago, we held a meeting of all of the regional collaboratives for genetics and newborn screening, brought to the table representatives of support groups and the consumers, the medical private institutions who are delivering care, both primary care and specialty care to newborn screening patients, and representatives of different components of state and national government who enter into disaster preparedness at different points in time because it's a very temporal event. You're very much on our own the first 24 to 48 hours of a disaster. Then federal things come in and state things come in, and then it gets pretty chaotic as you're transitioning out of the disaster.

The kinds of things we focused on during our meeting were identifying the needs of the metabolic disease patients since they tend to be the ones with the most time-critical and difficult types of therapeutics to access. We wanted to define the role of patients and providers, considered that redundancy was important. And as much as I like the state and the federal government, I like to cover my own back end to a large extent where possible. So we looked at redundancy from both what patients can do for themselves to be prepared in a disaster, what the institutions and providers can do for themselves, and we've already heard what the newborn screening program itself can do for itself and for others that are part of that broader program.

Our goal was to provide guidance back to the local institutions on the kinds of issues that had to be addressed, who would be responsible, including local, state, and federal entities, their own institution at times, provide guidance to families and patients, and then to provide recommendations to the regional collaborative groups for planned dissemination within the regions.

And I'll say the punch line now, which is fundamentally we've been waiting for this to evolve to the point where that contingency meeting and plan is now going to be in place. It obviously is a mechanism of responding with whatever preparedness you have in place. Sadly, we don't have a whole lot of preparedness in place so that the response I think is a bit blunted at this point, and our focus will be on improving the preparedness so that the response has more components with which it can interact to get its responding done.

We've seen this several times this week. Newborn screening isn't just the screening test. It's the follow-up and long-term follow-up of those patients. And I think one of the benefits that will come from the Newborn Screening Translational Research Network in its development of these long-term follow-up plans will be addressing that significant component to which the newborn screening programs have not had a very tight relationship in many of the programs. Some do have very strong relationships. Others don't. And by improving that communication and back

and forth of long-term follow-up information, a relationship I think will develop that will improve the continuity across the full breadth of the newborn screening program.
As we said, the newborn screening patients come in many varieties. You heard the view of the newborn screening laboratories that they can triage. They can identify those positive screens that require the most rapid of second-tier tests to be done and the most rapid communication out into the private sector for diagnosis and follow-up.
There is a subset of patients who are much more critical in their time needs and in the types of things they need access to. In any disaster, patients, chronic care and such, need the security and the basics. They need reliable information, and they need shelter. You move to the metabolic and genetic disease patients, they need those three things, but then they also need special food, special medications, special laboratories for which there may be only a handful in the country or internationally that can provide the diagnostics, specialized physicians who are in tremendous deficiency in medical care right now. And we certainly need more of those.
And highly specialized information. When patients with these esoteric rare diseases on relatively esoteric therapeutics get out away from their provider, they either have to find somebody who's equally knowledgeable about the disease or more likely end up in an environment where they're with a provider who is much less aware of the disease. So things that patients can have with them that allow that provider to access their health record, to access specialists who are able to guide them through what that patient might need at any particular point in time are increasingly important.
But our feeling was, given the nature of these patients, if we can get it right for these metabolic disease patients that come out of newborn screening, they're the canaries in the coal mine. I mean, this is one of the most critical population groups during a disaster. If you get them right, you're going to be able to get right a lot of chronic care patient management in these kinds of environments.
So the genetic disease patients, whether they come from newborn screening programs or are on therapeutics that are independent of those programs, have difficulty accessing treatment under the best of conditions. There are often little or no effective treatments, and your symptomatic approaches and presymptomatic approaches are based on your knowledge of the disease.
They may have trouble finding a pharmacy that stocks the drug they need. It's often mixed within the pharmacies in these tertiary care academic medical centers. So accessing some of these things can be quite difficult. And even for the patient to retain a supply can be difficult because these are expensive, by and large, and the payers tend not to let you have more than a 30-day supply, and if you're near the end of that supply, you're in pretty deep weeds if the disaster hits at that point.
So looking to whether or not there are mechanisms for improving that kind of availability of supply is going to be important and developing the resources to find the knowledgeable physician.
So we went through a number of steps along the way. The first people that hit the disaster site are the Feds through the National Disaster Medical Service. They have disaster medical assistant teams. There are two that are pediatric type teams. One of the things we've been negotiating with them is how to involve consultants from the biochemical metabolic disease community. I don't think they necessarily need to be on site, given the rarity of these diseases, but being available to these teams could be a very useful thing in a disaster.
CDC has told you already about the COTPER program. So I'll skip it.
An aspect that hopefully isn't a part of newborn screening but is part of what happens with

genetics and was important in Katrina was a mass casualty identification group, largely comprised of genetic counselors and genetic service providers who were very active during the World Trade Tower disaster, as well as in Katrina. When they hit Katrina, there were 200 unidentified remains that had to be linked back to their families. They had been in water for a very long time, could not be readily identified, and it was only through DNA identification that they were able to accomplish that. And they were on site to make all that available. And that's going to be part of the resource we develop within the National Coordinating Center.

At the state level, the EMAC is an act that is declared by governors basically that deals with a whole lot of the issues of liability, how people get paid during disasters, and such. Once that's declared, whether it be local or much wider, it empowers a lot of the contingency planning to take place. Some states have very well developed programs, and others are less well developed. And I'll show you some specific data on that right at the end.

And the regional collaboratives have become very active in this because they do build that bridge between the newborn screening public health programs and the providers within their regions and to some extent the patients that are in those regions because one of the fundamental goals of the regional collaboratives is to ensure continuity of care and access to care in your local community, be it by telehealth or whatever other mechanisms are available, to not have to travel hundreds of miles to access some of the kinds of esoteric care that's involved.

I'm going to skip the newborn screening lab because we just went over it.

Diagnostic confirmation, though, is not a straightforward problem. You have to think about this in two different ways. The disaster could occur within the local environment where the provider locally can access his own lab, but the disaster may also occur in a region where that esoteric testing lab is located that you've always used for your testing. So identifying backup sources of the same test is a mechanism of preparedness that the diagnostic sector can have available to it. The triage mechanism of getting those patients who have the most critical needs into care is obviously important.

Emergency care is important. These patients may hit an emergency room when they're relocated, and one of the things that the Region 4 group has done very nicely is developed some emergency care guidance protocols. There is a Midwest Emergency Medical System on which all of these emergency care protocols have been placed at all emergency departments in the Midwest are able to access. In some of the states, their patients have been given electronic health record access. I think the University of Minnesota has a mechanism in place where the patient carries a password that allows any provider to access their EMR within the University of Minnesota. And more of the states within that regional collaborative are trying to move toward these models.

So it's really the protocols, how you manage these patients specific to their disease, and accessing really their medical history to know what are the therapeutics they're on and what are the standard ways of approaching emergency issues.

At the level of local institutions and providers, the groups in Louisiana had a nightmare just getting reconnected to themselves as a group of providers for patients. They were fortunate that one of the dieticians actually had a laptop with the medical formula foods histories of many of their patients because they didn't have the electronic health record. If you saw that flood back when that happened, those institutions were maintaining their backup power supplies in the basements. If the water was up to your knees, you can imagine what the basement looked like. Now they're sitting on the rooftops in New Orleans.

I've mentioned the backup labs. Backup therapeutics are a difficult problem, and there are many mechanisms that can be taken to get at those, and I'll address those shortly from the perspectives

of the different people involved.
We've mentioned the medical records access, orphan drugs, and medical foods and formulas, and the difficulties of pharmacies, patients having stockpiles and insurance issues that impact their ability to stockpile. Places like Los Angeles, for instance, have a backup pharmacy accessible outside of the earthquake area to those institutions within the earthquake area. So there are various mechanisms, but that's preparedness, and without those things in place of how you have backup, you're pretty much stuck when it comes to responding.
Patients and families can do a number of things to their advantage. If there were mechanisms whereby those who had just been screened could access their information of the results of their screening, they would be one step ahead. If a pediatrician who has seen a patient somewhere and it's an infant can access a state's records to know that that screen has been done and see what the results were, it increases the advantage to the patient, having that emergency information and guidance.
Provider directories is something that's going to be very important when you're looking for backup, and we're developing those at the national level with a reasonable level of granularity to know where all the genetics groups are in the country, which ones do metabolic disease, which ones do hemoglobinopathies or endocrinopathies so that that level of granularity is available for providers in other parts of the country to access information about where those specialists are.
I'll skip over this. Communication is very important for obvious reasons. But it is. And power that drives all these various alternative forms of communication is an important issue. I know in Katrina the pictures are of the folks sitting in their cars with laptops plugged into their lighters, accessing satellite communications to be able to communicate among themselves. And there's a lot of that sort of stuff increasingly available tied to teleconferencing capacities and telehealth types of delivery services that can be brought together to improve the way we access providers and patients at long distances.
We did, about two weeks ago right before the CDC meeting, a quick survey through the regional collaboratives of all the states to get a sense of who was getting prepared. There was a reasonable level of preparedness developing in most of the states. Two states, New Jersey and South Dakota, had neither a plan, nor were they in the process of active planning. Obviously, that needs to be improved. And 38 of 44 of the states have specifically addressed the newborn screening laboratory functions, but not much look at the institutional level and the patient level.
Seven states had laboratory services contracted outside of their own newborn screening program, and that becomes very muddied because often there are constraints. For instance, the Oregon program backs up a number of states. They get into the trap of not being able to talk to patients. They can only talk to the newborn screening program who has to talk to the patients. So one mechanism of getting both to the providers and to the patients has been lost in those contracting kinds of arrangements, and I think it just means we need a little more granularity about the nature of the relationships.
Two states just said we defer to all the local hospitals and providers to be prepared and we assume they are.
And a lot of states have a disaster plan, but it's not specific to newborn screening.
Twelve states have addressed the diagnostic confirmation issue and begun to think about where do they get the backup diagnostic confirmation. That does presume that those are the patients coming out of the newborn screening program and not necessarily those who may already be out there.
Twenty-three states have developed contingency plans that, to some level or another, empower

patients.
So I mentioned the generic emergency plans being available, not specific to newborn screening, and the difficulty with the laboratories, the contract.
It became clear from the CDC meeting that the three major steps of this thing are preparedness, which empowers response, and when the response is inadequate, mitigation that finds out what went wrong and how you prepare to get it right the next time. And at this point in time, we need a heck of a lot more preparedness to allow an adequate response to take place to avoid a whole lot of mitigation after the next disaster, and that's what we will be moving toward in the near term. Following that CDC meeting and following our meeting back in '07, we'll now be bringing the regional collaboratives back together, looking at the plan that CDC has for contingency, and saying what is it now that we need to prepare for to build more resources to allow better response to take place. And we will begin to set that meeting up now once the CDC report is out.
Thank you.
DR. HOWELL: Mike, thank you very much. It's encouraging to hear that there are really detailed plannings at several levels in the laboratory and the clinical services.
Are there comments about any of these excellent reports that we've heard today? I think they were done for our information, and we will hear, obviously, more because these reports are still developing.
Thank you very much.
In view of the time, I think that we'll go right ahead and move to our subcommittee reports, and the first report is from the Subcommittee on Laboratory Standards and Procedures, and Gerry Vockley is presenting that report today.
+ DR. VOCKLEY: Okay. Thanks, Rod. I was told to be succinct, thoughtful, and wise, but if I could only be one, be succinct. So I have seven slides.
(Laughter.)
DR. VOCKLEY: And one of them is my introduction. So hopefully I'll be succinct.
I will break this down into a couple of categories. We have one major initiative that the subcommittee started a couple of years ago and has been trying to sponsor, and that is to look at a routine second screen in the newborn screening programs. And to give you a quick status update on that, it has really been quite a frustrating affair for the folks, largely Harry Hannon who has been carrying this out at the CDC.
The goal is to examine the use of routine second screening in newborn screening, and they had initially identified enough participating centers to cover about 25 percent of the newborns in the United States. Of the I forget whether it was 8 or 10 institutions in that list, they have been able to receive approval to do this retrospective project by only one IRB to date. And there have been a variety of hurdles from state to state and from center to center that have interfered with that.
But one of the really major issues that we think that the advisory committee can address in the future is to use some of the developing infrastructure that we're getting for clinical trials, and newborn screening follow-up, and rare disease treatments to be able to obviate the need or at least expedite going to IRBs for these kinds of studies. In a situation where the paradigm is shifting from individual investigators and local populations to multiple investigators and essentially nationwide studies, there's got to be a better mechanism for doing that.
So the major issue is the IRB approval, and we ask is there something that the advisory committee can do to refocus this and that would be a huge help in moving not just our laboratory standard type projects forward but I think will also be involved increasingly in trying to set research agendas for these populations.

One of the other hurdles has been getting some money for the local centers to do their thing. So it's one thing to say, well, just collect a little data for us and send it in. Sure, no problem. But that translates into hours and hours of time battling with the local IRB and then the follow-up necessary to keep those protocols active, as well as then the protocol-specific duties. It adds up to numerous unfunded mandates. As we look to extend these networks and coordinating centers and all of the other infrastructure that we're starting, a way of trying to not just keep asking people to do more but to actually provide them with some resources to help with that.

We had some observations on the discussions surrounding nominations to the standard newborn screening panel. Since we had the chance to see this in operation at this meeting for the first time, we decided that we should talk a little bit about that as it relates to the technical aspects of it. I think it is fair to say that we agreed that there were major technological issues related to our first crack at this with the Pompe disease, and there was some sentiment that we might actually be able to save the committee as a whole some time by really having perhaps an earlier and stronger decision point that says is the technology available to carry out this project. And if there isn't, regardless of how compelling the rest of the application is, then it's sort of dead in the water. So we may want to consider moving that kind of closer to the front end of the algorithm.

We also felt that we needed to emphasize the technical aspects of the disorder application and evidence review should not only evaluate the technology that's going to be involved in the newborn screening portion of dealing with the disease, but also in the confirmatory testing, in the availability of whatever commercial products are going to be necessary to implement that testing, kits or equipment, and then ultimately the standards that are going to be necessary to maintain QA for any testing for any disease that becomes added to the newborn screening panel.

And then finally, we had one cancellation in our schedule so we had the luxury to sit around and think a little bit about some directions that the subcommittee might be able to take in the future and how we might be able to help with other initiatives that are ongoing. And so these are very much just almost free-form ideas, but areas where the committee is certainly open to additional direction from the full committee, as well as ideas as to how we might be able to be more proactive in dealing with some of these issues.

So we talked a little bit about the concern that with an increasing number of diseases that are under consideration, will we have standards for all of the testing to deal with the QA aspects of it. And we're talking about analytical standards as opposed to behavioral standards, the development and availability.

We had some discussion about the evolving role of the FDA in approving genetic tests and reagents, and there was actually a fair amount of confusion as to where that stood. So we had as a suggestion back to the full committee that we actually invite the FDA to come and talk to us specifically about how it sees its evolving role in dealing with genetic testing, newborn screening testing, analyte-specific reagents relative to newborn screening and confirmatory testing.

This plays into our discussions on the Pompe application and that was to spend a little bit more time as a subcommittee reviewing the optimum mechanisms to assure that the technical aspects of candidate diseases for the standard panel have been adequately addressed. And again, if we can save some time for the full panel by heading something off at the pass that really just isn't technically feasible, then that we think would be a good thing.

We think there are some opportunities that are presenting themselves right now to be able to provide some technical advice again to this growing and varied infrastructure that's building around clinical trials and newborn screening. So any of these groups and networks, consortia that are looking into the issues of genetic testing, screening, population screening in the newborn

period or otherwise there may be some advantage to concentrating that into one group, and although at the moment, as constituted, we would not be adequate to handle that, it's one possibility for the subcommittee to take on a growing role in actually looking at the technical aspects of all of these issues.
We think there's a role for interacting with the Research Workgroup of the advisory committee, and in particular, as we identify gaps in the technology that people are proposing to use for newborn screening and confirmatory testing, it's a great opportunity to feed back to the research agenda that will be generated either as a result of the committee's recommendations on disease applications or even in advance as these consortia and coordinating groups and clinical trials infrastructures look to decide how best to spend the funds that they have available to them.
And then finally, at a very, very 10,000-foot level, additional topics that seem important down the road to us. The issues of screening at other ages. We spend a lot of time talking about newborn screening, but there may well be things that we should be looking for or would be logical to look for at age 1, at age 10, at age 20. I'm a pediatrician, so I don't think beyond that.
Proactive identification of important new technologies where, again, we may be able to help drive the agenda a little bit more in a proactive fashion rather than just being responsive to what people are bringing to us.
And then just as an ending cautionary note, we really think that in any of these reviews that the committee is doing and certainly true for looking at technology development and review, there's an absolute need for complete transparency as we do this. We all have stakes in our particular favorite diseases, and there really needs to be a complete transparency to be sure that there aren't questions after the fact related to recommendations to screen something versus not based on your particular favorite disease or technology.
So that's it.
DR. HOWELL: Thank you, Gerry. Your committee had a very busy time.
Let me comment about several specific things you brought up. One is the newly passed legislation entitled Newborn Screening Saves Lives which required that this committee will have now a full voting member from the FDA. So with the appointment of that person we've not yet received recommendations for that person, but that clearly should follow perhaps with their arrival.
The second thing is that I think all of us are concerned to hear about the continuing difficulties with IRB and the second specimen. We've not finished the February agenda, but one thing that has specifically been included in the agenda was a discussion about informed consent that's drafted already on that draft agenda. And that would be a great time to investigate, and maybe we could get a little more granularity to what was causing that.
The third thing is that, as you know, there's an Internal Review Group in the committee that currently looks at applications before they come to this committee. Piero happens to chair that group. But one of the things that you suggested, which strikes me as quite sensible, is that perhaps that committee could be specifically asked and requested to pay a bit more attention perhaps to the details surrounding the laboratory tests and so forth before it
DR. VOCKLEY: These applications are going to only increase in frequency and number, and it may well be that one person isn't going to be enough from a technical standpoint to handle that. *[3a flip]
DR. HOWELL: * certainly added to with all the right persons because the technology may be well outside the skill of this group and you would need to bring other members in.
DR. VOCKLEY: One of the other points that was raised was not so much because Piero was

very or the working group was very up front with their concerns about the technological aspects of the Pompe application, but in addition to that is actually putting in a triggerable action at that point that says the technology is just not ready. We're just not going to go any further at this time until we can get the technology that we need to actually do that.
DR. HOWELL: That can certainly be a recommendation, and we're going to hear another recommendation on that score.
Let me bring up one other thing. I think that the technology is interesting. As many people know, NICHD has had a major effort in funding new technologies for newborn screening. It happens to be a title of one of the programs in Duane's institute. And that has generated a great deal of interest. And there are some very clever things that are being funded there, and perhaps on one of the agenda items, we might identify some of those people with clever, new technologies to come to this committee.
Thank you. That was an excellent report.
Tracy, are you going to speak for you and Jana for the Subcommittee on Education and Training?
+ DR. TROTTER: Thank you. On behalf of my co-chair, Jana Monaco, and myself, I wanted to thank everyone who participated today in our Education and Training Subcommittee. There were a lot of knowledgeable people who had good ideas and are connected to the right places. So I think we're pretty happy to get going.
The last time we met in person in January, we had a discussion about the recommendation of a newborn screening repository. That's now come to be, that there will be a specific section of the NNSGRC website that will contain newborn screening material in multiple languages and information accessible to all of our target audiences. And so we talked a little more about that today.
A second part of that is sort of a translation protocol trying to create some sort of a standardized "gold standard" that can be at least used to look at things that translate material that comes to the repository from outside. I suspect that will be the majority of them. These are things that already are developed by some other region or some other user. And we will at least have some sort of a generic, formalized protocol, and at least up front, we're not saying that all materials will meet all the requirements, but it will be transparent if they don't. They will say, well, we haven't done parts four and five for this, but we've done one, two, and three, which is maybe all we have to start with. And that, we think, will stimulate the growth of this and will likely stimulate the quality of it on down the road as well.
This is a slide from a Pediatrics article in 2008 which is one of my favorite slides because it keeps saying that primary care physicians need to know more about genetics and about newborn screening specifically. We are, of course, identifying many, many more infants who are affected and enormously many more infants who are false-positives that need to be evaluated and worked up. We spent a lot of the last two days discussing how that can be, what the burden of that is. With that idea, we want to partner with certainly the academies that are on our subcommittee, pediatrics, family physicians, and the ob-gyns and many others who are focused on what the PCP role is in newborn screening, help them to understand their response to an initial out-of-range result, what can they do, where do they go, who do they talk to, how do they coordinate evaluations, how do they, if it indeed is positive, go on to provide that medical and coordinate that care. It is an area that is increasingly needed and yet difficult in educational platforms to find time to be heard.
We all said genetics information is exploding almost at the same rate that literacy in genetics is

going down, and that's not a very good combo. So we're trying in many ways and I won't go through all of these to approach that. We had reports from the American Academy of Pediatrics which we hope next week we're going to find out whether they will adopt genetics as a megatopic for the coming cycle of three to five years, which will make a big difference in what shows up on educational both annual meetings and the regional meetings and the publications as well.

And finally, we talked about how to best leverage the collaboration we have going here in the area of education. Our feeling was sort of the subcommittee and then the committee as a whole here really is to be in an advisory capacity. There are many current groups that are working both with the primary care physicians, especially physicians, public and family education and others, and I just named just a few of them who were in attendance. We made sort of a goal to each other that we would attempt to avoid the duplication, enhance the collaboration, try to get more specific things in the hands of people who need them, and avoid people doing extra work.

As everybody else has quoted the Newborn Screening Saves Lives Act, I will too. Section 1112 of this requires an information clearing house, and from the education and training folks, this is a very important concept. The mandates are education for all of the target groups in our area, to maintain quality indicators, to ensure Internet availability both interactive, quarterly updates, links to federal, state, and local sites, links to current research, and notes availability of federal funding for those problems, and to ensure nonduplication. And that's straight out of the writing there. That's sort of what we took as our mandate then to go back to the subcommittee and say how can we utilize what we've been sort of told to do and make that work best for the folks out there who are families dealing with this, physicians dealing with this, and their need for more education.

Questions?

DR. HOWELL: Thank you very much, Tracy.

One of the questions I would have is that the oft-quoted Newborn Screening Saves Lives Act has specific requirements in it, some of which certainly are directed to the federal agencies. And I wonder if Mr. Smith could comment about how HRSA is planning to respond to these and what will be the mechanism of that response, obviously involving other federal agencies, but I assume that the federal agencies will, indeed, respond to these directions.

MR. SMITH: Yes, indeed we will. I think our initial focus is on all those things that were due for the first 180 days, as you heard with the contingency planning group from CDC and, in terms of responding to this committee's past recommendations, by the October 21st due date. We did identify this education component as something that we would need to work on and coordinate with other federal agencies and with your subcommittee. As Dr. Trotter was talking, I was just making a note to myself. We need to get our staff who will be working on developing the web communications connected to the subcommittee so that we can work jointly towards that end.

As far as the rest of the act, we're looking to make an entire implementation plan, and Dr. van Dyck and his staff have been working with all the HRSA senior staff and we're also working with the Department to be sure we're coordinated across the Department. So we've been doing a lot of things that have probably been behind the scenes as far as your visibility of it, but as those plans develop, we'll be sharing them.

DR. HOWELL: So it's clear that the agencies are looking to do some of the things that you've recommended and can work with you. Great, super. Thank you very much.

That brings us to our final committee report on the Follow-Up and Treatment, and this is Coleen's committee.

DR. BOYLE: Actually I'm going to sit here because I don't have slides.
But our committee has been very active, and you all heard an excellent presentation by Sue Berry and Alissa Johnson.
We've been focusing as a subcommittee on two issues. One is the reimbursement relative to medical foods and formulas, and the second issue is trying to really flesh out the issue of long-term follow-up, both in terms of sort of a mile-high view of the major components of long-term care, as well as to identify the major roles and responsibilities of the major players and parties in long-term follow-up.
So Sue Berry and Alissa Johnson gave a very nice overview of our activities relative to the medical foods issue. We're trying to get a better handle on the burden of the problem among parents and affected individuals. We'll be doing that through, hopefully, the implementation of a well-developed survey in three of the regional collaboratives. So we hope to be reporting back to you sometime in the spring of 2009 about the results from that survey.
At the same time, we had a very productive meeting last June to really try to go into more depth about the insurance coverage/reimbursement related issues. Sue walked through for you many of the recommendations that had come from that meeting. We discussed actions around those items at our subcommittee meeting today. I think we made some progress there. I do feel like our medical foods group needs to work through some of those.
Clearly, there are some easy action items such as to work with insurers to identify and develop reimbursement codes that would facilitate billing and payment for medical foods, and we hope to be working with Mike Watson as he moves forward with the CPT codes, but there are clearly other reimbursement-related mechanisms that we need to think through.
Also there are some other easier action such as developing model state Medicaid policy coverage, as well as thinking about model state insurance legislation. Those are things perhaps we could be working on and maybe can report back to you at our next meeting.
In terms of the long-term follow-up issue, we did have a publication that came out in April of 2008. Alex Kemper was the lead author of that. It was published in Genetics in Medicine, and it looked at the major components or it identified the major components of long-term follow-up which were care coordination, evidence-based treatment, continuous quality improvement, and new knowledge discovery.
At our meeting in January, Alan Hinman really walked us through highlighting the major players involved in long-term follow-up, namely the families and affected persons, primary care and specialty care providers, the public health agencies, and then other major players such as the payers and the early intervention/special education areas.
We've been kind of going around and around about how to manage that and where to go forward and whether we should drill down with these specific players in terms of trying to identify the roles and develop sort of some models relative to the implementation of long-term follow-up. And I think we have come to consensus that we are going to move forward at sort of highlighting the major roles and responsibilities for all of the major participants in a similar type of white paper. And we're hoping that we can come back to you in our February meeting like we did with the major components for long-term follow-up and present that to the committee in whatever shape it is. But I'm hoping it's in final form to present to you at that time. So that's where we are with that.
And then the last issue we talked about was, obviously, providing input and guidance to other mechanisms that are out there that might impact long-term follow-up, and obviously this use case we talked a lot about that in the beginning that Denise made us aware of. And so we're

encouraging committee members, hopefully in our next call, to have reviewed that. We can't provide formal guidance as a subcommittee, but we can provide individual guidance to that. So looking for other opportunities like that.
DR. HOWELL: Thank you very much, Coleen.
I wonder if there are any questions or comments of any of the three subcommittee chairs. You all have been wise and succinct. The net result is that we're slightly ahead of schedule, which is always a good thing.
And that takes us to committee business. The first thing that I would like to do in the committee business session is that we've had the great pleasure of having Dr. Joseph Telfair be on our committee as an active member of our committee, as the liaison representative from the Secretary's Advisory Committee on Genetics, Health, and Society, and this is Joseph's last face-to-face meeting. And, Joseph, we'd like to thank you for your great service and we look forward to hearing from you.
DR. TELFAIR: Thank you.
(Applause.)
DR. HOWELL: The second item on our business is that, as you know, when nominations are made to the advisory committee, they first go to HRSA that checks them for completeness and references and things of that nature. And then once that's all done and everything is in complete order, they go to an Internal Review Group that basically looks at them and says this looks like this is a reasonable proposal and it should come to the committee.
The most recent Internal Review Group workup in this area was the nomination that arrived on Niemann-Pick disease, and you have in your folder today the outline of that review. But I'm going to ask Nancy Green to Piero Rinaldo actually chairs that committee, but as we've said repeatedly today, Piero is unfortunately with his dad in Italy. And Nancy has agreed to go through that form with you.
DR. GREEN: Thank you, Rod.
So the current name of this group is the Internal Review Workgroup. As Rod said, it's chaired by Piero, and the other members are Kwaku Ohene-Frempong, Rebecca Buckley, Rod, and Mike Skeels.
This nomination for Niemann-Pick was submitted by Ms. Barbara Vorpahl who is the Chairman of the National Niemann-Pick Disease Foundation.
All the committee members should have a copy of the assessment of the summary. This is a summary that is derived directly from the nomination form and the references that are submitted with that form, as well as some other publicly available data sometimes informs the review.
Rod, I'm going to ask you would you like me to read this?
DR. HOWELL: I would like you to certainly summarize the high points so that the committee members will have chance to
DR. GREEN: Okay, very good.
So the Internal Workgroup reviewed the nomination package over the summer. Actually the review was completed in July. So this does not reflect any data or publications that have come out subsequently. This conforms to the same format that we've used for the reviews of other nominated conditions.
Number one. The condition is medically serious. And of course, for Niemann-Pick, that is the case with a gradient of severity ranging from early- to late-onset. And as we've heard with other conditions, there are different clinical phenotypes. The one focus I think most relevant for newborn screening is the type A. It has an onset in infancy and a median age of death at 21

months. And then there are some other intermediate and later-onset phenotypes.
Number two. Are there prospective pilot data from population-based assessments available for this disorder? And the answer is no. There are no population-based data available, although there are some clinical trials underway. I would say that this is certainly the most troubling aspect of the nomination, as we've discussed in the context of Pompe.
Number three. Is the spectrum of the disorder well described to help predict the phenotypic range of those children who are likely to be identified from population-based screening? Here again, there are some aspects that are problematic for the nomination in that there's no clear evidence of a correlation between clinical and biochemical phenotypes.
Number four. The characteristics of the screening tests are reasonable for the newborn screening system. And as we heard earlier from Dr. Vockley's report, maybe we should add reasonable and available to that criterion. Again, since there are no population-based assessments, the answer is unknown. And it may be that in the context of some other ongoing pilots on the West Coast, for example, that maybe some of that information will be available at a later date.
Number five. If the spectrum is broad for the disease, then is there an ability to identify those children who are most likely to benefit from available treatments. Certainly for the type A that I mentioned, the one with the early and severe onset, certainly those children would be most likely to benefit from intervention, but there are no published studies demonstrating therapeutic efficacy for, I guess, the two proposed strategies for therapy: number one, hematopoietic stem cell transplantation; or number two, gene therapy. I would like to just note that in the submission package came some very interesting preclinical studies using murine models, but, of course, that's I think just to mention that there's some distance between what we have now and where we need to go in assessing impact of therapy on the course of Niemann-Pick.
And then lastly, are there defined protocols or FDA-approved drugs available for treatment? And again, no FDA-approved treatments currently exist, although clinical trials I mentioned are underway.
So overall the recommendation to the advisory committee is that the nomination not be forwarded to Evidence Review at this time, and when there are some population-based studies available, as well as some more clarity around therapies and the impact on outcome, that the condition be renominated for consideration.
DR. HOWELL: Thank you very much, Nancy.
Are there questions about this nomination with the key points that were problematic in the review?
DR. VOCKLEY: Not a question, but I just need to be certain that the record shows I'm abstaining from the discussion and the voting on this because my wife is involved with the Niemann-Pick Foundation as a genetic counselor. So I'm out.
DR. HOWELL: Thank you very much for that important commentary.
Are there any comments? So I think the concerns of this early review group I think are fairly clearly stated at this point in time.
We should vote on this because it's a formal recommendation to the committee, and we will not send a formal note to the Secretary saying that we've decided not to consider it, but it will be in the text of the material we send.
Can we have a motion about this?
DR. TROTTER: I'd like to move that we accept the recommendation of the nomination review workgroup not to forward this.
DR. HOWELL: Is there a second for that?

DR. BOYLE: I second it.
DR. HOWELL: Is there any discussion before we have a vote?
(No response.)
DR. HOWELL: Those favoring Tracy's motion that it not be forwarded to the Evidence Review Group at the current time, can we see a show of hands? Those favoring his motion?
(Show of hands.)
DR. HOWELL: And any opposed?
(No response.)
DR. HOWELL: We have one stated abstention in the form of Gerry. So it's a unanimous vote that it not be reviewed.
Thank you very much, Nancy, for that.
I will make a few more comments before we open up the thing, and that is that in the coming weeks, you're going to get some material from the Evidence Review Group about Pompe disease, about the concerns of the nomination. And they're going to send those to you. They're going to come to you, and we will need your comments on those very promptly. The requirement for those is so that they will go back in the material that is sent to the person that nominated this condition. And the deadline on that will be what time? Well, we obviously have to get it from the Evidence Review Group, but I think that once we get that, we would like your response quite promptly so we can get that afoot. So that's one bit of business that you'll have coming up very soon.
Is there any question? I think everybody is fairly clear about what we're going to do on that score. Gerry?
DR. VOCKLEY: Could I just ask that when that document comes, that it be modified with markup mode on so that we can kind of do a quick scan and at least be sure we're looking at the things that have been modified? Sometimes they come where it's easy to identify what's been changed and sometimes it doesn't.
DR. HOWELL: Well, we will make that request to the sender of the document on my right.
We had a long discussion of the excellent document that Ned had submitted for our review. And I think there was general agreement it was a very good document. We've had some recommendation that we bring that back up for a vote at this time. We have also had a lot of concern that some people still it's a dense document have not had a chance to look at it in detail and make comments. And since it's going to be the guiding light, what I would like to do is to see if we can send that document out
DR. LLOYD-PURYEAR: Again?
DR. HOWELL: Yes. The document out so that folks can make comments. I mean, Denise has a few specific things. Coleen has a few things that she wants to do. And then we can vote on that and then have it as our final thing.
We've already used it. It's obviously a very good document. The fact is it's a work in progress. And again people have worked on it very hard, and I think that they really want to get it going. And so we'll try to get that done quite promptly. But that can be done electronically. Then we will bring it up for formal discussion at our November meeting. We'll have to have a formal vote on the phone. So that's what we will do in view of the fact that folks really feel strongly about wanting to work on it a little bit more. I know you all are anxious to get it going, as am I.
DR. DOUGHERTY: Rod, I have a specific question about that. I'm wondering. It seems like the Calonge document has more specific criteria and items that should be addressed. I would say they should be addressed in an evidence review so that then we can match up the decision-

making criteria with the way the evidence review was structured. I spoke to Jim and he said, oh, yes, we're going to try to follow what Ned does. But I'm wondering if we should make that formal request to the Evidence Review Group that they use the same format or use some format to present the evidence review so that this comparison of the evidence review with our decision criteria becomes a little easier.
DR. HOWELL: Well, I think that the Ned document, as I understand it, is really this committee's decision about how we will review it. And so by definition, I think they should follow that. Do you understand it that way? So I think that, indeed, will follow I believe.
But anyway, you'll get this soon. Please make the comments, get it back to Michele so that we can really get this finalized. It's a great document. A lot of work has gone into it. And I have a feeling there are not a lot of things, but there are a few things that people feel strongly about adding, and I think we should do that.
+ Let me comment about the fact that our next meeting will be a webcast meeting, November 21st. It's at 1:00 p.m.
DR. LLOYD-PURYEAR: Twenty-fourth.
DR. HOWELL: Twenty-fourth. I'm sorry. What did I say?
DR. LLOYD-PURYEAR: Twenty-first.
DR. HOWELL: The 24th of November, just before Thanksgiving. You can start putting your turkey in. But anyway, it's at 1:00 p.m.
There will be a variety of things at that meeting. One is to review the document we just discussed, but we do anticipate we will have the evidence review back for SCID at that time. SCID will be discussed. And I think that Barbara has taken a flight back to Chicago, but I think although these meetings are announced publicly, et cetera, I think that as a matter of courtesy, we will certainly notify the persons who nominated it that it will be discussed. And as such, a decision could be made. In other words, if all the evidence is available and the group is comfortable reviewing it and so forth, there's no reason not to make a decision about it. So we'll advise the group that it will be discussed, a decision potentially could be made so that everybody is fully aware of that. This will be a telephone conversation, a webcast. And as always, all of these are open to anybody who wants to join in. So they're public meetings.
DR. DOUGHERTY: Just a question about logistics for that. Will the committee be receiving a briefing book for that webcast or will the materials be posted on the web prior to the meeting so we can review them? Last time we had the conference call, I was a little confused and didn't have a briefing book. I don't know if other people got one.
DR. LLOYD-PURYEAR: Committee staff had decided not to send out briefing books but to use that website so that committee members could access the materials on a website that was distributed prior to the meeting.
DR. DOUGHERTY: Because I didn't see materials on the website, but maybe that's me and my computer.
DR. LLOYD-PURYEAR: No. They were there.
DR. HOWELL: Well, the material clearly should be on the website, and the agenda should be there. And hopefully that will tick along.
I think we've had a lot of discussion, some of which was not even involved in protocol, but much of it was.
But anyway, I think we've gotten a great deal done today and we've really gotten through the first recommendation on Pompe disease, and I think that was extremely well done. I think we've learned a lot. And I think that the documents that we use for the function of the committee they

should evolve. I mean, I would hope that we'd be coming back to the documents and say, well, you know, since we've learned this, we should have a consideration of modifying that. So I would look upon these as our official documents, but I would certainly not want them to be unalterable. But I think that we've gotten a lot of things done.
I think that we have two formal notes that will go forward to the Secretary. One is that our formal recommendation about Pompe disease will go forward to the Secretary because that will be a specific recommendation. And the second thing is that we have formally endorsed the AHIC report on newborn screening, the health IT standards, and the case recommendation. So we will send that forward as formal recommendations so that there are two this time. So I think that's been an extraordinarily big accomplishment since we're just getting these things out of the barrel.
Are there other things that should come up?
We've got the webcast on November the 24th. Our next meeting is February 26 and 27.
+ And one of the things we need to do in the back of this book, you've got a calendar for May. Many of you probably have your calendar here on Outlook, and if you do, that would be great. But as soon as you can, if you can get the material to Michele so that they can start trying to make reservations for the next meeting that will be in May. And obviously, one of the dates on here is Memorial Day, which is May 25th. The APHL meeting happens to be also the 4th through the 8th. So there are a few other things. But if you could please get your things to Michele, that would be great.
Are there other business items to come before this group?
DR. DOUGHERTY: Agenda items for the next
DR. HOWELL: Well, the February agenda items we will certainly invite you. But let me tell you what has been suggested already for February.
A request that we'd have Mike Watson discuss the new Translational Research Network so people will have a little broader understanding of what is intended for that since that will have a tremendous impact on this committee. We will anticipate that we will hear something.
A use case update has been requested.
I've already mentioned that we have issues on informed consent, and that will be a good time to discuss the second case and the difficulties with that.
And the other issue that's been recommended is to have FDA comment about what they're doing with regard to the circumstances that Gerry mentioned.
Those are the things that have been recommended. Do you have some additional items?
DR. DOUGHERTY: Mine are in there.
DR. HOWELL: Sharon, you look like you have an item.
MS. TERRY: Yes, you're right. That's very perceptive. And I'm not sure it's ready for this time, but I think eventually this committee is probably going to have to look at the issue around blood spots and research and the privacy uproar in Minnesota and that sort of thing.
DR. HOWELL: Oh, I'm sorry. The other thing that's been recommended for the February meeting is residual blood spots. It didn't have an arrow by it. That's a fabulous discussion. Again, the Minnesota issue recently has highlighted that, and I think unfortunately some public misunderstanding about how those spots could be used, even if you were evil, is a problem. So I think that residual blood spots I would like to have on every agenda because they're so important in our research.
Are there other items? Peter, have we forgotten anything?
Well, hearing nothing, why don't we go home? Thank you very much.
(Whereupon, at 2:42 p.m., the meeting was adjourned.)