U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE ON HERITABLE DISORDERS
AND GENETIC DISEASES IN NEWBORNS AND CHILDREN

Thursday,
May 17, 2007

Rotunda Room, 8th Floor
Ronald Reagan Building and International Trade Center
1300 Pennsylvania Avenue, N.W.
Washington, D.C.

IN ATTENDANCE:

Committee Members

Amy Brower, Ph.D.
Executive Director
Medical Informatics and Genetics
Third Wave Molecular Diagnostics
315 South Fork Place
South Sioux City, NE 68776

Gregory A. Hawkins, Ph.D.
Assistant Professor
Department of Internal Medicine
Section on Pulmonary, Critical Care,
Allergy, and Immunologic Diseases
Center for Human Genomics
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157-1054

R. Rodney Howell, M.D.
Committee Chairperson
Professor
Department of Pediatrics (D820)
Leonard M. Miller School of Medicine
University of Miami
P.O. Box 016820
Miami, FL 33101

Jana Monaco
3175 Ironhorse Drive
Woodbridge, VA 22192

James A. Newton, M.D.
President
Alabama Neonatal Medicine, P.C.
7203 Copperfield Drive
Montgomery, AL 36117

Piero Rinaldo, M.D., Ph.D.
Professor of Laboratory Medicine
T. Denny Sanford Professor of Pediatrics
Vice Chair of Academic Affairs and Intramural Practice
Department of Laboratory Medicine and Pathology
Mayo Clinic College of Medicine
200 1st Street, S.W.
Rochester, MN 55905

IN ATTENDANCE:

Michael Skeels, Ph.D., M.P.H.
Director
Oregon State Public Health Laboratory
1717 S.W. 10th Avenue
Portland, OR 97201

Liaison Members

Joseph Telfair, Dr.P.H., M.S.W., M.P.H.
Member, Secretary's Advisory Committee
on Genetics, Health, and Society
Professor, Public Health Research and Practice
Department of Public Health Education
School of Health and Human Performance
University of North Carolina at Greensboro
437 HHP Building
1408 Walker Avenue
P.O. Box 26170
Greensboro, NC 27402-6170

Ex Officio Members

Coleen Boyle, Ph.D., M.S.
Centers for Disease Control and Prevention
Director
Division of Birth Defects and Developmental Disabilities
National Center on Birth Defects and
Developmental Disabilities
1600 Clifton Road, Mail Stop E86
Atlanta, GA 30333

Denise Dougherty, Ph.D.
Agency for Healthcare Research and Quality
Senior Advisor, Child Health
540 Gaither Road
Rockville, MD 20850

Peter C. van Dyck, M.D., M.P.H., M.S.
Health Resources and Services Administration
Associate Administrator
Maternal and Child Health Bureau

Parklawn Building
5600 Fishers Lane, Room 18-05
Rockville, MD 20857

IN ATTENDANCE:

Executive Secretary

Michele A. Lloyd-Puryear, M.D., Ph.D.
Health Resources and Services Administration
Chief, Genetic Services Branch
Maternal and Child Health Bureau
Parklawn Building
5600 Fishers Lane, Room 18A-19
Rockville, MD 20857

Organization Representatives

American Academy of Family Physicians

Norman B. Kahn, Jr., M.D.
Vice President, Science and Education
American Academy of Family Physicians
11400 Tomahawk Creek Parkway
Leawood, KS 66211-6272

American Academy of Pediatrics

Tracy L. Trotter, M.D., FAAP
200 Porter Drive, Suite 300
San Ramon, CA 94583

American College of Obstetricians and Gynecologists

Anthony R. Gregg, M.D.
Director, Maternal Fetal Medicine
Medical Director of Genetics
Department of Obstetrics and Gynecology
University of South Carolina School of Medicine
Two Medical Park, Suite 208
Columbia, SC 29203

Child Neurology Society

Bennett Lavenstein, M.D.
Neurology Department
Children's National Medical Center
111 Michigan Avenue, N.W.
Washington, D.C. 20010

IN ATTENDANCE:

Department of Defense

Lt. Col. David S. Louder, III, M.D.
Chief Consultant for Maternal-Child Medicine
Air Force Medical Corps
AFMSA/SGOC
110 Luke Avenue, Room 405
Bolling AFB, D.C. 20032

Food and Drug Administration

Ethan Hausman, M.D., F.A.A.P., FCAP
Medical Officer, Inborn Errors of Metabolism Team
Division of Gastroenterology Products
WO-22, Room 5171, HFD-180
US FDA, CDER, OND, ODE-3
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Genetic Alliance

Sharon Terry
President and CEO
Genetic Alliance
4301 Connecticut Avenue, N.W., Suite 404
Washington, D.C. 20008-2304

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Report from the April, 2007 Workgroup Meeting:
The Road Map to Implement Long-Term Follow-Up
and Treatment in Newborn Screening

C O N T E N T S

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P R O C E E D I N G S (9:08 a.m.)

DR. HOWELL: I'm pleased to call to order the 10th meeting of this committee in what is my favorite setting, frankly, as we sit here overlooking Pennsylvania Avenue. This place is hard to get, so we don't get here with great regularity, but I always enjoy being here.

We have a really full agenda with a lot of things that I hope will come forth in some primal type of thing, and I'm also pleased to recognize today at the table we have representing one of the new liaison members of this committee, the Genetic Alliance, and we have its CEO, Sharon Terry. We're delighted to have you in the Alliance at the table.

We're also pleased to have Tracy Trotter here today representing the American Academy of Pediatrics. The Academy has selected a new member, a new representative member to this committee, who is Tim Geleske. He could not be here today. We'll welcome him in the future. He's replacing Steve Edwards. Tracy is more than ably represented in the Academy and has represented the Academy in many areas of newborn screening, so it's great.

Let me go through just a few things. Number one, we're going to continue our discussion of the nomination and evaluation process for candidate conditions for the uniform panel. A report will be presented by Dr. Perrin on the proposal for the structure of the evidence-based review group, which has, of course, been a central point of discussion. This workgroup will be co-chaired by Dr. Perrin and a committee member.

We need to wrap up that nomination form and get that rolling. I think that we've had enough discussion of that and so forth. We should be able to get that done and get that behind us today.

We also will have a report on the long-term follow-up group that convened a meeting on April 18, and Coleen will be reporting on that. They've done a great job with an early version of a white paper, and follow-up treatment is obviously a critical area that we have been discussing and we'll need to continue to discuss.

Dr. Boyle, as well as two authors of this white paper, Drs. Downs and Kemper -- the paper is still in progress, I might point out -- will present the accomplishments of this workgroup.

We also are going to hear presentations from the Regional Genetic and Newborn Screening

Collaboratives, which are making great progress. The long-term follow-up activity will be reported by Drs. Downs, Singh and Eckman; and the laboratory performance activity will be reported by Dr. Rinaldo and Dr. Pasquali.
We also are going to hear several meeting updates, and I think that most people in this room are aware of the fact that there has been an absolute flurry of meetings. Most of the people in the room have done little recently but meet, but we hope we can bring that to an end.
Brad Therrell is going to tell us about the recent G6PD meeting that was held here in D.C. and the severe combined immune deficiency meeting that was held just this week in San Francisco. Some of us appreciated an opportunity to participate.
Dr. Louder, soon to be an even greater elevated Colonel Louder -- congratulations on your promotion, David -- will talk to us about the Defense Department newborn screening program.
Mr. Wigode of the March of Dimes is going to present relevant federal legislation. So you see our agenda is full, but we have more. We've got the three subcommittees that are going to meet, and as always these meetings are open, the subcommittees are open, and we always welcome public comment at all levels.
We also have a new member of the committee, Dr. Michael DeBaun, who is not here today, but he's a pediatric hematologist with a special interest in the medical and community services for newborns and children with sickle cell disease. Dr. DeBaun is an academic physician at the Washington University School of Medicine in St. Louis, where he holds the position of associate professor of pediatrics, neurology and biostatistics.
There have been a number of questions to me and others about the recent solicitation in the Federal Register for new members of this committee and so forth, and I'd like Peter, if he'd be willing, to at least say a few words about that.
Peter, could you comment, please?
DR. VAN DYCK: There was a Federal Register notice around the 1st of the year soliciting nominations for the members of the committee that are -- I don't want to use the word "expiring" --
(Laughter.)
DR. VAN DYCK: Ending their terms on the committee.
DR. HOWELL: I would hope not expiring.
DR. VAN DYCK: And that closed sometime in March. The Department is in the process of reviewing that nomination package that we've sent forward. The names will come at some time in the future, and probably before the September dates of expiration for those members.
DR. HOWELL: Well, that would be excellent. I'm aware, having been around Bethesda a fair amount of time, that sometimes names are a bit slow percolating through the very large system, but we hope that will go well.
We will want to approve the minutes of the meeting in just a bit. We also have committee correspondence in Tab 5 that I would like for you to look at. We have letters from professional organizations and from industry requesting appointment as liaison non-voting members. Those letters come from the American College of Medical Genetics, the Society for Inherited Metabolic Disorders, the Pediatrix Medical Group, and PerkinElmer Life and Analytical Sciences.
I might point out, as we think about this, that we currently have non-liaison members of this committee. The number of liaison members is limited to 11. If you read the minutes of the last meeting, and since I spend so much time in the air I read them carefully --
(Laughter.)
DR. HOWELL: -- there is a note that Dr. Puryear and I would have put down some ideas about how liaison members are chosen. This is not cast in stone, but these are the ideas that we came up with. We'll pass these around for your review. Again, these will, basically, once we look at them and consider them, will be a part of our standard operating procedures and so forth. But I'd like you to look at these, and as the meeting goes along we will want to review these letters and I think make some decisions about this so that we can quickly move along.
In Tab 17 are future meeting dates for 2008, and please look at those. Somewhere along the line we'll get back to those.
DR. LLOYD-PURYEAR: What we need to do, we have meeting dates for January. For May and September we still do not have meeting dates. So before the end of today, if you could mark the dates you're not available in May and September, I can turn that over to the contractor.
DR. HOWELL: Okay, thank you very much.
We've got some other housekeeping things that I will mention. I'll mention this one right now. The

restroom is at the back of the room, for those of you who haven't found it. As the day goes on, I will tell you where the subcommittee meetings will be. I won't tax your memory.
But the other thing is that this evening members of the committee who don't have other commitments and so forth have dinner as a group, and that's at Chef Geoff's, which is near here, which is a pleasant enough spot. Anybody who would like to go and join this group and who is available and so forth is welcome to do so. I think the key thing is to let Tamar, who is downstairs at the desk, know so that she can call ahead and give them some idea of the number of people who are coming. This is usually a pleasant activity.
Any other comments before we start?
(No response.)
DR. HOWELL: Okay, let's roll along. But the one thing we do need to do, we need a formal approval of the minutes of the meeting. The minutes of the meeting are at Tab 5.
Are there corrections to the minutes?
(No response.)
DR. HOWELL: If not, there are a few typos in it, but they're insignificant. (Inaudible) is misspelled one place, but I'll take care of the final spelling.
Can we have a motion to approve them?
PARTICIPANT: So moved.
PARTICIPANT: Second.
DR. HOWELL: So it's moved and a second. Those favoring, say yes.
(Chorus of ayes.)
DR. HOWELL: Excellent. We'll move along, then.
We're going to start off now, and our first presentation is the nomination/evaluation process for candidate conditions on the uniform panel and Dr. James Perrin from Boston.
Dr. Perrin?
DR. PERRIN: Well, thank you very much for the opportunity to talk with you a bit today about some of the planning that's gone into developing evidence-based reviews for the use of the committee. I'm very much indebted to the working group that met back in October of '06 to spend a day really thinking through what some of the choices were, some of the strategies available for working on developing better evidence for the committee's use in its work.
I think most of you know about the nomination process as it has been developed over the last few meetings by a number of members of the committee, the nomination form itself, which has been reviewed, and the fact that the process really is, for someone who wishes to nominate a condition or a disease for study or for newborn screening, to fill out that nomination form. It goes first to federal administrative review, and if it meets the basic guidelines of having all the information in the right place, it is then sent on for review by the advisory committee. At that point, the advisory committee really has a bunch of choices. One of them may be to say, well, we really would like to look at this in a good bit more detail and send this on to an external evidence-based review group, which is what I'm going to be describing to you a little bit today, for further evaluation and then return to the committee for final review and decisions.
There are other steps the advisory committee may take, and I'll comment on those in a few moments. This is, in general, what we've talked about. I'm highly thankful to Nancy Green for making this initial slide. Again, the nomination form, the federal administrative review, goes to the advisory committee, and then if the advisory committee wishes it goes to an external review group for evaluation, and then back.
So when we met in October of 2006, this group included a number of members of the committee, a number of external advisors, people who have been involved in evidence reviews in a variety of settings, and we also had a tremendous amount of help from Steve Downs, and especially from Alex Kemper, who has done a lot of work using Pompe's disease as an example of the process, understanding basically how that might work. But the reform basically deals with a series of issues here, and the major process is does the information provided on the form really clearly define a disease. I hope you'll look at these carefully because you may want to challenge these and say, in fact, these are ones you'd like to refine as we move forward.
What's the prevalence of the disease, especially in different populations, and is that known? Can the condition be identified reasonably well in screening? What's the evidence about screening and other actions after screening that can lead to positive outcomes? So presumably the initial nomination at least provides some evidence in these four areas, and actually a few more.

In the refinement of the nomination form, which really still needs to take place? There are still some terms that we need to have some agreement of the committee on what we really mean by these terms and come to as much specificity as we possibly can. I listed a few. These are probably not the only terms in the nomination form that need to be really well addressed, but they are what do we mean by "accuracy"? What do we mean by "availability"? Can we have some agreement on what those terms mean? What do we mean by "efficacy"? That's a fairly well-defined term in the field. And the issue of urgency, which is one that is on the form currently. Do we have a sense of what these standards are for urgency?
So these are all ones that we actually think are important to get clarity with members of the committee over the next few months time.
We have another discussion of sensitivity and specificity, and I think, as I understand where the committee is coming from, it is probably unlikely that the committee can set absolutely hard and fast rules about acceptable sensitivity and specificity, but we probably could at least define the floor below which a test is simply not acceptable. But this is, again, something on which we need to get as much advice from the committee as possible.
There are some issues about the evidence regarding costs which are not really on the form currently, and we want to have some issues described as well about the potential harms of screening as we do the follow-up forms, the nomination forms.
Now, one of the issues in the nomination procedure and process is that the advisory committee could really decide that there is not enough information on the nomination form to move forward. There's not enough evidence here to really send it off to an evidence review group to examine at that point, and instead there may be some value in some pilot work being carried out. Again, I think the evidence committee, the evidence review group, can help the committee determine what might be some appropriate pilot studies. But if the nomination form comes in and says we have clinical trials of screening tests, we've had no experience in applying the screening test in larger populations, that's an example where gathering those kinds of data may be critical to being able to go forward.
So among the options are really testing and treating the condition in one state using another state as a control, better evidence about prevalence and, as I mentioned a moment ago, screening effectiveness in population applications.
So what are some of the issues in evidence review that are particularly relevant to thinking about screening for heritable disorders? First of all, in most cases, not quite all but most cases, we're talking about rare to extremely rare conditions, lack of randomized controlled trials in many cases, and thus the sort of traditional strategy for looking at RCTs as the sort of gold standard against which to assume the therapy is effective will not in general pertain here.
Second is there's limited information on costs and benefits often, especially when you go across all potential outcomes; that is to say, if you think about this as being four major arms of true and false positives and true and false negatives, it may be that the evidence for the costs and benefits in all four arms may be very hard to come by.
There's also the issue that, again, Alex very eloquently spoke of in his work around Pompe's disease, which is that much of the evidence that's available may not be easily available, and traditionally in evidence-based reviews one looks almost entirely at published literature, but published literature may not be anywhere near satisfactory to answer questions here, and it's going to be very important to have a systematic strategy for determining, (a), how to assess unpublished literature and, (b), how to access unpublished literature, which are going to be primarily from the FDA trials where there have been such for some of the drugs, and there also likely will be proprietary data from some of the companies that are developing new treatments for some of the conditions of concern here.
There are a number of other issues in an evidence review relating to this population of questions, but these are some of the most critical ones as we go forward. So what we've talked about with the Bureau is having sort of three levels of an evidence working group that would include a core, stable evidence group staff with a project director who is knowledgeable about epidemiology, and especially methods relevant in this particular area, that would have someone representing public health, a consumer actively involved in the deliberations of the core group, someone with some experience in cost/benefit analysis, and someone who brings some content, because my staff that works on evidence reviews for the Bureau in some other areas has painfully little content expertise in the area of genetics. We don't profess any expertise in that area, but we do have geneticists that we would have on group, not to be knowledgeable about the specific tests so much as to sort of make sure that we're not too way off base and keep us a little bit grounded.

The evidence group we propose to be assisted by members of the advisory committee. In fact, there will be a couple of members of the advisory committee who would be regular participants in the evidence group, as well as ad hoc expertise for specific tests under consideration or for specific disorders under consideration, and we will develop a pretty clear conflict of interest policy relating to their involvement. In addition to that, we are in the process of putting together an external advisory group with broader national representation, not all based in, say, one particular community, that would bring in additional expertise in review methods in genetics and among health care providers.

All of these are ones we would like the committee to make sure you feel pretty comfortable with. These are not set in stone, but this is the proposal that we are working from now.

The time frame that we are talking about for this initial work to frame any remaining questions for the nomination form -- you folks have spent a lot of time and energy developing a very good form that I think we all agree is just about there, but there are some final pieces that need to be worked on, including the issues that I mentioned before of confirming definitions as far as we possibly can. We would expect that at the fall meeting of the advisory committee you folks would prioritize conditions that you really want to have evaluated. Again, my understanding is that the committee has not set those priorities yet. You have some candidates that you're thinking about as priorities on here, and I think that does mean that what current nominations are in your office, Michele, need to be reviewed and thought through by the committee, as well as whether you want to go out and make sure to be soliciting additional nominations from the community at this point so that that can be done as cleanly as possible at the fall meeting, and then after we've gone through these processes, then to really begin the process of doing specific evidence reviews.

We don't know enough -- and I'm going to be honest in saying that. We don't know enough about exactly how much work and time it will take given some of the difficulties with access to data. We hope that they will not take a long time and that we'll be able to get data pretty quickly and certainly come back by the spring meeting with some evidence for you folks to consider. But that's sort of the time frame that we're talking about at this point.

I believe that it's really important to states that the evidence in general is going to be along these lines. What is the condition that's prevalent as natural history? What do we know about the different forms of the condition, and again the prevalence and natural history of those? What is known about both screening and about diagnostic testing for this condition? What is known about treatment, and to what condition groups is that treatment applicable? What's the evidence for that? What are the risks and benefits of that? We would indicate clearly where evidence is absent and what information would be most critical in trying to help the committee make some decisions. We would present that evidence in summary table form for the committee to review. But most importantly, this group would not make recommendations to the advisory committee. That is not the role of an evidence review group. It is to give you more capability on which to base your judgments, because these are very complicated decisions the committee needs to make, and our role would be simply to provide the evidence that hopefully will help you make that in a more clear-cut way.

I believe that's my last slide. So let me stop at this point, and I suspect there are some questions, some ideas and revisions and other things you may want to suggest be done.

DR. HOWELL: Thank you very much.

Are there any general questions of Dr. Perrin?

(No response.)

DR. HOWELL: The group has accepted fundamentally the nomination form that we've discussed extensively, with the idea that it might well have some slight changes as the evidence group worked as far as defining these things a bit more and so forth. I guess what we need to do is several things. One is that in Tab 6 there's a letter, a cover letter, that would go to persons who are nominating conditions, and you need to please look through that and see what you think of it. This would basically go with the nomination form with some background and how it would be handled and so forth. Then we need to give approval for the idea of moving ahead with the group as Dr. Perrin has described the evidence-based group that will have members of this committee on it, and then other members as he has discussed.

Coleen?

DR. BOYLE: I just had, I guess, maybe one question or clarification. Is that appropriate now, or do you want me to wait?

DR. HOWELL: Yes, sure.

DR. BOYLE: Okay. I was a little confused about the issue of pilot studies, because I thought when we had

talked about this in the October meeting we had thought about this as being a pilot phase, that perhaps we would take maybe one or two or three conditions that were kind of on a spectrum in terms of evidence and that they would help guide the process and would really help formulate it or develop it or finalize it. So I guess it was a little different than what you had presented to us.
DR. PERRIN: I think there's some confusion on wording. There are two notions of piloting here. One is exactly what you're saying, Coleen, which is piloting this process with two or three conditions, and that clearly is happening there. I think the other notion of piloting that came up in the October meeting, which I think really falls back more to the committee than to the evidence group, is to say, well, gee whiz, you really don't have much information on how this test works when it's done in populations. All the evidence for the test sensitivity and specificity comes from referral populations or whatever else, little evidence about effectiveness in larger populations. It may be that the committee will say, even before it goes to an evidence review, that you want to suggest to the nominators that there are some ways of getting some pilot data that would make the nomination itself substantially stronger. So there are two different kinds of pilots there.
DR. HOWELL: Michele had a comment.
DR. LLOYD-PURYEAR: If you look at the minutes on page 17, we agreed, or you agreed as a committee, that this would not be a pilot, that once we began now, it would be real and not a pilot. So we're not in a pilot once we accept this. You guys have accepted the nomination form tentatively, knowing that there will be some revisions. Nancy Green and Marie Mann were supposed to develop a letter to accompany the nomination form. We were coming back to this meeting to present a process of evidence review which is being presented. Once that's accepted, then the nomination and review process begins, not as a pilot but as real.
DR. HOWELL: Denise?
DR. DOUGHERTY: Now I have two comments. One is that it's understood to be an iterative process that we will revisit. So it's real, but we don't pretend to have the final answers at this point.
DR. LLOYD-PURYEAR: That's right.
DR. DOUGHERTY: Nor does Dr. Perrin.
DR. PERRIN: So in that sense it is still a pilot, right?
DR. DOUGHERTY: Yes.
DR. PERRIN: I agree.
DR. LLOYD-PURYEAR: It's a for-real review.
The letter looks fine to me. We'll probably have a vote on it, but will we see the final nomination form before it goes out, since you said there may be some changes? I know you said we've seen it a thousand times, and we have seen it a thousand times, but I don't have it. I mean, it's hard to know where the last version is.
DR. HOWELL: I'm sure we can get you the last version.
Tony?
DR. GREGG: Will the feedback to the larger group be in some standardized format, and have you talked already about what that format would be, bullet points with level of evidence? I suspect that could be difficult because in many cases the level of evidence wouldn't be very high.
DR. PERRIN: I think that we're probably not talking about a traditional level-of-evidence approach because it's very hard to do that given the evidence that will be available. I'd call it more subjective, but I think what we will try to do is provide you tables which describe the evidence. We'll give you some thinking about the strengths and weaknesses of the evidence provided, but using a fairly traditional strategy for weighing evidence that, for example, some of the evidence-based centers do, is very difficult to do given the kinds of evidence that really does exist here.
So I feel as if this is not a pilot in the sense that we're going to get you evidence that the committee can act on, and when the committee acts, presumably that's a final decision, a real decision. These are not pilot decisions. On the other hand, I think, as Denise said, we really know we're all getting into an area that is relatively untested, and we don't want to completely reinvent wheels, but we're going to need to do some work together to figure out indeed how best to present these kinds of data to you, among other things, and I'm sure the first time around it won't be what it will be the third time around.
DR. HOWELL: Sharon?
MS. TERRY: So on the letter, I think we just need to broaden it. I know that the instances of "an economic interest in" or "acts as an officer or director" are just examples of a conflict of interest and the interest statement itself will be probably more regular in the sense of any funding or any connection with regard to

finances, et cetera, and I won't go into wordsmithing, but I have some ideas about that, so I'll just give them to the committee later.
DR. HOWELL: Any more questions or comments? It seems like Dr. Perrin and his group has done a very good job of doing this, and I think we should encourage them to move ahead and get busy with this process. We need two liaison members from this committee, and I would like to ask Piero and Amy, who is in the air on the way here, if they'd be willing to serve as liaison to Dr. Perrin's committee? Would that be acceptable? And we'll ask Amy when she gets here. It will serve her right for being late.
(Laughter.)
DR. HOWELL: But in truth, her flight was delayed because of weather and so forth. She'll be here later today.
Is there general agreement about the letter? Do you need to vote on the letter? Everybody is nodding yes and so forth. Is there any concern about the letter?
Piero?
DR. RINALDO: I remember when we had some discussion about encouraging a team approach rather than having individuals nominating, really trying to put together the various expertise needed, not only going from the specialist and from the clinicians, because that perhaps will be the best way to address all the items included in the nomination form.
I'm a little concerned that an individual, a person with an interest, may decide to just do a quick search and put together a nomination that I think will be very valuable also in support of the work and the speed of the work of the evidence review group to really have some people with knowledge of a condition being involved. I think the spinal muscular atrophy group comes to mind. I know in this committee we had a presentation, and I really think they did a fantastic job because they came here and it was a patient advocate, it was a laboratory specialist, a basic scientist, and a clinician. So I was very impressed by the fact that these people were working together and generating a product that was very comprehensive.
So I was wondering if there's a way to add a paragraph to this letter encouraging people not to act individually but rather trying to rally the necessary expertise.
DR. HOWELL: There's a comment about expert input, but it could be valuable to talk about it because I think that, obviously, if you have all these folks who have looked at it -- and I would also like to encourage people to work with the states or other national laboratories so that you really know and have information about the test, its reliability in a public health setting. Obviously, that will be critical.
Tracy has a comment.
DR. TROTTER: I agree with that completely. One of the templates we might use is what the CETT program for rare disease genetic testing has used in terms of making a requirement of applying for a grant, having the pieces in place. It just seems logical that those pieces should be in place before Jim's group does a whole lot of work looking at something and saying, well, these pieces aren't in place. It wouldn't be too hard to say those four pieces that Piero spoke about --
DR. HOWELL: Let me make a suggestion. Piero, why don't you, during the course of the morning, draft a little thing that we will put in down where it says "welcomes nominations and expert input," and you can put a little thing in and then bring it back to the committee. Tracy can assist you.
DR. RINALDO: Joe was warning me that that's what happens when you open your mouth.
(Laughter.)
DR. HOWELL: And Joe, as usual, was right on the money.
(Laughter.)
DR. HOWELL: I think the committee is very supportive of moving ahead as you presented it. Obviously, there will be some little refinements to the form that will be iterative, as Denise has pointed out, and we will hear about those, but we really need to get moving on this. We've been talking about it for what seems like forever, and it seems like the nomination form now is in relatively good shape. We have an evidence plan that I think will satisfy everybody about how the evidence is gathered and the specific plan of gathering the evidence, which will be very good.
Is there general agreement that we move ahead with this? We'll seek Piero's and Tracy's additions, to be sure. I don't think that these nominations are going to fly without this group effort, but I think it's nice to put that in up front rather than at the end and so forth.
Jim, do you have any other questions?
DR. PERRIN: No, but thank you, and I look forward to working with you.
DR. HOWELL: We look forward to great things. I think the question of how this will come to the committee, certainly we would anticipate it will come in a form that will be easy for us to see what the

thoughts are.
(Applause.)
DR. HOWELL: And Alex Kemper and Nancy Green will be involved in this, as they've been participating as we've gone along. So that will be great.
We're right on time. Isn't that terrific? So now let's go to the agenda, if I can find it, to see what's next. I think that we're going to hear from our distinguished colleagues about the meeting that was the April 2000 workgroup meeting and that Coleen had chaired. Obviously, you know Coleen is a distinguished member of the committee representing the CDC.
Thank you.
DR. BOYLE: Good morning, everyone. It's great that everyone is here. I'm very pleased to be reporting the work of my subcommittee, or I should say our subcommittee. As you all know, we have three subcommittees, and the one that I'm trying to shepherd through is the Subcommittee on Follow-Up and Treatment.
Just to review for you the subcommittee numbers, there's a list of the numbers. Many of them are in the room today, and those who are not will join us by phone this afternoon as we continue the work of the subcommittee.
Actually, even though the subcommittee is focused on follow-up and treatment, we've been focusing most of our energies over the last year on the issue of long-term follow-up, and by long-term follow-up, Carol Greene has been the person. I don't see Carol back there, but I know she's there. She's been the person who has most engaged us in the issue of extending the concept of long-term follow-up to include treatment. Obviously, there are a number of guidelines that you are all familiar with relative to short-term follow-up, but there's little guidance in the area of long-term follow-up. As a subcommittee, we've actually decided the best course of action in terms of trying to move this field forward is actually to try to step back and to really come at it from a fairly high level and to look at the overall goals of long-term follow-up, and actually even stepping back a little bit further, trying to understand what is long-term follow-up.
I just present here for you some of the existing definitions of long-term follow-up. The reason I'm presenting those is just to show you the variations in themes relative to what others consider the essential components of long-term follow-up. This is from the CLSI report of 2006, where long-term follow-up is defined as something that allows for the evaluation of the benefits of newborn screening. So it doesn't necessarily encompass that issue of care for individuals with the disorder, but it does, if you read down further in that definition, it does talk about a facilitation of care and services, treatment and services, but not necessarily the actual delivery of care.
This is another definition by Mike Watson in the publication from last year. It's a little bit more broad in its extent here, where long-term follow-up essentially extends the period of follow-up substantially to monitor continuously the medical management and the care coordination. Again, this is a little bit challenging in terms of trying to understand exactly what this means, but when I read it I do think of treatment as being included within that. But obviously, the second part of that statement, "long-term follow-up also allows the assessment of the efficacy, sustainability and safety," that really relates to that ongoing monitoring and evaluation of care and management for this condition and that continual feedback loop.
So in terms of what our subcommittee has been working towards, it really is trying to flesh out what long-term follow-up is and the major components of that. So we have been working with Alex Kemper, who is sitting over there, and you're going to be hearing a little more from Alex, Steve Downs, and Jim Figge, who I don't believe is here today, to actually try to develop a position paper, and that position paper really does take that much higher-level view of long-term follow-up by trying to define what those major components are and who are the major participants and systems involved in long-term follow-up. I'll talk about the next steps.
But as sort of the next steps from that, I see us sort of working our way down from that higher-level view in terms of actually trying to understand the roles and responsibilities of those major participants.
What we've done so far is Alex and Steve and Jim had developed essentially a white paper or a paper that people could react to. We had a meeting of stakeholders in late or mid-April, about a month ago, where we brought in folks from a number of different perspectives. The major perspectives are the major systems that would be impacted by long-term follow-up, including the obvious perspective of the individual and the family, primary care, specialty care, public health, the finance and regulatory perspective, as well as the information systems that will be required in terms of making such a system work.
I'm just going to present a little bit of the feedback that we received at the meeting on the 18th, and then

Alex is actually going to follow up with you and walk you through some of the thoughts that he's had and Steve and Jim have had relative to the development of that position paper. Really, the feedback that we heard from those who attended, and several of you in the room actually attended that meeting, is that these are the major components of long-term follow-up. So this may be obvious to you, but I'd just review that those definitions were the definitions earlier. You can see some but not all of these components reflected in those definitions.

So long-term follow-up includes the issue of clinical care and treatment for the long term, and the actual coordination of care and services. From a public health perspective it includes this important aspect of quality evaluation or surveillance; that is, the ongoing monitoring to assure improvement in the care and management of the individual.

Then finally and very importantly, because many of these conditions are relatively new in terms of their discovery and relatively new in terms of the effectiveness or the efficacy of their treatment, it needs to have this research platform where clinical and intervention activities can be managed.

In terms of some of the basics that we also heard, the overall goal for long-term follow-up is really to achieve the best outcomes for children and their families long term. There was a lot of discussion about the lifespan issue, and that is how long is the system responsible in terms of follow-up and management, and it was very clearly indicated that this really is a lifespan approach and that there is a critical period in terms of transitioning, particularly in adolescence and early adulthood. But because of the emphasis of this committee being that of children, our initial focus is really to the age of 18 or 21, still to be defined.

Then we also talked about sort of the broad framework or are there broad frameworks out there from which we can either borrow or steal, or are we already operating under a broader framework. Some of us, like myself, have a little bit of a challenge with these broader models and broader frameworks, but I do think they have things to offer, and obviously one of those frameworks is one of the chronic care model. But this really within the context of fairly common disorders such as asthma or ADHD that have been adapted for childhood disorders. Then there are some really disease-specific models where they're much more silo oriented, and I think there have been some benefits to that approach as well. So what we thought was that it needs to have sort of a hybrid, take some of the components of both of those aspects.

Just to highlight for you some of the issues around the major components in terms of clinical care. One of the major issues that came out was the issue of access and manpower issues, clearly in the area of specialty care, but also in the area of primary care as well. Then I think the second bullet is extremely important, and that is the need to collate and distribute best practices and existing evidence. I know through the work that's being done through the ACMG and other work that's funded by HRSA that that issue or that guidance is beginning to be developed.

In terms of coordination of care and services, this was really felt to have multiple components based in public health, as well as a component that's based in clinical care and clinical medicine. Obviously, it's the bridge between those two that's really the challenging part. It was thought by most in attendance that the medical home is really the point of coordination.

Then borrowing again from these disease-specific models, it was felt that perhaps much of the care coordination does really need to be disease specific. From a family perspective, the emphasis was that there should be a single point of contact for families in terms of care coordination.

Evaluation and surveillance. I think it was acknowledged that this is an issue that is extremely important but definitely underdeveloped. Long-term tracking of the natural history and the treatment history really are essential in terms of quality improvement, and this really is a public health mandate, and this really is an essential function for public health. It was also acknowledged that from a federal approach, we tend to be fairly siloed and that there really needs to be more federal integration around issues related to evaluation and surveillance.

From the research perspective, I think there was unanimous agreement here, although it wasn't an advisory committee function, but I think people felt very strongly that care improvement -- and I think that's how they reflected on research, as really reflecting care improvement -- is really an integral part of long-term follow-up and it needs to be built into that system. The surveillance piece of it could really allow the infrastructure for clinical research both from an observational standpoint as well as from a clinical trials standpoint.

Key to that was the translation of that information back into practice. We always talk the talk in saying that we are, at least here at CDC -- at CDC we do this a lot in terms of making sure our research is translated, but I'm not sure we're successful all the time. So this is really key, particularly in this area.

So as I already mentioned, the thoughts were leading more towards sort of a hybrid model where there's

a strong clinical component and a public health component, but the real key to that is the translation or the information exchange and how to link those two components.
Family issues and the issues related to the individual with the condition were obviously extremely important, and the emphasis really was on this comprehensive focus, not just on the medical issues of the individual but thinking about the developmental, educational and social-emotional aspects; also, the concept of family empowerment in that the family is a critical component in the long-term follow-up system and engaging them in the self-management. Then there was also a lot of discussion around providers and how providers need to be trained in terms of how to partner with families in this exchange.
Finally, we had a lot of discussion about information technology, personal health record, the importance of this from all of the perspectives, and that a personal health record or some type of information exchange is extremely important in the development of this long-term follow-up system.
So in terms of next steps, you're going to hear a little bit more from Alex and his co-authors in a few moments about the development of a position paper. I think we're still working that issue. We spent the second half of the day, actually, of the April meeting, facilitated very ably by Alan Hinman, in terms of talking about specific roles and responsibilities. Although that probably won't be a part of the position paper, that's clearly, at least as I see it, sort of the next steps from what it is that we're doing, but it was a very lively discussion around that issue.
I'm going to turn it over to Alex, and he's going to give you a little bit more on this. Or I'll be happy to handle questions if anyone has any questions, or we can handle them at the end.
DR. HOWELL: Mike?
DR. SKEELS: Actually, I have sort of a quick question for you.
DR. BOYLE: Sure.
DR. SKEELS: I'm very excited by what you're doing. I appreciate it. I feel like you're getting some traction, and this is something that I think has been overlooked for a long time.
Just sort of a quick question about the medical home as a point of care coordination. Could you say a little bit more about that? Because the medical home is a great concept, but it's not the reality for many, many families. Could you just talk a little about that?
DR. BOYLE: Alex is going to talk a lot more about that in his talk.
DR. SKEELS: Okay.
DR. BOYLE: So maybe we'll hold that thought until then.
DR. KEMPER: Just as a way to preview, I certainly agree with you about that.
DR. SKEELS: What I was really asking is whether you could share a little bit more about your committee's discussion about that. It sounds like that's exactly what you're going to do.
DR. KEMPER: Yes, and I'll make sure that I say more about that as well.
DR. HOWELL: We're pleased to welcome Alex Kemper, who is director of the Program on Health Services Research at Duke University, which is obviously a wonderful university. I went there.
(Laughter.)
DR. HOWELL: Alex' work focuses on the implementation and evaluation of screening programs for children, and so we'll look forward to hearing his wisdom.
DR. KEMPER: Well, I'll try to be wise. I can't necessarily promise that.
Last time I was here I was talking about Pompe's disease, and now for something completely different.
One of the things that I wanted to say right off the bat is any draft of the white paper that you might have seen is just that. This is really a document that's evolved, and I can most certainly guarantee that whatever draft you might have isn't even the most recent draft, because things have changed.
I've gotten lots of help, and I did list all the members of the subcommittee up here, but certainly they've been very helpful, as well as many other people.
In terms of what I'm going to be discussing over the next 15 or 20 minutes or so is some thoughts that we have around definitions of long-term follow-up, examples of current long-term follow-up programs, and then spend a fair amount of time talking about high-level conceptual models of how long-term follow-up might work and use that to bridge to what I think the next steps will be.
Again, this is going to be a very high level picture. I actually took out the picture I usually have of the international space station because I think everyone has gotten sick of that and replaced that with Skylab.
So in terms of defining long-term follow-up, I think that we can agree that it's the overarching goals to achieve the best possible outcome for children and their families. How to go about doing that is obviously complicated. In terms of the components of long-term follow-up that we've all considered, they include chronic disease management and provision of treatment, age-appropriate preventive care and health

promotion, both condition-specific for whatever the child or person might have, the individual might have, as well as the other services that that individual might need. Long-term follow-up includes those activities to expand the evidence base around the condition and treatments for the condition. I think that quality improvement is an integral process to the whole thing. Certainly we can always do better, and we need to think about how we can monitor that. Then I think that long-term follow-up is really a process that goes throughout the lifespan from the time of diagnosis. One of the things that we spent a lot of time talking about in the subcommittee meeting in terms of this white paper is where do we follow things up, and I think that the issues of transition from pediatric health care to adult health care is a difficult and thorny one, but we shouldn't lose sight of the fact that really our goal is to provide long-term follow-up for the lifespan of the individual.

So getting to the medical home, here is a picture that I actually took from Raleigh Children's Hospital. I can't claim it for my own. But of the many different illustrations of the medical home, I think that this is one of the best. I think that the Maternal and Child Health Bureau should get a lot of credit for work that they've done around issues of the medical home, and certainly key aspects of the medical home include coordinating and providing health care, preventive care, continuity of care, and single point of care. I'm not going to be talking about issues of cost-effectiveness of care. That certainly goes beyond where we've gone in the subcommittee.

Important to recognize about the medical home is it's not necessarily a physical location or any specific type of provider. It's not a specialist who can provide a medical home, or a generalist who could provide a medical home, and certainly the location of where somebody's medical home could be changes over the course of time.

Now, certainly there is a lot that's been written about and a lot that's known about the proportion of children that have medical homes and the current ability of providers to actually serve as a medical home for individuals, and I'm going to be getting back to this again, I think getting to the question that you raised earlier.

But I think before we do that, it would be helpful to back up and look at examples of long-term follow-up and where things have been successful. As I was thinking about putting together this white paper, one of the first things I thought about was the work that's done through the Children's Oncology Group. For those of you who don't know, virtually every child in this country who is diagnosed with cancer is placed into a trial, and it's led to dramatic improvements in childhood cancer. As part of the work that the Children's Oncology Group does is that they have recommendations for how to monitor for the late effects of cancer treatment. It includes some active surveillance as well, and the group has done a very good job of learning about what the long-term adverse effects are of some of the cancer treatments.

But I think there are a couple of things that we should think about that makes this different than what we've been talking about for newborn screening. First of all, the follow-up for late effects of childhood cancer is really aimed at individuals who have already completed treatment, unlike individuals who are identified through newborn screening and really have a chronic illness. The other thing is that the Children's Oncology Group doesn't specify exactly how the follow-up care should be coordinated. It lists the kinds of things that should be done and provides forms for reporting long-term outcomes, but it doesn't really say who has responsibility and whose role it is to do what.

I think another good model is the Comprehensive Sickle Cell Centers. There are 11 of them funded by the NHLBI, and the Sickle Cell Centers do provide care coordination for the children that they follow, and they conduct basic and translational research and have really helped to expand the knowledge about treatments and also helped to make sure that children receive the care that they ought to. An example of that would be trials related to hydroxy urea, and then the clinics also identifying those children who should be on the hydroxy urea therapy and ensure that they get it. But it's important to recognize that with just 11 centers, many individuals with sickle cell disease don't receive their care through these centers.

Another example that I wanted to highlight was the clinics accredited by the Cystic Fibrosis Foundation. They credit about 100 care centers, and through these they provide comprehensive care, and these CF Foundation clinics, accredited clinics, are also actively involved in quality improvement and research. So I think there are certainly a lot of things that we could learn from these other sorts of clinics, and I think that one of the issues it brings up is what is the role of specialized single-gene disorder clinics versus providing care through a more distributed model such as the medical home.

So from there I'd like to turn to model building. One of the things that I was asked was to put together a high-level conceptual model of how newborn screening ought to work, and I quickly found that it really is like building a ship in a bottle, getting this very complicated thing encapsulated. The other thing that I

learned about models is that sometimes they can behave in ways that you might not expect, and certainly they don't necessarily reflect reality, which is why I have a picture of the Titanic, the Pinto, and a model of the Hindenburg. I would certainly discourage any young child from getting a model of the Hindenburg. But I do think that although these models aren't supposed to be perfect, it is a good starting point for the development of a practical roadmap, how do we go from what we have now to a coordinated system of long-term follow-up care.

So the first thing that we all looked at was the chronic care model, and this model illustrates the relationship between the community and the health care system with a goal of providing safe and effective care that's family-centered and evidence-based and coordinated and timely and efficient. There are a couple of things I want to point out about this kind of model, and before I forget, as Coleen mentioned, it has been used to develop systems for long-term follow-up care for more common childhood conditions such as asthma, and it's also been used to rethink how well child care should be provided.

So the issues for us are that the chronic care model lacks specificity for newborn screening, such as the heterogeneity of the condition. So if you take a condition like MCAD and sickle cell disease, which require different types of therapy and different elements of intervention, it's hard to lump all those things into one chronic care model like that.

The other thing that's important is that there's no clear spot in the chronic care model for public health.

So one of the things that we developed over the course of the subcommittee was a different, very high-level model. In the center of the model were individual and family outcomes. That's what we're trying to improve. There are four things that impact these outcomes, including the condition-specific elements, elements related to the individual and the individual support, the environment and the health care system, and there are numerous different spots that you could imagine impacting on these outcomes, including support for affected individuals and their families, new knowledge discovery, care coordination, and continuous quality improvement.

If you think back to the goals of long-term follow-up that we talked about, including health promotion, chronic disease management and treatment, quality improvement and expanding the evidence base, those things actually map onto this model nicely.

So in terms of thinking about the future, in the April meeting we considered the roles and responsibilities for implementing long-term follow-up. We spent a long time talking about barriers to developing long-term follow-up, some of them which aren't modifiable and some of them which unfortunately in the short term aren't easily modifiable, such as a lot of insurance issues and those sorts of things.

We also spent a lot of time talking about the role of health information systems, which as Dr. Hinman so wisely pointed out, is really a tool and not a solution, but thinking about how we can actually use health information systems to overcome some of the barriers, and I can talk more about that if you want later.

So my goal is, I think, to develop a staged vision for the future with explicit and achievable practical goals, perhaps in the context of a logic model, perhaps not, but looking at where can we be in a year, where can we be in five years, where can we be in ten years, and I think as part of that process defining the relationship between all those who are involved in newborn screening, but specifically public health, care providers of all stripes, and researchers.

So with that, I'd like to stop and entertain questions.

DR. HOWELL: Norm?

DR. KAHN: On both the previous presentation and embedded in yours, Alex, is the assumption that long-term follow-up extends to age 18 to 21, and I'm curious as to whether your committee is considering extending the vision of long-term follow-up into adulthood.

DR. KEMPER: That's an excellent question and something we spent a lot of time on. My feeling is certainly that the goal should be long-term follow-up over the life of the individual. For most of the subcommittee meetings I tried to focus things on 18 or 21 years of age just because the transition issues are so difficult and I wanted to make sure that we could address the issues for the younger children, but I do think that it should be long term.

The other thing that I had to defer this question to Dr. Howell is how much of that is under the purview of this committee, since "child" is in the name of it.

DR. HOWELL: The charter of the committee is newborns and children. So I guess that technically we should probably address newborns and children, although obviously the adult issue is critical and so forth.

DR. KAHN: Well, I'll accept the wisdom of the committee. If at any point your committee or the larger committee decides to expand its charge, we do have at least two representatives of groups that deal with adults on this committee and would certainly be willing to contribute to a broader perspective.

DR. KEMPER: And I think, just sort of building on that, I think if you look at the history, for example, of the maternal PKU story, I think that there is a very compelling argument to look at these issues throughout the life of the individual.
DR. HOWELL: Joe?
DR. TELFAIR: It's critical when you have a discussion on long-term follow-up that you also begin to understand -- even though I know it's the purview of this committee to look at children, if you're talking about adolescents and you're talking about these issues, transition becomes a critical element. So it may be that as part of the ongoing work that you have a set of recommendations related to beyond this period that will be able to work hand in hand, because transition is critical, particularly in this area. I would say that even though I know this committee has a limit there, I am assuming that transition to adult care issues are part of that purview. If I'm wrong, please correct me.
DR. HOWELL: I think that all of us would agree that you really need to think about the whole thing through the lifespan, and I think the issue is that we're a federally charged committee and the law which created us says children and newborns. So we can get a reading on that, but I think that at the current time we really will need to focus on newborns and children unless we get the direction that that's wrong. Mike?
DR. SKEELS: I'm not sure who to address this question to, but the more screening we do, the more biological variation, the more spectrum of affectedness we see, and something I've always been puzzled about with long-term follow-up is who do you follow? I wonder if you could shed any light on that. Where do you draw the line and say this is a diagnosis? Of course, the Catch 22 is that unless you follow as broad a population as you can, you won't ever really learn where to cut off.
DR. KEMPER: I just do whatever Piero tells me to do.
(Laughter.)
DR. KEMPER: If he says it's a real condition.
DR. SKEELS: Okay. Well, now I know.
DR. HOWELL: One of the things that has come out of your comment is as this committee has discussed things, there are a variety of very clear research questions that have been addressed, and we've not talked about that, and there are things having to do with IRBs, the storage of information, and the residual blood spots, variation and so forth.
One of the things that obviously we need to be very seriously considering is research relating to newborn screening and so forth. One of the things that I would like to do is establish a working group that will look at research issues, and I want to ask Mike Watson to chair that -- Mike is somewhere here -- with me and other members of the committee, and we can talk about that as time goes along.
But the other thing I'd like to do at the current time before we hear any more comments is that many of the people here are not aware of the fact that the NIH has an active research program in newborn screening.
I think Gilian Engelson is here in the back. Could you come up, Gilian? Gilian is the project officer at NICHD for this proposal, and I'm going to ask her if she will make a few comments. I happen to know, since she works right with me, that she has just presented a few slides on the program, and hopefully she has her mass storage device with her and can show you them.
DR. SKEELS: Rod, excuse me. Can I just follow up on what I was saying? I think this is an important issue, and Coleen was going to comment.
DR. HOWELL: Okay.
DR. SKEELS: I just want to say that you're talking about research in defining what is and isn't a disorder as if it were something that happens in an academic setting. What I'm saying is that one of the purposes of long-term follow-up is to inform practical decisions about what we should be screening for, and we can't wait until research sorts that out because we're the ones that have the data. Unless we define what it is that we're going to follow and use the data to feedback and inform, research won't do us any good. Can you just comment on that?
DR. BOYLE: In terms of the work of the subcommittee and the meeting on April 18, it was clearly an issue that was discussed and acknowledged as being extremely important, and obviously gaining additional knowledge would require surveillance and follow-up on those children. So it was put out as clearly an issue of concern and something we need to follow through on.
DR. HOWELL: Maybe Gilian would be good enough to make a few brief comments on what the NIH is looking at. But the bottom line is that the NIH vision would include the things that you're talking about, clearly involving the public health level and so forth, without question, and not in some isolated lab on the

10th floor in Bethesda.
Gilian?
Gilian Engelson, I might point out, as you can see, is a Master's of Public Health in NICHD, and she's a project officer for the current research program in newborn screening.
MS. ENGELSON: Obviously, I'm going to talk about the newborn screening research efforts at NIH. Here's just an outline of what kind of interests there are at NIH that are relevant to newborn screening. I would say NICHD would be the lead institute for newborn screening, but there are various other institutes that are interested in specific conditions that we screen for, such as NIDDK for metabolic conditions and hemoglobinopathies for NHLBI, and hearing impairment for NIDCD.
This kind of gives you a general outline of what our research priorities are. We're definitely interested in translational research, development of screening technologies and improving therapies of screenable conditions, ones that we screen for currently and ones that we hope to screen for, looking at the natural history and long-term outcomes of treatment, and behavioral and social science research.
We have one current funding opportunity that is out right now. This is open until 2009, and it's really focusing on the development of therapeutic interventions for conditions that we screen for currently and ones that we hope to screen for, as well as just supplemental treatments.
We have three different types of funding mechanisms. The R01 is the standard NIH grant, and then R21s and R03s are more exploratory. There are three application deadlines each year, and this is co-sponsored by NIDDK and NIDCD, and you can go to grants.gov for more information on that.
Through our program announcement we've awarded several grants through this funding opportunity. A few of them are based on galactosemia, one is on SMA, one is on hearing loss due to CMV, and one is on globoid-cell leukodystrophy.
In parallel to these grants on therapies, we also are looking at novel technologies in newborn screening. In September of 2006 we awarded two three-year contracts to look at the development of creating comprehensive multiplex technologies. One went to the University of Washington with a PI of Ron Scott, who is looking at tandem mass spectrometry to expand to lysosomal storage disorders. The other one is going to Ken Pass in New York State utilizing the Luminex bead array technology. Right now he's kind of looking at conditions that we currently screen for, but the expectation of both of these technologies is that they'll expand to other conditions beyond what we screen for.
So Bob mentioned this translational research network, and we hope that the two funding opportunities that we have, the contracts and the grants on treatment, will kind of flow into this translational research network. We can validate these technologies and treatments, as well as provide increased access to dried blood spots and other samples for researchers. We also want to look at longitudinal health outcomes which kind of link to the long-term follow-up issues that you guys had mentioned, and all this has to be linked in some way through informatics systems.
In doing all of this, we realize there are a lot of policy issues relating to informed consent, IRB issues, state policies relating to how to use dried blood spots for research. This pretty much tells you that we want to tie in the public health programs with the clinical researchers, repositories, as well as databases. This might give you a general idea of what it might look like. This is just a general concept. We hope this might link in with HRSA's regional collaboratives, but to pull together the grants and the contracts, investigator-initiated grants, and have one coordinating center to link them to the clinical research centers and state labs and diagnostic labs, as well as current registries and other databases and repositories.
One side project that we're working on which the National Library of Medicine is really taking the lead on is Information Rx, which are essentially prescription pads for information for health care providers. The education subcommittee had a presentation on this by Cathy Fomous at NLM. They're essentially prescription pads where, if a family gets a diagnosis or a screen positive for a condition, the health care provider can just write the name of the condition down on this prescription pad, give it to the family to go to the website and get more information that is authoritative and consumer-friendly. There has been direct outreach by AAP and ACMG and ACOG, as well as AAFP, and there's a website address for information on how to purchase these pads, actually get them for free.
Lastly, how can the advisory committee help? NIH definitely welcomes your guidance and advice on what research needs are in newborn screening, as well as the development of this translational research network, what the infrastructure might look like, what the components might be, linkage to public health programs if we need to do that, policy and legislative issues, as well as ELSI issues and any other advice you may have to offer.
That's it.

DR. HOWELL: Thank you very much, Gilian.
Any questions of Gilian?
DR. TELFAIR: Thank you for presenting. The area you mentioned that you are interested in is in launching new outcomes. You also had some of the areas of social and behavioral sciences, and then you mentioned ELSI issues. The committee that I sit on actually covers a lot of that in the work that they do in terms of concerns. I was wondering if you could say a little bit more within those three contexts what it is that NICHD is interested in related to screening in those contexts, like longitudinal outcomes that are science related, as well as some of the ELSI issues.
MS. ENGELSON: I think we keep it rather broad in terms of that we certainly want to see how newborn screening results might impact the families. Of course, informed consent issues, how best to educate them about newborn screening and how they might respond to the services that newborn screening programs provide. It's a whole slew in terms of behavioral and social science issues, how diagnosis of some of these conditions that may have behavioral treatments in the long term, if we ever get to that point, where we don't necessarily have a medical treatment for it, may be advantageous to the families.
DR. HOWELL: I think it's also, as Gilian listed on the slide, when NICHD gets a grant relating to newborn screening specifically that has certain other aspects, it might be jointly co-funded with one of the other institutes. They might go to NHGRI or things of that nature to co-fund some of those things. But I think that the charge is very broad.
DR. DOUGHERTY: This is all very exciting, and if I'm allowed a little advertising, AHRQ just came out yesterday with its Federal Handbook on the Use of Patient Registries that is a 219-page document, "Registries for Evaluating Patient Outcomes, A User's Guide," and it addresses the IRB issues and other research issues, and it will be out in hard copy in two versions soon, one the full report and then a 13-page summary that will contain a checklist for registry developers. So I'll leave some of these press releases at the table downstairs. I hope we can work together using some of the work we've done. It was co-supported with CMS.
DR. HOWELL: The reason that I asked Gilian to do this is that it's obvious, as you start looking at the long-term follow-up and so forth, that there's an immediate need for research in all sorts of areas, about the diseases, the families and so forth. So I think the time has come, as we're thinking about long-term follow-up, to also think about what are the important research questions and try to get that conveyed to the research funders; i.e., the NIH and others, to try help support that.
DR. TELFAIR: Can I just make a point on this matter? I'm sorry. It's actually a point to the committee. Thank you.
I know, again, going back to the point that was brought up earlier about the purview being that we stop at children, I would say and actually I would argue that if you're going to look at issues of long-term follow-up and you include the family in that matter, that you do have to take a long-term perspective to really do that, because the ecology of the family is broader than just that. So this is just a point for the record.
DR. HOWELL: I think a good point. Again, the NIH obviously can set its limits where it chooses, far outside this committee, and I'm sure they will regardless of any comments we make. But I think that the group will be responsive to suggestions about key areas. I know from talking with Gilian that one of the issues that's come up with some of the awarded grants and contracts at the current time has been significant problems with IRB clearance of some of the things that one might like to do. So the IRB issue becomes very important to try to figure ways to make that efficient.
Jana?
MS. MONACO: Yes, I just again wanted to comment with what Joseph was saying. Is there any allowance at all to look at the current adults that are living with the disorders to benefit the research that's being done on children and for the long-term follow-up? Has that been addressed in your subcommittee?
DR. BOYLE: In terms of the issue of the lifespan approach, I think we have heard from all perspectives that that's very important and that there are critical points of transition that are also to be highlighted. In terms of the specific agenda in terms of looking specifically at adults, we haven't gotten into that detail yet.
MS. MONACO: I'm just curious, because obviously they got to adulthood for a reason prior to a screening, and it would be nice to learn how did they, under what conditions and circumstances did they reach adulthood without, or if they did have problems, how they were managed over time.
Then I just had another comment going back to the medical home issue. Was any troubleshooting done to overcome those barriers or to suggest getting over those barriers? Because we just had a NYMAC regional collaborative family conference, and we all did surmise that the medical home, like Mike said, is

a great concept, but in reality it's not really a work in progress the way we would all like to think it was.
DR. BOYLE: In terms of your first point about looking at success stories, I think that's an excellent idea. Again, I think it gets back to Rod's idea of really trying to highlight important research-related activities, and I guess I would differ a little bit from what Rod was presenting in that I feel like we can learn a lot from surveillance data, observational data. It doesn't have to be necessarily -- once we create a program or once we create a follow-up program, there's a lot to be gained in terms of knowledge, and that type of knowledge. But in terms of the medical home, again I feel like we're really at the beginning in terms of thinking through this issue. So all of these challenges that you all are posing are things that have been brought up within the confines of the committee and at the April meeting. In terms of actual development of ideas in terms of solutions, I don't think we're there yet.
DR. HOWELL: Before we break, I think I'd like to ask Tracy if he would comment at all on the medical home, because certainly that's been an area of interest and focus of the American Academy of Pediatrics.
DR. TROTTER: Yes, absolutely. We're finding, unfortunately, the same thing everyone else is finding, that the concept is wonderful and the reality is difficult. But it is a priority from the Academy, and a priority of all primary care people is to try to be that home, and a big thing that's going to impact that is the educational component of groups like this and ACMG and the National Coordinating Center to help primary care folks feel comfortable being that medical home and being the coordinator of that care. It's a group effort, and it certainly is in progress, I guess I would say.
DR. HOWELL: Norm has a comment.
DR. KAHN: Yes. Thank you for bringing us back to the medical home and giving credit to the American Academy of Pediatrics, which created the term in 1968. So it's been around for a long time, but it's really beginning to catch on. I would just like to contribute to the committee that there are now recently a joint set of principles on what constitutes a medical home. They're not oriented toward children with special needs. They're oriented toward a primary care base to the health care system. But the American Academy of Pediatrics, the American College of Physicians, the American Academy of Family Physicians, and the American Osteopathic Association recently adopted joint principles on what constitutes a medical home, and I'd be happy to submit them to the committee.
DR. HOWELL: That would be very helpful.
Before we break, and we're anxious to break, Coleen, is there anything specific that this auspicious group can provide to your committee as you proceed to do good work?
DR. BOYLE: Well, I'm hoping that by the time we meet next September, that we'll actually have some type of white paper, position paper, that we can have in draft for you from the committee.
DR. HOWELL: Bonnie Strickland apparently would like to say something. Is that correct? At least Michele tells me that Bonnie Strickland wants to talk.
DR. LLOYD-PURYEAR: We're encouraging her.
DR. HOWELL: Okay. Do you want to come to a mike, please, Bonnie?
DR. VAN DYCK: Bonnie has a lot of responsibility for the medical home in the Bureau.
DR. HOWELL: Okay. We would not want to omit HRSA. We might not get lunch.
(Laughter.)
DR. HOWELL: Do you want to turn on the microphone, please, Bonnie?
DR. STRICKLAND: Thank you. I don't know if I want to have the notoriety of having a lot of responsibility for medical home. We have been working on medical home for a long time, and I think it is a work in progress. The Academy, as has already been mentioned, has taken on a lot of that responsibility in pediatrics. Actually, I think in my mind it is more than a work in progress. Our national survey of children with special health care needs and our national survey of children's health, which was a national survey of families, over half of families say that they do have a medical home. So half isn't good enough, that's for sure. This is families of children with special health care needs and families of all children in the National Survey of Children's Health.
I think it's an interesting concept for long-term follow-up because for us it's grounded in the child's source of primary care with co-management and coordination with the subspecialty. So everyone is responsible, not just one person, but it promotes well child care, and we all want to think of the principles of children first, not disease first, but with a strong emphasis on co-management.
The only other thing I want to say is there are a lot of models emerging now. Jim Perrin, who spoke earlier, heads our national initiative on developing the evidence base, finding the evidence base around medical home, and he's just completed a literature review that is fairly promising around the characteristics of medical home. So I think we're on the right track. I think that the subcommittee really

should consider looking at medical home in the chronic care model as a viable framework for long-term follow-up. Thank you.
DR. HOWELL: Thank you, Bonnie. It's encouraging.
Joe, can you be quick?
DR. TELFAIR: Yes, really quick. I just want to remind us that in the notes of our subcommittee, Dr. Richard Antonelli presented on this issue of medical home and the issue of care coordination in terms of the practical aspects and the things that people are having a problem with. He addressed a lot of very practical, ground-level issues that I think are already in our notes. That's just for the record.
DR. HOWELL: Well, it's encouraging that this long-term concept does seem to be catching on, as we've heard from our colleagues here.
We'll take a break now and we'll resume at 10:50. So we'll have to move quickly to hear about the regional collaboratives.
(Recess.)
DR. HOWELL: One of the extraordinarily important programs that has to do with all aspects of the newborn screening effort at the current time is HRSA's regional collaborative newborn screening efforts and so forth, and Steve Downs, who is director of general pediatrics and children's health services at Indiana, is going to present the long-term follow-up project within his regional collaborative.
Steve?
And also Rani Singh is going to be presenting later.
DR. DOWNS: Thank you. I'm a little overenthusiastic about my work, and so I have much more to talk about than I can possibly squeeze into the fair amount of time. So you'll forgive me if I zip through this a little bit fast. I am merely the figurehead for a large group of people at the Children's Health Services Research Group at Indiana University at the Regenstrief Institute, which is our important partners particularly in the informatics work here, and I'm going to talk about a thing that we call adaptive turnaround documents and how they can be used in newborn screening and promoting a medical home with respect to that.
I'm going to talk about, if I can move fast enough, two aspects of the same project. The first is regional health information networks to improve newborn screening and follow-up, and the second is data standards to ensure newborn screening results. The second one is really a prerequisite for the first, as I hope you'll see when I'm done. This, of course, is supported by a grant from the genetics section of the Maternal and Child Health Bureau through a Region 4 genetic collaborative supplemental grant. I should say a lot of this work is also built on top of a grant from the Agency for Health Care Research and Quality that went to the Regenstrief Institute that provides some of our information systems underpinning.
This is all stuff you know, so I'm going to blow past it pretty quick. We know that expanded newborn screening largely due, but not entirely, to tandem mass spectrometry has resulted in the potential to screen for well over 50 conditions. We know that screening for these has the potential to prevent morbidity and mortality, and it may even save costs overall to society. But there are some challenges because most of the conditions are quite rare, and therefore the physicians who are particularly the primary care physicians are unfamiliar with most of these conditions. Families need guidance when there's a positive screen. Diagnosis and treatment have to be timely or we're not going to achieve the benefits that we're trying to achieve. This leads to a question that most newborn screening program directors tell me is a major challenge, which is where is the baby? When there is a positive screen or a questionable screen or a missed screen, it can be a challenge to find where the baby is to make sure that the response to that problem is timely. As we've discussed a little bit, we don't have any formal mechanisms, at least at a national level, for long-term follow-up.
One of the solutions that we are working on is the use of a regional health information network. Now, we have a regional health information network in central Indiana, as I'll show you. These things are beginning to be developed in other locations as well, and so what we're talking about here is a pilot project for kind of a future world, as you'll see. But once we have a regional health information network in place, we need a way to provide two-way communication with primary care providers.
So our project objectives were to use adaptive turnaround document technology, which I'll describe in a moment, to facilitate communication between newborn screening programs, subspecialists and the medical home to provide just-in-time information to primary care clinicians and families to reduce the risk of missed opportunities to screen, and to facilitate the tracking of children with detected conditions.
So what is an adaptive turnaround document? It's a computer-generated sheet of paper that delivers tailored information from one place to another. It's scannable so that it can capture structured data directly

into a computer using a scanner, using a fax machine. What does this mean? Well, imagine that when a positive newborn screen is found, that a physician who has no other information technology beyond a fax machine receives a fax like this that indicates that the child has an elevated C8 and there's concern about MCAD? In addition to that information, there is information provided to the physician as well. This is taken right off the American College of Medical Genetics' ACT sheets, but it could contain any information that was deemed appropriate that tells the physician what to do immediately.

In addition to this, we have a section at the bottom that gives the physician an opportunity to indicate what was done about that problem. So, for example, the newborn's clinical status was assessed, the infant was stable at the time they were seen, the family was provided the attached educational materials that came with this notification, a plasma acylcarnitine has been sent, and referral has been made to a metabolic center. Note also the physician might just as well be able to indicate that the family could not be contacted or this is not my patient and you need to start looking elsewhere.

Well, in order to generate a form like this, we need to have a knowledge base which is indicated on the left side here, where a set of if/then rules can inspect a database of newborn screening results and if something is found can put this information on a form that can then be sent out automatically to the physician, including correcting this information. Now, if the physician checks off what their follow-up has been and whether they've been able to follow up and use a fax machine, then that information can automatically go back into the newborn screening tracking program so that similar notifications can be provided to newborn screening staff and appropriate responses can happen.

So how do we apply this adaptive turnaround document technology on a regional basis? We're using what's known as the Indiana Network for Patient Care, or the INPC, which I'm going to describe briefly, and I may have to skip through some of these slides so I don't consume all of the time this morning. But the INPC involves five hospital systems, which include over 15 hospitals, county and state health departments, RxHub, which is a prescription clearinghouse, and Medicaid administrative data. This slide is old. This understates that there are over 660 million results stored so far.

This is the State of Indiana, and the box shows the region that is currently covered by the INPC, although it's gradually expanding and we hope over the next five to ten years will involve the entire state. I don't expect you to be able to read them all, but each of the little dots on here represents a participating health care organization.

How is this accomplished? We have implemented this -- and when I say "we" meaning the Regenstrief Institute -- has developed what's called a federated repository, and in this model data from different sources, different hospitals and clinics and so forth, are stored in separate physical files, and a global patient index links the data about a single patient among all of these different files. The files have the same data structure and a data dictionary so that they can be combined when they're needed. Data arrived by HL7, which is a communications standard that some of you will be familiar with but probably not all of you -- I'll talk about that in a little bit -- those messages are parsed, translated, and deposited in their respective databases.

So here's kind of what that looks like. This illustration talks about immunization registries, but you can imagine that you might have an immunization registry and an electronic medical records system, and then you have a global patient index. So whereas the immunization registry has its own medical record number for Jane Dow, and the electronic medical records system has a different number, the global patient index takes each of those and stores those within that index so that they can be linked together. The other component of the system is a concept dictionary, and the concept dictionary says that even though each of these organizations may store their immunization under these various names, the concept dictionary has a set of coded terms that map to each of those names, and it applies those to the each of the different files so that, again, there can be a comparison made between the two.

Now, if you've got those two things, the global patient index and a concept dictionary, then you can add in multiple different sources, and that's the way the whole Indiana Network for Patient Care is organized. What we are doing is taking advantage of this and a particular information delivery environment that exists through this system. It's called Docs4Docs. Docs4Docs is a results delivery system. It's designed simply to deliver the potassium level on this patient, on this date it was this, and send it to the physician who ordered it. The way this works is all the hospitals send all their laboratory reports through the same mechanism, this system called HL7. HL7 results messages flow through this Indiana Network for Patient Care, they get grabbed by this Docs4Docs system and sent by fax or through secure inboxes to the physicians who ordered them, and this eliminates mailing costs. The reason I mention this is because that creates a business model for operating this thing. It saves all the laboratories and hospitals delivery costs.

This is what an HL7 message looks like, and I'll let you study it. I just want to show you that these are actually, believe it or not, somewhat human readable. The OBX here means that what follows is a bunch of clinical observations. Here's an example of a clinical observation. It has a code number, it has a short name, asthma without status asthmaticus not otherwise specified, and it tells you what vocabulary that code number belongs to, in this case ICD-9, which I'm sure any of the physicians in the room are familiar with.

So the way this works in our environment is this is as close as I could get to a newborn. But the newborn blood spot sample is sent to our Riley Hospital's newborn screening lab. That information is sent actually in a proprietary format to the Indiana Network for Patient Care, which converts it to HL7 so that it can be sent to the Indiana State Department of Health's newborn screening data repository. At the same time we generate an appropriate adaptive turnaround document message if there is an abnormal or if a repeat is needed. So the physician will receive something similar to what I showed you.

The primary care physician who sees the baby can then respond to that, send it through a fax machine, and it goes back to the Indiana Network for Patient Care, where we have a repository and where subsequent messages can be forwarded to the Indiana State Department of Health.

There are three ways that we foresee these adaptive turnaround documents enhancing newborn screening programs, providing just-in-time information to the medical home, preventing missed opportunities to screen, and to facilitate long-term tracking of children with identified conditions. So the just-in-time information to physicians, we've looked at this, so you have a sense of what that's going to look like. Just-in-time information for the family is something like this that arrives in the physician's office so that they can pass this on to the families. This particular one I'm not happy with. We're working on the literacy level, but the idea is that physicians can deliver information to the families so they know how to respond to the particular abnormal result that they receive.

Avoiding missed opportunities is probably, in my view anyway, the most exciting and the most complex project that we're undertaking. You'll recall that the Indiana Network for Patient Care is continuously receiving HL7 messages throughout central Indiana. We can capture the HL7 messages from neonates who were seen for any reason, ER visits, well-child checks, laboratory tests, physician visits, and we can check those against our newborn screening reports to match those children, and we can alert the physician who is seeing that child at that time if there's an abnormal or a missing screen. So we can tell the physician, by the way, this child has not had their newborn screen yet, you should do that right now, or we can say this child had an abnormal screen, do that right now.

So the hard part about this is receiving a message from out in the world and deciding whether or not this is a child that's in your newborn screening registry. Recall what these HL7 messages look like. We're looking at a particular segment, in this case called the PID segment. That means patient identification segment. It has information about the patient that we extract and stick in a database. It also has this segment, which we call the MK1 or next of kin segment. This has information about mom which we extract and put into our database. Now if we have a different record that came from a different HL7 message, some things are not going to match. Baby Doe may become John Doe, and ethnicity may not be reported in a particular thing, or the phone number may have changed. But you'll notice that all of the other things do match.

So what we do is we use a probabilistic scoring scheme to figure out which records belong to which child. So imagine you have two files that have 10 medical records each. That would mean there were 100 possible combinations of records if you paired them up one by one. If you sent a human in there as the gold standard to figure out which of those matches were real and which ones were not real, you might find that 10 of them were true links. That is, 10 of the people in each of those potential pairings were actually the same person, and 90 of those pairings were not. And if you looked among the true links and you found that the last names matched in 9 out of 10 of those, and they didn't match in one because of a misspelling for example, that would mean there is a 90 percent agreement rate for last name among all of the true links. Likewise, if you looked in the 90 that didn't match and you found that two of them by random chance happened to have the same last name, you'd say that there was 2 percent agreement for the last names among the non-links.

Now, if you take those and you find a record that agrees on the last name, that's 45 times more likely to be a true link than a non-link. If you repeat that process by applying these weights for every field in the record, you can develop a score, and likewise if they don't match you have a negative score calculated in a similar way, so you can decide whether or not a patient is the same or not. We've applied this process to the newborn screening data and the HL7 data, and I just don't have time to explain what all this is, but

this little crescent right here represents children who were seen out in the world but for whom we could not find a match in the newborn screening data.
Now, some of that turned out to be noise because hospitals all over central Indiana do not always send perfectly formatted HL7 messages, but I can tell you that within a one-month period of time we found roughly five children for whom there was no newborn screen on record, and on human review of those records we were not able to show that those children had a newborn screen.
Now, the last thing I want to mention that we can do with this is facilitate long-term follow-up. Once we know that a child has a particular primary care physician, on a regular interval we can send that physician a letter like this asking for follow-up of that child, and we ask them to fill out information so that if they're no longer seeing the child, there's a chance we may be able to get follow-up information from that, and we can read that by optical character recognition. We can find out when they were last seen; we can ask a few simple questions. I don't think you can ask too much of the busy primary care physician, but we can find out if the developmental follow-up and the growth follow-up were normal and whether or not they'd been hospitalized, and how many times. This is an example of something that we might look at for MCAD, for example.
Now, I'm going to wrap up now because I'm sure I've gone over my time, but I want to mention this one other aspect of the work that we're doing, and that's the development of a LOINC standard. LOINC stands for Logical Observation Identifiers Names and Codes, and this is a standard vocabulary activity. I have to tell you this is the world's most boring work, but it might be the world's most important work in the informatics community.
Most clinical labs are able to send laboratory data by HL7, but they use idiosyncratic codes, whatever they have developed internally, so other computers don't understand them. LOINC codes are universal identifiers for laboratories and clinical observations. They facilitate the exchange and pooling of results, and it interdigitates with SNOMED, which is another disease classification standard.
So our current coding is idiosyncratic. Each lab has its own system, including ours. It's condition based. That is, the original data that led a geneticist to decide the child screened positive for a condition gets lost because we're not capturing the original data, and it's too interpretation-dependent. It's non-standard. If one state uses one cutoff for an analyte, it will be different from another state.
This is what it looks like in the Riley lab. They have these codes that are somehow supposed to embed what the analyte was, but they're inconsistently done, and the information it provides was that this analyte was increased or decreased above or below a particular cutoff point rather than telling us what the value actually is.
What we're working on is a code that's just a number. There's nothing meaningful about it except that it's indexed to a particular number. It tells us that we're looking at decanoylcarnitine on a blood spot. So it defines what the test is and it tells us what units to expect. So if we attach that code number to a value, we now know exactly what the output of the tandem mass spec was.
The advantages of using LOINC is that it's an accepted coding standard by the Office of the National Coordinator of Health Information Technology, and that's necessary to share data on a federal level. The data supporting interpretation is shared, so we're not stuck with whatever a particular state decided was a positive or a negative. So they're comparable. And it allows us to pull together national cohorts based on analyte values. So that makes it possible for pooled data, optimizing cutoff points, a lot of the work that Piero Rinaldo has been pioneering here, recruitment for trials based on analytes rather than based on an early diagnosis, and the natural history studies based on a consistent case definition now becomes possible. So we think this is going to be a sine qua non for really pulling together a federal registry of this kind of information.
With that, I'll call it quits.
DR. HOWELL: Thank you very much, Steve.
I think in view of the fact that we were a little late returning from the break and we're a little behind, I'll ask you to direct your questions to Steve after the session and so forth. I think we'll move along.
We're going to hear next from Dr. Rani Singh, who is assistant professor of human genetics and pediatrics, and director of the genetic and metabolic nutrition program at Emory University. She's going to tell about a project that's going on in SERGG.
Rani?
DR. SINGH: I do want to thank the committee for giving me a chance to share this project we are getting ready to undertake. We are not as advanced like Steve just mentioned in terms of how far stage we are, so we are really starting from the very beginning in looking at this. But I'm very excited as a clinician to

see the way newborn screening is going, to share the model from going from a reactive disease model to the one where we actually can do the proactive intervention in these newborns and not have to start the treatments when the disease had already started and some of the damage has already occurred. It's been very exciting with the new expansion. We sometimes have difficulty ourselves recognizing if it's the same disease, and it's wonderful to start intervening before any of the damage has already started. So it actually gives us a first-time opportunity for health promotion and disease prevention.

This is a slide from Dr. Rinaldo which many of you have seen, with expansion. These are complex diseases requiring lifelong interventions, and there are many gaps in terms of training and clinical knowledge of these diseases. I can't help but share with you one of the gaps as a nutritionist. We realize that all these in red require nutrition intervention as a potential for management, and we felt all the dieticians or the clinicians were really not trained at this time in this, but it's a lot more complex than that, as we heard earlier today.

So moving on, we felt that in our initial first two years of a region, that as we are moving nationally, the growing need for tracking, for long-term follow-up, even the definition was an issue where we felt the long-term started at the point of initiation of treatment. With substantial long-term follow-up, some states in a region were stopping at 18, others are grappling with transitioning. So it was a real eye-opening experience for us to group together and discuss this.

We realized there were inequities among our states in long-term management of disorders, and even in the diagnostic laboratories in terms of how far we go with diagnosis to really ensure some of the disorders as we are evolving. There was lack of information, training, varying resources and access to care. Poor transitioning throughout life was very definitely noticed, poor care coordination, and lack of data tracking to build evidence. So we definitely felt this is a project that we really want to focus on. So I'm going to share with you a little bit of our vision and some of the project activities we have planned to address these needs.

We all definitely agreed that whatever system we develop must integrate the public health infrastructure and the private sector, and we heard the importance of public/private partnership all morning. We definitely feel that the co-management concept came out in our discussions very strongly with medical home. As someone had asked the question earlier, in our region it really felt that it has to be co-management, and there were different models of co-management which are workable and others which are not working. So that's one of the goals of this project, and Alex Kemper in our region would be chairing that aspect of the project.

Transitioning, emergency preparedness issues have been a focus of our region. We feel that providing timely management and treatment services are important to develop data systems for monitoring outcomes and quality improvement. We feel that we must start utilizing robust communications to facilitate and maintain access to services, and our region had developed a telecommunications system among professionals in the last cycle, but we are hoping to move on more into telemedicine and sharing with other clinicians and providers or stakeholders as we evolve to share the knowledge as we go along.

We also feel that whatever system we develop, we want to acknowledge and remain flexible to accommodate rapid technology and knowledge change and really spend time thinking through the first couple of years what kind of systems we want. In order to do that, our biggest goal for the information system we are envisioning to be able to provide the care coordination, address the stakeholders' information needs, and create data linkages not only within our own system but also in the systems which are already existing, and also try to build evidence for standards of practice and infrastructure for research.

So the challenge is how are we going to do this? This is our vision. We feel that the public health infrastructure of already screening is pretty strongly placed in the public health structure, and at this time our project will focus on tandem mass spec diseases and hemoglobinopathies, particularly in transitioning with hemoglobinopathies, and that's the next thing from Dr. Jim Eckman you'll be hearing about. I will be focusing more on the tandem mass spec diseases.

So we feel that the follow-up infrastructure must interface with this, and we see that in our region, doing the evaluations, that we have come quite a long way in terms of connecting the screening piece and the short-term follow-up piece, and we benefitted a lot by our collaboration with Dr. Rinaldo's project on this in terms of trying to standardize some things that really boosted and facilitated our region to move quickly and start seeing that this partnering was helpful. But I feel that in moving on, we all acknowledge that the follow-up system, followed by confirmatory testing and diagnosis and treatment and management, is where we need strengthening and to work towards information sharing and closing the loop and

constantly providing feedback not only for outcomes and evaluations on an ongoing basis, but building the infrastructure for the future research. We feel this gives us an opportunity all the way from newborn screening throughout life, which is what the need came out in our region. So at least we'll get the process started at this point.

We feel that the technology today could help us bridge this, and we will be collaborating with Public Health Informatics Institute to use the technologies to try to start bridging this. We have formed a strong lab core or a lab workgroup looking at the issues. We'll be moving on to looking at the diagnostic issues, quality control issues with the diagnostic concept, and the long-term follow-up workgroup which will focus on the treatment and management aspect.

Moving forward, we feel that the system is not just connected among the newborn screening piece only but we will have a core on medical home, like I indicated Dr. Kemper would be chairing that aspect of it. We have got consumer and family groups involved. We hope to build a system which will address the needs of clinical services, emergency rooms, pharmacies, policy and legislation.

So our planned activities at this time, there are four activities, and I'm going to address three. The fourth is the hemoglobinopathies. The first phase will be in partnership with the Public Health Informatics Institute. We will utilize all the stakeholder groups to ascertain an information system to basically identify what the needs are for practitioners, patients, state public health departments and consumer groups. We'll start a very tight dialogue with guidance from Public Health Informatics Institute.

This is not my area of expertise, but this is a model, the phase model, an illustration of the model which Public Health Informatics Institute would be using the principles and approach in order to come up with the needs of that information system.

So we will charter the project and recruit the participants. Basically the first two years we'll be looking at the essential functions of the information system. We hope to start implementing in year 3. Year 4 will be coordinating and tabulating all the positive cases, and we have actually started already. This process is already ongoing as we speak. This was the collaboration which we did with Dr. Rinaldo for all the positive cases for laboratory, but we are in the process of building a Web-based access to all our states where we would build on that already-existing information we are collecting, which we will continue to share with Dr. Rinaldo for his project but also use that information to build the new concepts and ideals, what are region is looking at, and we'll build the evaluation piece in that.

Our second activity will focus on the treatment and management protocols. We'll be looking at both nutritional and medical management plans. First we'll gather all that's ongoing at this time from every state, what the principles are, and all these results we'll start sharing, and that in itself, when we were doing the laboratory piece, it resulted in a tremendous amount of knowledge and consensus how we all realized what are the areas which need more looking, and we benefitted from each other's strengths at that point. We hope to use that information to start really the evolution of the best practice models in these diseases from newborn screening.

So again, we would start with the process of current assessment, what's already happening, but we also will stay very open in the second year. Once we have collected the protocols and strategies, we will see what's happening nationally. The mountain states have already done some work, and Oregon already has a database. So we'll see if what we have collected can be merged not only within the region but also outside the region to come up with our best practice models and nutrition plans. So both these models will be piloted and evaluated and distributed throughout the region through the system.

The last activity we feel we want to start building evidence. We want to start acknowledging practices which we are doing currently, do they have evidence in the literature. So we are going to start a regional journal club because we are already building a telecommunications system in our region where we can, without traveling, talk to each other on the computer. So we hope to start a journal club with each disease at the time and start documenting what evidence already exists, what practices are already currently on evidence, and what is just being done intuitively based on the clinicians, because there are a lot of diseases at this point where we are not sure we have built all the evidence. So this will help us identify and involve all the health professionals. This will be open to all the genetic health professionals, both from public health and from academic institutions.

So having done that, this is actually what I already told you. We'll develop a model which we can share both regionally and inter-regionally. I won't go into this. This can be integrated with the differential short-term, intermediate and long-term outcomes. But basically what we hope to see with this project, at least we'll initiate the components of the newborn screening information system as a resource for improving care coordination. We'll try to put in place a data tracking system which will include positive cases beyond

the biomarkers for management that are currently being used and the diagnostic resources that are available, and we'll try to start building an evidence-based library which will help us to not only provide immediate resources for natural history but also offer an infrastructure for future research.
We'll be partnering with other organizations like Genetic Metabolic Dieticians, and we have already talked to American Dietetic Association. They have a huge strategy in place for building evidence, and two diseases they'll be working with us on is PKU and MCAD, and that can be distributed throughout the world through the evidence-based library. Then, of course, we will build the management protocols which will be easily accessible to all the stakeholders with this information system.
So with that, I will thank you.
DR. HOWELL: Rani, thank you very much for a very nice presentation.
I think we will move promptly on to Dr. Eckman, who is professor of hematology and oncology at Emory University. He's going to discuss his long-term follow-up effort.
Jim?
DR. ECKMAN: Before we get started, apropos of the earlier discussion, I have two confessions. One, I'm an internist. I take care of adults and not children. Two, I'm a hematologist, not a geneticist. I want to thank you for the invitation and really thank the genetics section of the Maternal and Child Health Bureau of HRSA for thinking about childhood in a very broad sense. I'm going to tell you today, I think, why I think that's so important and talk about some SERGG initiatives in sickle cell disease.
I have to tell you a little bit of history to tell you where I'm coming from. I started this journey in 1978 when I went to Georgia to take care of sickle cell adults and looked at what we had available, and at that time there were a few states that were doing pilot projects, particularly New York, which was developing data to suggest that newborn screening would be a great idea for sickle cell disease to improve the prognosis for individuals detected.
When SERGG formed, we had a sickle cell workshop, and a group of us came together and we convinced the group that that was a good priority. Out of that came a HRSA-funded project that established a task force that was led by Mary Harris, a Ph.D. geneticist, Tom Kenny, a pediatrician, and myself, an internist, and we decided that we would try to bring newborn screening to all of the states in our region as one of our priorities.
We struggled, and four states actually started working on statewide newborn screening programs in the early '80s, and then when the PROP study was funded and the NIH had a consensus conference, it was decided that all states should do newborn screening with sickle cell. CORN at that time got together a working group immediately, the day after the consensus conference, sat down and outlined what these programs should look like, and that became the template for the funding that rolled out through HRSA.
The task force helped all of the states in our region get up and running, and we extended our services to six other states in the nation, and all of those were states that developed very early on newborn screening programs.
The next slide shows why that is so important. This is the most recent data from Texas showing the impact of newborn screening on sickle cell disease. This cohort over here on the left shows that 85 percent of sickle cell disease patients now are surviving to adulthood. When I came to sickle cell, the opposite was true. Most of the patients were dying in childhood.
The importance of cohort studies is shown here. Here's a long-term follow-up of patients followed in Jamaica early on, before prophylactic penicillin, and later, after prophylactic penicillin, compared to the Texas outcome. You can see that there's actually not just the improvement in newborn screening but there seems to be continuous benefit at all ages for individuals that are detected in these programs.
We looked at short-term outcome over three years and found that sickle cell patients who were diagnosed in four states in our region through screening actually had a better outcome at three years than our infant mortality at the same time.
Well, this data was really encouraging, but now we have a large number of adults who are successfully getting through childhood and have to deal with the disease, and there are some real challenges for them. The disease exacerbates in the late teens and 20s, both in terms of frequency of pain crisis and we're now publishing a series that suggests there's a fairly high death rate in the 20s from sickle cell disease. Many of our patients do well medically but they don't develop the best adaptation for their disease. I'm an internist and I see this, and I see behaviors in the adults that I wish were extinguished early in childhood. They lack independence, they have learned helplessness, they exhibit chronic illness behavior rather than chronic healthy behavior, and then a lot of the recent improvements in pediatric outcomes have been obtained through the aggressive use of transfusions. So they come to us needing

transfusions because we know we can't stop transfusions at any age once patients had a stroke, and they develop problems from the transfusion like iron overload, and at that time they disappear from the health system. Then many of them end up with chronic pain states that have to be dealt with.
Well, one of the things I thought of and I've been working on for a number of years now is how can we solve this. Well, one of the important things I think is that you need to use newborn screening as a way of teaching families how to raise a child with a chronic illness so that that child will not only do well medically but will do well socially and economically when they become adults. We have to improve the medical home, and then we have to develop successful transition programs between pediatric care and the adult care.
The early family intervention would have to address medical issues, and they do that very well now. But more importantly, we have to educate the parents, we have to do extended family education. This is a closet disease in families, and we need a liberation of the families. We have to improve social support, psychological functioning, and economic functioning.
There are models for this, and I've looked at the work of David Olds, which looked at high-risk mothers in three different areas of this country and documented that the nurses who aggressively track these mothers prenatally and postnatally for two years have a major impact on the outcome for that child, for the mother. They have less substance abuse, legal problems, dependence on welfare, and risky sexual behavior. To accomplish this, nurses are required (inaudible) a very rigorous protocol.
The problem with this model is it's expensive and it's initiated prenatally, but we're hoping we can modify this to sickle cell disease and use his work as the basis for an intervention that we can start at birth using newborn screening.
Now, transition is another issue, and what's been found in Dr. Telfair's work and others is that three groups need transitioning, the individuals who have the disease, their care providers, the whole family, and the pediatric health team, who very often don't want to give up these individuals.
To where? To nowhere. There are no adult providers now for sickle cell disease, and there's a lack of general knowledge about sickle cell disease in the adult population. Who really takes care of these individuals? Well, they go to emergency departments. They go to hospitalists when they're hospitalized. It isn't their family doctor who takes care of them. It's a hospital-based physician. They may have a medical home, but if they do, it's going to be in general internal medicine and family medicine, not the last one on the list, which is the oncologists and hematologists. We really take care of a minority of these patients.
So what can we do? Well, the patient's medical home is in the primary care community, so we have to define medical home broadly and encompass the areas where they're actually getting care. Now, I can't solve all of the problems around that, but what we decided to do was to focus on protocols for specific problems and address those protocols in every community resource that would come into contact with the individual.
A big one, and I can't really do much about this, is we need adequate funding for primary care. That's beyond me. But what we can do is develop protocols, not guidelines that are gathering dust on every physician's shelf around the country, but protocols that they buy into because they've helped develop them. So for the generalist and physician extenders, they'll be at the table. For the emergency room docs, they'll be at the table. Protocols for hospitalists, they'll be at the table. Then we do have to have a network of Centers of Excellence, and we're actually better equipped there than anywhere else.
Well, I can't solve all of the problems around these various groups, but we already have decided in the adult provider network to take on pain as the most important issue for the patients and try to figure out ways of improving pain control. So that's going to be our model for this initiative, not to try and solve all of the problems related to their disease, but focus on pain.
The protocols will be developed with the two HRSA-funded projects in our region. They will focus on pain management, and we will develop protocols for home management, emergency rooms, and inpatient services.
Our assessment tools for management will probably be pain diaries, as the recent information shows that most of the pain is dealt with at home, not in the medical setting at all. So we'll use these diaries to manage the patient, and then this will also be our outcomes assessment. The patients will not come to us and give us data unless we're providing services to them. If we're focusing on their most important problem, which is pain, I think we can actually collect the outcome information.
Now, the other part of this is that it has to start early, and I really believe this begins at birth. It has to be developmentally based, and I think we're going to use pain as a model there. We'll leave the last two. Those are things we don't have to talk about.

The other thing I think we need to know is that we're really well poised to do this transition project. The American Academy of Pediatrics had a position paper on transition. It was authored primarily by Drs. Reiss and Gibson, both of whom are in our region. We also are blessed with Dr. Telfair in our region, and I'm hoping that we will be able to put this together in a way that will basically use the first bullet as the important one; that is, the individuals who are transitioned, the family, the adult, and the provider, need future orientation. So at birth, the orientation is that they're going to become successful adults, and all through their lives that's stressed for the individual, for the family, and for the care provider.
In terms of assessment of outcome, this is a really immense undertaking. We really can't assess every individual in the region, but in our region we are blessed with outreach clinics. The Medical College of Georgia has clinics in a large part of our area that are housed in the public health departments. We're partnering with the Medical College of Georgia in an NIH Comprehensive Sickle Cell application, and we're developing complementary networks for the northwest part of the state. But Alabama and North Carolina also have similar structures, and we're hoping that in SERGG we'll be able to bring these groups together and focus on common approaches to data collection using the two HRSA demonstration projects as focus, probably with some sort of a case/control type of approach.
I think the other thing that has to be done is we have to use existing database models. The CDC hemophilia model is good. The MAH Centers collect clinical data in the databases in their model. But we really need to go beyond the medical model and we're hoping to add social and economic and psychological functioning so that we'll have a broad database and hopefully collect information that will show this will improve outcome, not just at birth but all throughout life.
Thank you. I hope I didn't take too long. This is a website if you want information about sickle cell disease, and we publish a monthly newsletter. Sign up by email and we'll send it out to you. Thank you.
DR. HOWELL: Thank you very much.
(Applause.)
DR. HOWELL: I think that these are three excellent demonstrations of pilot type projects that are going on in the regional collaboratives which are clearly going to be an important base of activity concerning newborn screening.
I think in view of the time, I think that we should move ahead. The committee is going to have, as usual, a working lunch, which is in the Polaris Room A on the Concourse Level. The regional collaboratives are having a meeting in the coat room, which is the little room that's just down the stairs.
Michele has suggested we have two questions. Does anybody have a question?
Denise can always have a question. Thank you, Denise.
DR. DOUGHERTY: Well, I guess I'm wondering, for the HIT experts among us, if these individual long-term follow-up approaches get going, how easy will it be or hard will it be to integrate them with something that may be more national with national standards? That may be a question for Steve or Alan Hinman.
DR. HOWELL: While Steve is coming up, of course, one part of the regional collaboratives is the fact that there is an organized national coordinating center. But Steve can comment about that.
DR. DOWNS: Well, it relates to what I said about standards being both the most boring and the most important aspect of what we're doing. So the answer to your question is it depends on whether the individual efforts adhere to the standards for data transfer and for data coding that currently exist or work collaboratively with the standards organizations to create the standards that they need where they don't already exist.
DR. HOWELL: The other thing that's interesting that I think many people know is the Secretary has as one of his major interests at the current time electronic medical record or personalized health record. Interestingly enough, in conversations with his office, one of the areas that they're going to have as focus for that happens to be newborn screening. I think that's very encouraging because it will provide an opportunity for some standard language and things of that nature that will permit, hopefully, this effort to be more national. But in looking at applicable areas for the electronic medical record, they, I think quite correctly, assume that newborn screening might be a good place to start, because there is a lot of work coming out of health departments with reporting and so forth. So it will be exciting.
I think Danuta had a question, Dr. Krotoski in the back.
DR. KROTOSKI: Thank you so much. This is also to the first speaker regarding the coding. My name is Danuta Krotoski. I am at the National Institute of Child Health and Human Development, where I oversee the institute's international programs. So my question has an international complexion. But in terms of developing the analyte coding that you were discussing, clearly having a coding system that enables one

to compare across states is very valuable, but are you working with anyone or considering working internationally, for instance with our neighbors in Canada, Europeans, other countries that have active newborn screening programs in place?
DR. DOWNS: The LOINC Consortium, the group that certifies LOINC codes as standard, is an international organization. In fact, one of the people who is working most closely with me, Gilbert Hill, is in fact Canadian. It's ironic that you would mention Canada in particular.
DR. HOWELL: Thank you very much.
With those two questions, we will indeed now go to lunch. We will resume promptly at 1:00. Thanks.
(Whereupon, at 12:00 noon, the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:07 p.m.)
DR. HOWELL: The regional collaboratives apparently are still dining in the coat room. The coat room must have very good food. But I see some people coming. The coat room should be closed on such a warm day.
But anyway, we're about ready. We need to get rolling. I'm pleased to have Brad Therrell here to talk about the current status of the newborn screening programs, and he's also going to tell us about two recent important meetings related to newborn screening that he's attended.
Dr. Therrell?
DR. THERRELL: Thank you very much. Those guys downstairs, they can just stay there because a lot of them will be having comments on what I'm going to say.
So what we've done is, as usual, we have gone out and we've asked the programs to tell us what's happened in the last year since the last time we reported to you. The comments I'm going to show you are comments that came from programs who chose to respond. It may not be all the programs, so I'm not going to say this is 100 percent what's happening in the country, but it's pretty close.
I've got several slides, and they're just summaries of what's going on. But Arizona wanted you to know that they are now up from 8 in April of 2006 to 27 disorders, and that cystic fibrosis screening is to be added June 30 of this year, which will make them have 28 conditions, and then centralized hearing screening follow-up has been implemented. So the one they're lacking on the core 29 is hearing screening.
As I was just talking to Dr. van Dyck, it's not the fact that babies aren't being screened for hearing; it's the fact that they haven't been mandated for hearing that's keeping people off the list. So it's a little bit misleading when we look at core conditions mandated, because sometimes it's not mandated and you still get almost 100 percent.
Arkansas, which was one of the lower states in terms of disorders, they've just gotten expansion approved in October. They're now seeking legislative approval, and their fee is expected to increase from $14.83 to $89.25 per newborn. They at least have a plan, and their plan is to hire additional staff by January and to then begin a public awareness campaign in March, and then to begin expanded screening by July of 2008.
California had been lacking biotinidase and CF. They have now gone through pilot testing for those two, and the official start date for both conditions is July 17. Don't ask me why these dates are like they are. Sometimes they're the 1st, sometimes they're the 6th, sometimes they're the 17th.
Delaware. June of last year they began biotinidase screening. In October they began CF screening using IRT/IRT, and you'll see that this is an issue as I go through some of the states, whether to use IRT followed by an IRT in two weeks or IRT/DNA on the first specimen. December the 1st they added carnitine reuptake deficiency, and they're initiating steps to move toward a Web-based reporting system.
Florida. Their expanded screening began in 2006, January, and they're expected to add cystic fibrosis in July.
Georgia began their expanded screening in January with a fee of $40. They're currently using an automated voice response system, an autofax system to respond back to physicians on a 24/7 basis. They're doing cystic fibrosis by IRT/DNA. They have planned linkages to vital records, and they're planning electronic transfer of demographic data from some hospitals. Georgia, as many states, has just had a lot of legislative difficulties with the program, actually, and after working to get through the legislature, then the budget was vetoed by the governor. So they're back to square one in terms of looking at expansion and who is going to do the expansion, whether it's going to be done by the state lab or an outside laboratory. They actually had an audit that showed the state lab was the most cost effective

in Georgia.
Illinois is another state that's had a lot of legislative activity. They are currently working on a rule change to add CF using IRT/DNA. They're expected to start CF screening in the summer. They're going to first do six-month limited screening and increase the fee to cover this, from $47 to $59. They're also putting out $600,000 in grants for genetic counseling to go with CF.
Now, the legislature has been hit with some bills that sort of came from left field, one of which is to add five lysosomal storage disorders, and the five are listed here, and that bill I'm told yesterday has passed the Senate with a unanimous vote and is now awaiting some action in the House, and the House is actually slowing it down a little bit and giving them three years to implement the program and that sort of thing, because as of yet Krabbe is the only one being screened of that group, and it's being screened in New York right now. So there's still some question as to what to do about the others.
They've also had a bill introduced to support Fragile X screening, and the program knows nothing about this bill. They're just being told that it's there by some of the legislators.
Kansas had an active legislative session. They finally did pass expansion. Kansas law actually says that the program has to pay for everything related to newborn screening. So if they're screening for something and a baby comes up with that something, then the program has to pay for it, and that's been holding them back. So they now have had some legislation that will say they can cover treatment products on a sliding scale, whereas before the program had to cover everything. So they're looking at expansion in July 2008, and they have $800,000 available to do that expansion. So we'll see how far that goes as to how much they expand.
Louisiana is working to expand screening to 29. They have all in place except CF, and CF is supposed to start in July. The laboratory testing has been done in Iowa since Katrina, and that's supposed to come back to the state, and the state is moving to a new building, a new laboratory building. If that doesn't happen by July, then Iowa will do the CF screening for them in July.
Maine is also planning CF screening, likely to be implemented in January.
Maryland added CF screening in June last year using IRT/IRT, and they've gotten a lot of new instrumentation and software. They're now doing more automated preparation for both mass spec and some of the non-mass spec disorders.
Michigan has been approved to expand their program to include 49 or the 54 recommended, and I'll show you the ones they are not including in their recommendations. On October 1st, they anticipate starting up CF. They've added a courier service, and they're expanding their lab hours to include Saturdays.
Missouri started their CF on January 8 of 2007, and that was a pilot. They're expected to start their screening in July. They're also moving to a new laboratory building at about the same time. CF follow-up has been contracted to the CF centers, and biotinidase deficiency screening will be added late 2007 or early 2008. So they will be up to the core panel.
Montana was another state that was doing the fewest of any of the states, actually. So they have a bill proposed to expand the mandatory blood spot screening from four to 28. That bill was supposed to have been acted on in April, but we haven't been able to find out what's happened to it, so maybe it's passed. Additional funds have been requested to expand the follow-up and subspecialty services.
Nebraska, their newborn screening committee recommended changing the optional tests right now to mandated tests. In other words, they offer expanded mass spec testing to patients as part of the program at no expense, and they get 96 percent acceptance. But they decided to go ahead and mandate, and they have not yet been able to reach accords on that with the health department director to ask for funds from the legislature. So we checked again yesterday and they still have not reached an accord there.
New York last year added Krabbe. They became the first state in the country to do a lysosomal storage disease, and in the first 166,000 they found two high risk, two moderate risk identified of the 16 referred, and I think I understood at the SCID meeting that they now have maybe confirmed one case. They have also switched their hemoglobin procedures. They were the last state to be doing the traditional procedures of salose acetate and cytreone electrophoresis. They've now moved to HPLC, and they do HPLC/IEF confirmations. They have piloted and then contracted with a specialty delivery service, and in the past year they've added a new newborn screening program director and a new newborn screening medical director.
New Hampshire screens for 13 conditions, including toxoplasmosis, which only one other state screens for, and they are anticipating a start date for the 19 additional MS/MS conditions on July 1.
Ohio on August 30 of last year began CF, and they also began carnitine uptake deficiency screening.
Oklahoma began screening for MCAD June 5 last year, and they now offer genetic counseling with

certified genetic counselors for conditions including sickle cell trait. They are adding in the MS/MS conditions in a staged process. They hope to have that completed by December 2008, and then they'll add biotinidase after that.
Oregon. On January 1st, 2007, New Mexico was added to the Northwest Regional Screening Program, and CF was added to the Oregon testing program in 2006, and to New Mexico and Alaska in 2007. They also have a new laboratory being constructed, and they expect to move in August of this year.
Rhode Island added 17 conditions, so they now have the core 29, and that was completed July 2006.
South Carolina, April the 2nd, 2007, begins screening for tyrosine I, II, and III, and they have a contract with Mayo to provide second-tier succinylacetone testing, and I think that's probably the first state that's done that, or there are others that you have contracts with.
DR. RINALDO: It's not a contract.
DR. THERRELL: It's not a contract. Oh, you're just doing it for free.
DR. RINALDO: It's supported by the regional collaborative.
DR. THERRELL: Good. Anyway, this is an interesting one to take a look at as we go through here, because a lot of people are sort of wary of what to do with the tyrosinemias.
They've updated their cutoffs for IRT and 17-hydroxy progesterone.
South Dakota, currently they use an in-state laboratory for contract services, and that laboratory subcontracts with Texas and Massachusetts for some of the tests. They just put out a new RFP, and that's been awarded to Iowa. So Iowa will begin their screening June 1, and they'll add CF screening also at that time. That has generated some press in South Dakota because of the money going out of state now, because always in the past they had in their RFP that the testing laboratory had to be in-state.
Texas has had a lot of changes. December 6 last year, they added 19 MS/MS conditions using MRM. So that means they're targeting those conditions and are not doing a full scan to see what other conditions there might be there. January the 8th they added biotinidase deficiency. They have not yet added CF, although the legislation said they should expand to meet the core conditions within available funds. So right now they've decided that available funds won't cover CF, but they're planning to add CF as soon as they can. They implemented a new reporting format which has been fraught with some other issues in Texas that are being worked out right now, and they're updating their voice response system for 24/7 coverage, and they're looking at improving their demographic entry system that they have right now in some of the hospitals to directly download demographic entry to the state laboratory.
Vermont currently tests for 28 of the 29 conditions, and they're working on an administrative rule change which would give them CF added to the program, hopefully by the end of the year.
Washington State is reviewing continually additional disorders for possible inclusion, and the University of Washington has applied for an IRB approval to do a pilot study to detect lysosomal storage diseases, and you saw earlier from NIH that the University of Washington has a contract to look at lysosomal storage disorder testing.
Finally, in West Virginia, another state that was down on the totem pole, they've now mandated expansion from 7 to 29. July 1, 2007 is their Phase I, which will add CAH, CF and biotinidase -- in other words, everything that's non-mass spec -- and then in July of 2008 they'll add the mass spec conditions. That second phase also includes couriers, increased genetic counseling services and so on, and they're exploring the telemedicine opportunities there.
So just to show you graphically what's going on in the country, this shows you which programs have mandated the conditions and which programs haven't. So if you have a red bar, you've mandated it and you've implemented it. If you have a red crosshatch, you've mandated it and you haven't implemented it. If you're a white icing on the cake, you're offering it as an option and it's not mandated at all. So you can see across the table, and the one that's growing rapidly, as you can tell, is cystic fibrosis, which is out here on the end. The small ones are HIV, toxoplasmosis and G6PD deficiency, which are done in only one or two states.
Now, if you translate that to the percent of babies that are actually being screened, not just the states, this is displayed the same sort of way. If you're red, it's mandated. If you're red with crosshatch, it's mandated but not yet implemented. If it's white, it's icing on the cake. So you can see that we're moving steadily up in terms of babies being screened for the core conditions, and CF again is the one that's moving rapidly right now.
Just for fun, we gave you a plot of the MS/MS detectable conditions to show you the variation across the states and which states have mandated which conditions in the mass spec panel. So you can see it's not cut and dried that everybody is going to do everything, and again it's displayed the same way.

Then this is a map that I showed you last year showing all the states in June, and the ones that were circled were the ones that had the core conditions, and there were 12 at that time. Here's the same map now, and you'll see there are 16 if you actually look at them. So we've gone from 12 with the core 29 to 16.

DR. LLOYD-PURYEAR: That's 2006.

DR. THERRELL: Sorry, 2007. Yes.

Now just a couple of current issues and news, and then I'll go to the meetings.

There is getting ready to be a CAH kit change again. So this is an issue for the programs because now they've just adjusted their cutoffs up, and now the test is going to be more sensitive and more specific and they're going to have to adjust their cutoffs down. So you're going to hear this in the next few months as issues in the state labs.

Filter paper kits. There have been problems with the manufacture of the filter paper. Filling orders; there are a lot of backorders, purchasing problems in the states, and some printing issues. So that's been an issue that's been discussed a lot.

CLSI, the Laboratory Standards Institute, has a standard for filter paper collection which is called LA4, and the fifth revision is just getting ready to come out. Dr. Hannon is the chairman of that committee.

CLSI is also beginning to work on guidelines for screening and transfused infants, and you'll see that one over the next year or so.

There's still this issue about which protocol is best for CF, IRT/DNA or IRT/IRT, and then there are a lot of research considerations going on particularly with the lysosomal storage disorders, SCID, and G6PD.

So that will transition me into two conferences that we want to tell you about, and I'm just going to hit the high points of the conferences. There are some other people in the room who were at those conferences who may want to say more.

The first was a conference to look at the utility of screening for G6PD deficiency to prevent severe neonatal hyperbilirubinemia. It was convened by Vinod Bhutani from Stanford. It was here last weekend.

The aim was to look at whether assessing G6PD deficiency status in neonates, with emphasis on certain high-risk populations, might have an improved predictive accuracy on the predischarge on specific bilirubin measurements in looking at the risk of severe neonatal hyperbilirubinemia and kernicterus.

That was a very interesting meeting. What we found there was that right now in the country G6PD screening is offered by pediatrics and it's a part of the mandated panel in the District of Columbia, it's available in the hospitals in which pediatrics has contracts, and most of those are in the Pennsylvania area. So if you look at the country, G6PD is really available in D.C. and mostly in Pennsylvania. However, there is very little outcome data from any of those programs, more outcome data than not in Pennsylvania from the hospitals, but the District of Columbia has essentially no outcome data.

This had a huge impact on what we were discussing because it turns out that there's not a whole lot of data in the country on kernicterus and the impact of kernicterus on different racial groups and that sort of thing. So in the end, this group was left to ponder a couple of questions, and I've actually asked Nancy Green if she would talk about those in just a second.

Just to show you the meeting, this was the group. It was a very small group of about 16 people. This is Dr. Bhutani on this end, and we included a couple of people from Asia because G6PD screening in Asia has a long history and we wanted to hear about that as well. You'll see the person in the blue in the back is Dr. Beutler, the famous Dr. Ernest Beutler, who was actually there and gave us a lot of input and a lot of insight into these testing procedures. I think his comments at the end were especially important to the group in terms of point-of-care testing might be more important for G6PD, the mutation panels that are being used right now in this country as a primary screen might not be the appropriate panels, and that sort of thing. Nancy can comment on that in just a second.

Let me show you the other meeting as well. This was a meeting on severe combined immunodeficiency research that was held just the other day. It seems like yesterday, right? It was in San Francisco, and it was convened by Jennifer Puck to consider how best to organize and implement newborn screening programs for SCID and to identify possible investigations and collaborations that might be useful in moving the process ahead. Several people in this room were at that meeting.

There we found that newborn screening tests actually have been worked out and are available at the University of California at San Francisco with Dr. Puck. Also, Wisconsin has developed their procedure, and Wisconsin is actually going to begin screening within the next year. So Wisconsin will be our beta test site, as New York is for Krabbe.

The current testing procedures seem to be subject to high recall rates, and so the issue was what's the

best way to do that screening. The tests that Jennifer Puck has are called TRECS. So is TRECS the best way or is there another Luminex procedure or some other type of procedure that could better be used, or as a second tier are these things better, and what about the value of the second screen? Is that worth anything, and would it help as a second tier?
So there are newborn screening tests in development in New York, in Missouri and some other places, Washington perhaps, and Wisconsin is going to be starting in the next year, and the collaborations that were identified exist in Wisconsin, New York, California, Missouri, Maryland, Massachusetts, and perhaps some others. So representatives from all those laboratories were in the room, and both of these meetings will have extensive reports generated, and those reports will be available to this committee over the next year, I suppose, when they're finished.
I think the G6PD meeting in particular had more questions that went unanswered than the SCID meeting. The SCID meeting could actually lay out some proposed things to do over the next year, whereas G6PD, there were not enough data available to really answer the questions there, and so that research agenda is going to be, I think, centered around information gathering.
If you don't mind, I'd like for Nancy Green to make a comment on the G6PD meeting.
DR. GREEN: Sure, Brad. Thanks. That was very well described. It was an incredibly informative meeting. The issue for G6PD is that the screening and the research is focused on prevention of neonatal kernicterus, as you mentioned, rather than some of the other later manifestations, specifically hemolytic anemia. So as Brad mentioned, there is an issue of the timing, because to prevent neonatal kernicterus, one would need to know the results of the G6PD screening earlier and therefore suggest the potential at least for point-of-care testing, which is not simple. The other is that the disease is incredibly common, 1 to 2 percent in the U.S. population, and yet the penetrance is very low. So like hemochromatosis that we heard about and some other disorders, I think the research needs to be done to look at that. Certainly, just as sort of a tidbit, it may be that G6PD in combination with some sort of bilirubin conjugating enzyme defect would manifest in the neonatal period, so to screen for something that's common and not for the other more complex issues is questionable.
The studies have not been designed to look at later hemolytic anemia. So I think, as Brad said, a robust research agenda will need to come from that meeting.
DR. THERRELL: And just to finish up, this is the group that met at the SCID meeting. You'll see faces there that you recognize. This was Dr. Puck speaking to the meeting in the beginning, and this is our esteemed chairperson, also speaking to the people at the meeting.
You may have some comments on that meeting, Rod.
DR. HOWELL: Just a brief comment. I thought the SCID meeting was a very productive meeting because it brought together a group of very distinguished immunologists with the screening group, and they had not as a formal group been together. It was extremely informative for them. There's a tremendous amount of information about technology and so forth as far as treatment and outcomes and so forth. So I think that will continue to be a very exciting thing.
The G6PD brings up an interesting problem, because some of the technology that surfaced in response to the NICHD request for new technology focuses on point of care, which we've not really talked about very much in newborn screening, but certainly there are technologies out there that would permit point of care in the nursery if that became appropriate for G6PD.
Harry?
DR. HANNON: Based on Brad's information and the fact that we discussed this morning about an evidence-based protocol to add disorders to the screening panels, and now we've got legislatures and states making these decisions, and we get caught up in this also, how do we integrate those two to make the two work together? That's a question for you, Rod.
(Laughter.)
DR. HOWELL: That's a very simple problem.
(Laughter.)
DR. HOWELL: I think that the bottom line is that it's extremely unlikely that the legislative activities will go away. I think they will probably continue. But in the meantime I think that we can continue to try to get good information that might be more effective in driving some of these legislative solutions.
DR. HANNON: Yes, we get caught up in this complex issue because of agreements that we didn't think out in the beginning, like providing reagents for LSD testing as a protocol, and then we get a call from a parent or a member of the state legislature saying, well, what are you doing about recommending this test? Of course, we've got (inaudible) to distribute, and while I won't say that the CDC does not

recommend any test, so we got caught in a Catch-22. So we have to be careful about how we walk these lines.
DR. THERRELL: The other thing interesting about G6PD was that after the meeting I thought about the military because there was a comment there that the military knows the G6PD status of all their inductees, so that's a group that needs to be at the table that wasn't at the table when we had the meeting.
DR. HOWELL: Well, perhaps Colonel Louder can tell us about G6PD.
I think in view of the time, unless there are some other critical questions or comments -- Coleen has a comment.
DR. BOYLE: I just wanted to ask a really quick question about G6PD deficiency. Since we've spent a lot of time on the issue of kernicterus and the reemergence of kernicterus, do we know for some of the recent kernicterus cases that they might have an underlying G6PD deficiency disorder?
DR. THERRELL: The answer to that is no.
DR. HOWELL: I asked that question and the answer was no, which strikes me as rather remarkable.
DR. BOYLE: Well, this might be something we can follow. We've been actually looking for an epi aid for a newborn screening-related issue, and this might be something we could follow up on.
DR. GREEN: There's a little bit of data from the kernicterus registry which is not representative, but there are over 100 patients. If I recall, Marie, about a quarter of those patients had G6PD deficiency?
DR. HOWELL: It looks like a great project for an epi intern.
Colonel Louder is now going to tell us, just one day prior to his esteemed promotion, about the comprehensive newborn screening program in the Department of Defense.
DR. LOUDER: Thank you.
I'll apologize ahead of time. I won't be here tomorrow for obvious reasons, got lots of family in town, lots of things to do, cell phones buzzing right now. So I'm having lots of fun.
Anyway, for those of you who were in Minneapolis a week or two ago, this is a very similar briefing to what Kathy Camp and Scott McLean brought then. I changed the slides a little bit, so for those who were at that meeting, there will be a quiz at the end of this talk to see what's different.
(Laughter.)
DR. LOUDER: Again, I'm very indebted to Kathy, who is here with us right now, Scott McLean, who is a geneticist in San Antonio, for really putting this briefing together and allowing me to bring it to you all.
This is the mission of the military health care system, and this is important because it gives an opportunity to think about what we do. As much as I sometimes puzzle over that, pediatric care is not the center of the military health care system. I think that's very relevant in this day and age as we've been at war with lots of deployed people for a long period of time. With some notable exceptions, the military health care system is reporting incredibly low morbidity and mortality rates related to being at war. We've got a wonderful health care system that takes care of those warriors. It has some lumps and bumps in it maybe when we get them back here. I think we're addressing that right now, but it's really working well for our warriors.
So the perspective of this military health care system, it's a global mission, with the focus on the war fighters, and I added some information right here. Our funding comes essentially from Congress through the military. We have specific defense health care funding that is fenced from other defense funding. It's a number that continues to grow every year, and it is scaring a lot of people, as it is on the civilian side as well, because it keeps on getting bigger and bigger and bigger. We talk a lot about the fact that we have this benefit program and that to sustain that benefit is going to require probably prohibitively large sums of money as we go several years out.
That being said, it's one defense health plan, but the brick and mortar and the people are owned by the individual services, the Navy, the Army, and the Air Force. So as much as we would like to move in unison, the fact of the matter is that each of those services has fundamentally different missions, war missions, has different approaches to the allocation of even pediatric health care. So we will see some dissimilarities in things from time to time.
Right now the way we get money down to the lowest level is by having a facility, a clinic or a hospital, say I'm going to produce this many RVUs or other measures of productivity, and then we prospectively pay that up front. We do some balancing, as is typical in the federal system, as we move through the fiscal years. But the primary dollars are allocated based upon what you anticipate to produce in terms of health care.
One of the great things about our system is that prevention and early detection are embraced. All three

services have a focus on a healthy population and are out to try to assure that the folks who are going to war, as well as the folks that they go home to, are as fit and healthy as we can make them.
Now, the U.S. military is almost unique in the sense that it actually takes care of kids and/or spouses. Chuck Callahan, who is chief of the medical staff at Water Reed, put together an overview of pediatrics in the military that was published several years ago and identified that since the 18th Century Army surgeons took care of kids and that in 1946 the first military pediatric residency was put together. We have several all throughout the States. I'm the product of one of them. I would like to think that I have reasonably good training.
But the other important thing is to recognize what do pediatricians bring to the war fight. This is a very service-specific thing. I will tell you that the Army considers physicians to be physicians, and that the Army takes their pediatricians and sends them out to take care of adults at times of war. They operate as brigade surgeons, the most forward physicians doing basically primary care on largely adolescents, but they're out there taking care of adults. I have a neonatology friend who is in the Army who was doing detainee health in Iraq. So folks are out there.
We do have folks who go out and actually are pediatricians, and we in the Air Force right now have pediatric intensive care capability in both Iraq and Afghanistan. Last summer the Navy deployed a ship out to Asia and did a lot of goodwill stuff, and we're looking at doing something similar in South America this summer. So we deploy people as pediatricians as well.
Finally, and this is sort of fun and not a dig against any of my different colleagues here, but the pediatricians, probably through the negotiation skills that we learn with our patients, make pretty good leaders in terms of working with other people and stuff like that. So we see a lot of pediatricians who become chiefs of the medical staff and other leaders within the organization, and they deploy in those roles to the war fight.
Now, this is a snapshot of the military health care system, and you can see right here just the numbers, the different flavors of folks that we have. We are increasingly hiring civilian providers in family medicine and pediatrics and in internal medicine to supplement the fact that we don't have as many in uniform as we might like. We're also going through processes of converting uniformed physicians into either contract or civil service civilian positions.
We have almost 200 treatment facilities, 95 of which perform newborn screening, and those facilities are scattered all over the globe. If you look at the number of births, a little over 100,000 both in the direct health care system and in the indirect health care system, that's roughly equivalent to the State of Virginia in terms of volume, about number 13 if you rack us up against the other states. What you'd have to expect is Appalachia is Korea, and the Eastern Shore would be Italy in terms of the number of time zones that we span with those facilities.
Now, historically what's happened is that the newborn screening program at any individual military hospital has been that of the state, and this is a scattering of different facilities. You can pick your favorite one. Perhaps some of you were even born in or have visited these hospitals.
So if you're an infant born in the direct care system, which is a military hospital, quite likely the screening that's performed is that that is the state's screening program. Being a federal institution we're not obligated to use the state program, but more likely than not that's the one that we use. Or, and several of our facilities are doing this, they've contracted with a private laboratory, and our overseas programs that are generally in countries that don't have what we would consider to be acceptable screening programs actually contract with states back in the States to do our newborn screening.
So here are our challenges. As probably everybody knows, our military families travel frequently. It's not uncommon to basically have a baby and a couple of weeks later be moving somewhere else. The health care system is all over the world, as we've talked about, in 14 countries, 42 states, and there are just that many newborn screening programs. Our patients, our families, are increasingly moving back and forth between the direct care system that I represent and the civilian health care system that a lot of you represent. We have a lot of interface issues from that standpoint, and that's quite often where we don't get handoffs of information that we would like to have.
This is one of the things I always like, because when I was working in Germany it always seemed that people were having their first kids while they were in Germany, and of course the family was all the way back in Michigan or Wisconsin or someplace like that. So the grandmas weren't there to help the new mom take care of the new baby.
Finally, this is a big thing, and we touched upon this right now. Alex, help me out with the number here. It's about a million kids who are touched by parents who have deployed or are deploying right now, a

million kids in the United States. So that creates a lot of issues. It's not uncommon, and we've seen this probably in the news and in the newspapers, here is dad in Iraq literally looking at a picture of his newborn baby over the Internet, maybe even a video, maybe even real time. But that's the reality that we're facing right now.
So what I can tell you is that pretty much -- and I was told earlier that back in the '80s there was a great plan to make things work a little better, but it was really in the 1990s that we had a patient who had sickle cell disease that was in a location where it wasn't tested overseas. So that didn't have a great outcome for that patient. So in 2002 the Army looked at doing a better job as the Army in terms of doing newborn screening, and at that time what they did was that they came up with a policy to try to improve just that, asked for input from the other services.
In 2004 TRICARE, which is sort of our broad oversight for our military health care system, decided to look at this. The Navy actually took the lead and said for our Navy facilities we can do better, we can deliver a uniform standard, and they by and large have moved forward to do that. Then in 2005, which is just a couple of years ago, TMA, TRICARE Management Activity, developed a plan to look at doing better with newborn screening, and that's about when I joined up with them and about when I got here.
So this is what we're thinking about. We want a program that's global, one that's comprehensive, one that's responsive, uniform and universal, all the ideal things that I think we would want to see in a program. Now, we would like to think we have some advantages in the military. I was talking to Jana a little bit about this before because Jana has been part of a medical military family and has received a lot of care for her children within the military health care system, the interfaces of that, and now the civilian health care system, and as we talk about medical home, what I would like to believe is that we're doing better than average in the military in terms of engendering that concept. When I talk to our Air Force pediatricians and Air Force family medicine docs, we really try to push this forward.
But you have this relationship with the patients that you own those patients, and in fact in the military any patient that is enrolled to us has a provider by name. Now, the question is are we good at getting that translated into an actual interaction, and it varies. It depends upon what's going on in that clinic and what's going on with that particular provider. But we really like the idea of a medical home.
We own a lot of our subspecialists at a lot of the MECCAs, so we're able to work with that. We do have an outpatient electronic medical record. It's still in its growing phases. It's called AHLTA, but ultimately we're going to have a ton of medical information that we can sift through, and what the epidemiologists will like about this system is that its ability to record symptoms and signs and results is very structured. So it's going to be very searchable in terms of looking for relationships. In fact, it's really designed to look for spikes in symptoms and locations and say, hmm, there's something funny going on in Miami this week, and it's not just because Dr. Howell has come back into town --
(Laughter.)
DR. LOUDER: -- but there may be something that we need to go look for.
Finally, we have command and control. What that means is that we have families that can come see us at our big places. The largest impediment to getting in to see the doctor is finding a parking space. We don't have co-pays. We have 100 percent rolled. We can reach out and touch the parents and say, hey, we really need to get your kid in here, and that works out nicely.
So we have a team process. We've been meeting for about two years now. You all and the organizations that you represent have done a lot of the heavy work for us in terms of we aren't too concerned about which diseases. We just said, hey, we've got this wonderful report, the AAP says it's a great report, so we're going to go with those diseases. Oh, great. Thank you. Okay.
We're looking at these activities. We're working on developing a registry, and I think the folks that came up with the registry stuff that I'm going to take back to my registry folks, because ultimately with our electronic health record, we should know exactly who has what, and we may be able to play with some of the interesting variance and actually see what happens with them over time.
We've been very focused on the educational plan. Kathy Camp has been very instrumental with that. Then it was about a year, a year and a half ago, they said gee, we have this civilian thing going on, we have our military thing going on, why don't we send Dave to go play with the civilians a little bit, and that's why I'm here with you all right now. I go back and tell them what you all are up to.
So what's our vision? Where are we trying to go? Well, we want this big, wonderful uniform standard. So what we're hoping for -- and we put this out in FEDBIZOPPS, and this is back in February -- we're looking for a laboratory contract. It will be a centralized laboratory. What we want is results in a couple of days. What we want is accessibility, secure accessibility of that information. If we have a positive result, we

have access to just-in-time, right-on-time, but we have quality information to guide the family and the physician at the time of that notification with what to do now and what to do to confirm the diagnosis and where do we need to go to get help.
So we're still working a lot of these things. I think a lot of these things are going to gel once we start to actually perform this. One of the things that I think will come out of the Walter Reed stuff that came out over the last several months is that case management of individuals is going to be a very big deal in the military, and I think that we can tag right on to that for our newborns, and I think that's a good thing.
We're going to be looking for oversight, obviously quality improvement, and we want to play well with others. So as the regions are putting things together, one of the questions is you're in Texas and you have a kid, and are they part of Texas? The answer is yes, maybe, but let's find the right thing for the kid at the right time.
Anyway, it's very gratifying to be a pediatrician, a neonatologist in the military. It's very gratifying to be in the military because we get to serve some absolutely wonderful people. Even their parents are a lot of fun, too.
(Laughter.)
DR. LOUDER: We had a question about how kids cope with the stress of parents deploying, and that's a very complicated question but something that we actually take a look at and try to help those families deal with that.
So at this point I'll conclude and I'll take any questions for the time that we have remaining.
DR. HOWELL: Thanks very much.
Are there questions of Colonel Louder?
DR. TELFAIR: Yes. Thank you for your presentation. Coming from a military state, North Carolina, I know that you also have other personnel in the health care system. I wondering if you could speak a bit about the roles of nurses, techs and physician extenders in assisting what goes on.
DR. LOUDER: Well, what we try to foster is focusing on the primary care team. We have a modular approach to primary care where we link specific technicians, which are quite often LPN equivalents, registered nurses and medical assistants, and they work together as a team. So what you would envision is that this requirement and making the phone calls and stuff like that doesn't just fall on the physician to do it at 7 o'clock at night when he or she is done seeing their patients for the day but can be acted upon. We're actually going to work even more with those nurses, the RNs, to beef up their ability to case manage, to identify patients, to know what the right next thing is, and to be available for those families on the telephone should we need to do that.
Did I answer your question?
DR. TELFAIR: Yes, you did, and can I ask a follow-up question?
DR. LOUDER: Sure.
DR. TELFAIR: The issue of medical home, if that is your model, it's really tied to medical home, and I was wondering is it a case coordination sort of approach to medical home, or do you use some other means?
DR. LOUDER: I think of medical home as a relationship where that family knows that that clinic, that physician is there for them, and just as importantly that clinic, that physician, that provider team doesn't wait for the family to come back in to ask for something, but if they need something they go out and get it. So I see it as a two-way relationship of mutually assured optimization of the health of the individuals. Part of our quality metrics include measuring preventive things, HEDIS-like measures, but we actually score our physicians on that and say, hey, are the kids who are enrolled to you, are they getting all the appropriate immunizations by age 2? If they aren't, here's your list of patients, go out and go get them.
DR. HOWELL: Are there other questions?
It's my understanding that you are not currently screening for hearing loss. Is that correct?
DR. LOUDER: That's not correct. Yes, we implemented that when that came out back in the '90s.
DR. HOWELL: Okay, good, because I thought that was kind of strange because that is one of the few things that the U.S. Preventive Task Force has bought into.
Any other questions or comments?
(No response.)
DR. HOWELL: If not, we will break, and after the break we'll start our committees. Let me point out that the education and training will be in the Gateway Room, which is on the mezzanine level and not as in the program. Lab standards will be in Polaris B, and then the follow-up, et cetera, will be in Polaris 3. Then finally I mentioned earlier dinner tonight at Chef Geoff, and that will be at 6:30, and it's at Chef Geoff and so forth. We'll miss Michele tonight because Michele is going to be out living it up with her family,

celebrating her birthday.
(Applause.)
DR. HOWELL: Actually, her birthday is not until later, but she'll be out of the country, being a world traveler.
The latest news is that I think these meetings are moving by the minute. I think you probably have to knock on each door and see who's there. But the follow-up and treatment has been moved to the Washington Link, which is on the concourse level. I think you all know that. But if you go into the elevators in the corridor, those of you who are clever elevatorologists, the elevator which is on the left will go directly to the concourse, and the ones on the right won't. So if you're patient and you push the buttons on the left, you can go directly to the concourse. The Washington Link is on the concourse level, as is the other committee that's in the Polaris down there.
Michele has a word to say.
You can't request birthday presents.
DR. LLOYD-PURYEAR: No, but we still haven't discussed committee correspondence yet, and we were going to talk about that tomorrow when we talk about the standard operating procedures, but there's one letter that's completely out of place. It's in with the calendars, and it's one of the letters from an organization that's requesting representational status on the committee. So it's behind the calendar, if you can move that and make sure you see that.
DR. HOWELL: Before we go, since we will not be back here today, earlier today Piero had brought up the fact that the letter that will go with the nomination form might be improved if it expanded a bit about the importance of cooperative efforts and so forth. Piero has written this paragraph to be included in that letter, and I'll be interested in your response. It has the long initials of this committee, encourages the preparation of the nomination form by a multidisciplinary team effort. Examples of relevant contributors of the evidence data being requested include laboratory and clinical specialists of the condition to be nominated, primary care providers, researchers with knowledge of the molecular and biologic basis of a condition, patient advocates, preferably representing organized support groups, providers of newborn screening services that would include the private laboratories that do newborn screening, as well as the state labs, and experts in ethical, legal and social implications related to issues.
I think that's a rather inclusive paragraph that certainly makes it clear, and I think that's reasonable. Would you all agree with adding that to the letter that goes out?
Then again, the other thing to look at tonight for the committee is to look at the document that came out about liaison representatives, because tomorrow we will discuss those. We have several letters that are in the book from organizations that are requesting liaison membership, and we'll discuss those in the context of this document.
Sharon?
MS. TERRY: I just had a quick remark about the piece that Piero added. I wouldn't especially call out ELSI people. I think the others are absolutely critical to this process. I think a lot of that's already embedded in advocates and researchers, et cetera. So I just wouldn't call it out.
DR. HOWELL: Joe?
DR. TELFAIR: I have to respectfully disagree with my esteemed colleague, as you would say, Dr. Howell.
MS. TERRY: We can say "except Joseph."
(Laughter.)
DR. TELFAIR: I understand your point, but the reason why we added that is because there is a broad group of persons who work in the health services arena who do other work who are often left out off the list. So it gives them an opportunity. Instead of having a very long list, categorically these are the areas in which they work. So I guess we thought that that would be a really good way to cover them. We knew it would be a longer list, so I would have to say that.
MS. TERRY: I withdraw my comment.
DR. HOWELL: Sharon has melted with diplomacy.
(Laughter.)
DR. HOWELL: So we will add the whole thing, then.
Is there any further comment about this? It certainly gives a clearer indication of the importance of a broad group of experts and advocates and families and everybody coming together to come up with a nomination.
Michele?
DR. LLOYD-PURYEAR: I also need by tomorrow morning your calendars. I only have calendars from one

person. It would be nice to have it by today.
We have tentative dates which people tentatively have agreed with, and I just want to make sure those are still okay.
DR. HOWELL: We'll have a short break.
Mike?
DR. SKEELS: Just a point of clarification. Do you want us to mark out the dates we can't attend?
DR. LLOYD-PURYEAR: Can't come.
DR. SKEELS: Cannot come. Okay. And do you want that for the months where the dates have already been scheduled tentatively?
DR. LLOYD-PURYEAR: The only ones that are absolutely certain are in January.
DR. SKEELS: So you don't need the January calendar back from us? Okay.
DR. HOWELL: Off we go, and we'll see you all back here in the morning. The meeting in the morning begins here at 8:30.
(Whereupon, at 2:05 p.m., the meeting was recessed, to reconvene at 8:30 a.m. on Friday, May 18, 2007.)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE ON HERITABLE DISORDERS
AND GENETIC DISEASES IN NEWBORNS AND CHILDREN

Friday,
May 18, 2007

Rotunda Room, 8th Floor
Ronald Reagan Building and International Trade Center
1300 Pennsylvania Avenue, N.W.
Washington, D.C.

IN ATTENDANCE:

Committee Members

Amy Brower, Ph.D.
Executive Director
Medical Informatics and Genetics
Third Wave Molecular Diagnostics
315 South Fork Place
South Sioux City, NE 68776

Gregory A. Hawkins, Ph.D.
Assistant Professor
Department of Internal Medicine
Section on Pulmonary, Critical Care,
Allergy, and Immunologic Diseases
Center for Human Genomics
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157-1054

R. Rodney Howell, M.D.
Committee Chairperson
Professor
Department of Pediatrics (D820)
Leonard M. Miller School of Medicine
University of Miami
P.O. Box 016820
Miami, FL 33101

Jana Monaco
3175 Ironhorse Drive
Woodbridge, VA 22192

James A. Newton, M.D.
President
Alabama Neonatal Medicine, P.C.
7203 Copperfield Drive
Montgomery, AL 36117

Piero Rinaldo, M.D., Ph.D.
Professor of Laboratory Medicine
T. Denny Sanford Professor of Pediatrics
Vice Chair of Academic Affairs and Intramural Practice
Department of Laboratory Medicine and Pathology
Mayo Clinic College of Medicine
200 1st Street, S.W.
Rochester, MN 55905

IN ATTENDANCE:

Michael Skeels, Ph.D., M.P.H.
Director
Oregon State Public Health Laboratory
1717 S.W. 10th Avenue
Portland, OR 97201

Liaison Members

Joseph Telfair, Dr.P.H., M.S.W., M.P.H.
Member, Secretary's Advisory Committee
on Genetics, Health, and Society
Professor, Public Health Research and Practice
Department of Public Health Education
School of Health and Human Performance
University of North Carolina at Greensboro
437 HHP Building
1408 Walker Avenue
P.O. Box 26170
Greensboro, NC 27402-6170

Ex Officio Members

Denise Dougherty, Ph.D.
Agency for Healthcare Research and Quality
Senior Advisor, Child Health
540 Gaither Road
Rockville, MD 20850

Peter C. van Dyck, M.D., M.P.H., M.S.
Health Resources and Services Administration
Associate Administrator
Maternal and Child Health Bureau
Parklawn Building
5600 Fishers Lane, Room 18-05
Rockville, MD 20857

Executive Secretary

Michele A. Lloyd-Puryear, M.D., Ph.D.
Health Resources and Services Administration

Chief, Genetic Services Branch
Maternal and Child Health Bureau
Parklawn Building
5600 Fishers Lane, Room 18A-19
Rockville, MD 20857

IN ATTENDANCE:

Organization Representatives

American Academy of Family Physicians

Norman B. Kahn, Jr., M.D.
Vice President, Science and Education
American Academy of Family Physicians
11400 Tomahawk Creek Parkway
Leawood, KS 66211-6272

American Academy of Pediatrics

Tracy L. Trotter, M.D., FAAP
200 Porter Drive, Suite 300
San Ramon, CA 94583

American College of Obstetricians and Gynecologists

Anthony R. Gregg, M.D.
Director, Maternal Fetal Medicine
Medical Director of Genetics
Department of Obstetrics and Gynecology
University of South Carolina School of Medicine
Two Medical Park, Suite 208
Columbia, SC 29203

Food and Drug Administration

Ethan Hausman, M.D., F.A.A.P., FCAP
Medical Officer, Inborn Errors of Metabolism Team
Division of Gastroenterology Products
WO-22, Room 5171, HFD-180
US FDA, CDER, OND, ODE-3
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Genetic Alliance

Natasha Bonhomme, B.A.
Genetic Alliance
4301 Connecticut Avenue, N.W., Suite 404
Washington, D.C. 20008-2304

March of Dimes Birth Defects Foundation

Diane Ashton, M.D., M.P.H.
Deputy Medical Director
March of Dimes
1275 Mamaroneck Avenue
White Plains, NY 10605

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P R O C E E D I N G S (8:35 a.m.)

DR. HOWELL: Ladies and gentlemen, let me welcome you to our second day of our 10th meeting. We're going to begin with our subcommittee follow-ups. The subcommittees had very active and productive days, I'm told. Dr. Boyle is attending her daughter's graduation this morning, and so in her absence, Dr. Denise Dougherty will present the results of the Subcommittee on Follow-up and Treatment. Denise?

DR. DOUGHERTY: We're having a little technical difficulty.

DR. HOWELL: We're having a little technical problem, but I'm sure that will be promptly resolved with all the talent that's gathered there.

The other thing that's at your desk, while we're waiting on that, is that yesterday Piero made a recommendation that the nomination form have a little more explicit comment about working as a group effort. He had written a paragraph, and we got written comments about his paragraph. So we have before you there three paragraphs, all the same thing. Read those during the course of the morning, and we will talk about those a bit later. But that will be inserted in the nomination document, the cover letter that goes to the people recommending.

Denise, it looks like you're up and running.

DR. DOUGHERTY: We did have a lively and well-attended meeting of the subcommittee, with many others in attendance.

Our agenda was twofold. We wanted to discuss the activities post the long-term follow-up expert meeting that was held April 18th, 2007, to outline the process for what needs to be done next. And the second agenda item was on metabolic foods and formulas. Two draft survey tools were discussed, as well as next steps for the committee.

On the expert meeting/white paper, the meeting summary needs some revisions, and Carol Greene has brought those to our attention and was volunteered to make those revisions. So she will be doing that.

Then we discussed the papers and other follow-up activities. The first and most important is, we believe, to have a three-page report to the advisory committee summarizing the expert meeting agreements on long-term follow-up goals, long-term follow-up definitions, and the four essential components of long-term

follow-up, as well as mention of the organizations and individuals who need to be involved.
You heard the summary yesterday, if you were here, of what the conclusions from this long-term follow-up meeting were. So those summaries by Coleen and by Alex Kemper will be the sources of this brief document. The first author will be Alex Kemper. He'll give a draft to Coleen, and then it will be circulated to the entire subcommittee. And we expect to have our version to the full committee back in September for our September meeting for discussion and potential endorsement and possible publication either by the advisory committee or some other dissemination, such as a journal.
The second next steps were less well delineated. Second, in addition to the three-page paper, three roughly, there should be a fleshed-out version, something like the document that Alex Kemper and colleagues were preparing as background for the expert meeting and that they've worked on since then with a little more detail than this three-pager. But that has yet to be worked out. Alex and his colleagues will be giving Michele some ideas, and that will be worked out with the committee. That could also possibly be published.
Then what we're focusing on here in this three-pager is just to report what the expert meeting was to be about, which is to come to some consensus, maybe not formal consensus, on what the elements of long-term follow-up are according to our meeting. We did not have the meeting specifically to match roles and responsibilities with those elements. We had the meeting because there was no document that was a participatory document that actually said what long-term follow-up should include. So you could never know whether long-term follow-up was being adhered to because we didn't have a statement saying what it should be.
But then a follow-up activity would need to happen, which is to develop an action plan to actually implement those elements, if you all agree to them, and put the roles and responsibilities next to those components.
Metabolic foods and formulas. The issues are well known to the patient community and the nutrition and dietician communities. There's variable coverage for foods in private health insurance plans and, as a practical matter, in other plans as well. That was an unintended consequence perhaps of not having foods and formulas considered drugs. This need is well known. Surveys are being developed, however, to gather systematic data because there's no source of systematic data on what the gaps are and what the needs are.
So the subcommittee and others provided advice to people developing the surveys and to ourselves on survey development and implementation, surveys of metabolic dieticians, surveys of parents, survey of legislation, which is actually being done by Alissa Johnson at NCSL, also advice on strategies for getting these nonpayors to listen to compelling examples and the data once it's collected and other strategies to gather facts.
So the next steps. We didn't really have an action item for the whole committee. A subgroup of the subcommittee, or a task force, whatever we want to call it to stay in the legal bounds, because there's no committee member on it, is going to continue to discuss whether we have enough data to bring to the advisory committee which you could then make a recommendation or an endorsement. Otherwise, a possible next step for the advisory committee is to endorse a fact-finding activity or using Susan Berry's existing data, and if a clear national strategy emerged, the committee could endorse. That could include more widespread advice on billing, model legislation, or other steps. So on this one, stay tuned.
Michele, we were missing you. We were saying Michele has some clear ideas about what to do next on this, and we wish she were here. So if you have anything you want to add, or does anybody else who was at the meeting have anything they'd like to add, correct?
DR. TELFAIR: Thank you very much. Just one part of that is to endorse -- I thought we were endorsing or we did endorse the fact-finding activity to be engaged by that subtask or subgroup to do and use Ms. Berry's existing info. It was not "or." It was "and."
DR. DOUGHERTY: Okay. I guess we do need agreement from the committee that this task force should be created that will look at Susan Berry's data and other fact-gathering activities and come back with a recommendation to the subcommittee first and then to the full committee.
DR. TELFAIR: Right. That's what I thought we walked away with.
DR. DOUGHERTY: Okay. It was a little unclear there at 5 after 5:00, at least to me.
DR. HOWELL: Are there other comments about this report and so forth? What are the implications of asking a task force to do this? When I think of implications, I'm thinking of practical implications as far as any funding or staffing or anything of that nature.
DR. DOUGHERTY: I'm not sure how that works. The task force didn't want funding right now. They were

just going to have some phone calls and figure out what data were becoming available, how they could put it together, and then report back to the subcommittee.
Rani has a statement.
DR. HOWELL: Rani?
DR. SINGH: Rani Singh from Region 3.
There is a committee which was formed to address this issue, medical foods, which has already been working and was providing guidance for the parents survey. So I thought the idea was to continue with that and to bring the information back.
The ultimate goal I think, which was discussed, was really to get some final commitment in terms of our guidance from the committee. Is that --
DR. TELFAIR: Well, it was one of those long conversations that had a lot of information presented and there were different levels of agreement as to -- sort of the group that was doing the survey or planning the survey seemed to me to have moved along pretty good. The question was what should be the focus of the survey. The plan initially was to focus on families and get information from them. The suggestion came up to also talk to legislators. Another suggestion came up to talk to providers. So it seemed to me that as a committee member we were being asked to consider a number of avenues and means of getting at this information.
So I left with the impression that what we agreed to was that we would continue just as a group to support the survey that was going but also there was a clear need to put in place some amount of information that we can make a determination as to should we endorse some of these other proposals that all seem very reasonable to do but should we do that. So that's where the fact-finding part came in.
If enough information already existed, it's not necessary at one level, but if it does exist, it may be inadequate at another level. So we just needed information as a committee to be able to help make a decision as to what we would support and move forward.
So that was my understanding of where we were. I know it took a while to get there because there was such a large amount of information.
DR. SINGH: Thank you.
DR. TELFAIR: Did I sum it up?
DR. HOWELL: It seems to me that what's happening is that your group, a group you're involved with not formally related to this committee, is doing a survey and you're planning to report back to the subcommittee. Is that correct?
DR. SINGH: No. I'm personally involved with the group which is involved with the survey here.
DR. HOWELL: Well, that's what I said. You're doing the survey totally unrelated to this committee. This committee.
DR. SINGH: Yes.
DR. HOWELL: Yes, that's what I'm saying. This committee. So your plan is to continue your survey and report back to the subcommittee. Is that correct?
DR. DOUGHERTY: Or to discuss other fact-finding -- there are several surveys. There's a survey of metabolic dieticians that's being developed. There's a survey of legislation, and there's your survey of parents. I'm not sure the surveys actually need to be completed before coming back to the subcommittee and the full committee to say, and this is what else we need to happen. We didn't talk about the time lines for the various surveys.
So the subcommittee itself is not doing a survey. There's no survey on behalf of the advisory committee.
DR. HOWELL: That's correct, but the point is that you're going to listen to the reports of various groups. I see Carol is nodding back here, but I assume she's involved in another survey that will report back to the group also. Is that correct? Can you be brief, Carol?
DR. SINGH: Thank you.
DR. HOWELL: I hesitate.
DR. GREENE: There are three surveys. Two were in progress as part of the subcommittee being sort of shepherded or developed or being discussed by members of the subcommittee, not on behalf of the advisory committee, but working with some of Coleen's folks. That has turned into a potential for a survey of parents.
There was also interest in surveying the legislation, but that can easily be done with --
DR. DOUGHERTY: Alissa Johnson.
DR. GREENE: -- Alissa Johnson.
And we learned at the meeting of a third survey that's being conducted completely independently by the

dieticians of the dieticians.
I am reminded that one of the functions of the advisory committee is to give advice on what data needs to be collected, and Michele had made some interesting comments about whether the next steps might involve collection of more data in potentially other ways. So I think this has evolved into a let's see what's out there and come back to the committee.
DR. HOWELL: That's what I understand. In other words, there's a series of surveys that are being conducted independent of this committee but will advise your subcommittee.
Let me make a personal comment. When phenylketonuria screening first started and I was running the metabolic group at Johns Hopkins north of here, we had this same discussion. I might point out that was before most of the people in this room were born because the problem is that Lofenalac was not covered by many people, and we couldn't figure out how to get it for the patient. So that discussion, I can verify, has been going on for more than 40 years.
I would suggest this group really think out of the box because one of the problems is getting special funding for nutritional things when virtually everybody in the U.S. is on a special diet. One of the problems is how to identify these really very important nutritional materials for patients who will have suffered terrible damage without them and separate that from the really literally millions of people who have special diets because of a variety of "needs" that are not well verified. I think that's a big problem, and I would encourage the group to really think out of the box about how to do that.
DR. DOUGHERTY: There is one more that Susan Berry mentioned. Coleen knows of information that has already been collected. So I think she wanted the subgroup to look at that as well.
DR. HOWELL: So we will expect a number of specific products for this committee in September.
DR. DOUGHERTY: Yes.
DR. HOWELL: Reports and so forth and a document. I assume that you clearly have in mind then publishing your data on long-term follow-up in a peer- reviewed journal so that the definition of long-term follow-up in this area will be a product of this group, which I think will be very good. Excellent.
Any further comments about Denise and her committee? They obviously had a busy day.
(No response.)
DR. HOWELL: We are next going to go to the Subcommittee on Laboratory Standards and Procedures, and that will be reported by its chairperson, Dr. Amy Brower.
DR. BROWER: Good morning. Thank you for the opportunity to give you an update on our meeting yesterday. We were joined in the lab subcommittee by 18 colleagues and had a great discussion.
We started out with an update from Dr. Harry Hannon and other team members on the routine second specimen study. To date, CDC IRB review is complete. Remember, this study has two parts, a retrospective section and a prospective section. The IRB concluded that the retrospective study is a category IV exempt and that the prospective study may not be considered human research.
What's currently being undertaken is that there are state- specific IRBs that may be required. APHL is going to create a spreadsheet to track the progress of the states that are participating in this study as they move through their IRB process. APHL is working on an electronic data collection form, and we hope that that will be complete and out for review soon.
We also had a group discussion regarding the expansion of this study to tandem mass spec, and this was something that was originally brought up to the committee as a whole when we were considering this routine second specimen study. So we're well aware that this study is a first step and hopefully will create a template for future studies regarding routine second specimens.
We got an update from Dr. Rinaldo on the Region 4 data initiative. The project is continuing and progressing very well with significantly increased participation both nationally and internationally, and Dr. Rinaldo will give us an update after the subcommittee reports more in detail.
They have established performance metrics. So I'm just going to highlight a few things that are important as we think through the laboratory harmonization on our subcommittee. So performance metrics have been established, focused on detection rates, positive predictive value, and false positives.
The collection of the data and the analysis tools that are being generated enable data comparison across labs within regions, across regions, within a single lab as a single entity, and around the world with the international participants.
There's a sample exchange program that's complementary to the CDC proficiency program, and the efforts are facilitating the narrowing of the cutoff ranges.
We also had an overview from Dr. Hausman on a recent FDA presentation at APHL. So Dr. Hausman walked us through Dr. Harper's presentation at APHL. Really, our main question was what is the FDA's

role in oversight of the newborn screening laboratories. As a group, we discussed that FDA's focus currently is on the reliability of the test and the intended use of the test. Currently FDA's regulation in the newborn screening world is really focused on the manufacturers of the reagents, whether they're research use only, analyte-specific reagents, or IVD kits.
We had a question as a group whether laboratories that perform other states need FDA clearance, and Dr. Hausman was going to follow up on that item for the subcommittee.
We also had a lively discussion about collection cards and a reminder that these cards are regulated as medical devices. We had a discussion that currently there's a single source of cards and that there's a current crisis in the newborn community due to the difficulty in acquiring the cards. Dr. Hannon gave us an overview of APHL and CDC's efforts in sending a joint letter to the company to alert them to this crisis, but it was a matter that we thought we should bring to the full subcommittee to make sure that everybody was aware of the issue.
We also had a discussion on cystic fibrosis. The implementation of CF screening is an important example in DNA analysis. We identified a potential research study related to the variability in current screening practice and associated outcomes. We discussed the differences in the screening algorithms that are currently being used, as well as the makeup of the DNA panels that are being used.
In addition, we talked about the different approaches to carrier identification and communication to the families. We feel, as a subcommittee, that this is an area that would be appropriate for a research study and further analysis.
We also talked about Dr. Phil Farrell's initiative on facilitating laboratory adoption of CF screening. We understand that Dr. Farrell is on sabbatical at CDC and is helping many newborn projects implement CF screening. We also understand that Dr. Farrell is working with the CF Foundation to derive guidelines on a mutation panel that should be included in the newborn period.
In addition, we talked about secondary targets. We identified that there is variability in the screening of secondary targets among the states in the United States. There's a difference in the language and also the categorization between whether it's mandated, offered, and reported. Dr. Therrell's group has offered to do a survey and report back to the full committee in September regarding how many states are mandating, offering, and reporting these secondary targets.
We discussed the need for the education of providers and the public regarding secondary targets and had some anecdotal information from Dr. Therrell on getting calls from parents saying I want the full panel or I want more than just the 25 targets. Can you give me the 50 or so? So there's some understanding that needs to take place and education in the community. And we thought we'd bring that to the Education Subcommittee and ask them to consider that in their efforts.
We wanted to remind the committee and the public that there is a publication called "Counting Conditions" that walks through the issues of primary targets and secondary targets that's very helpful for all of us to understand this issue.
In addition and finally, we talked about pilot studies, and this is really related to the nomination of new conditions to the screening panel. The nomination form does include the key components for ensuring a test is variable. So as the Laboratory Subcommittee, we're focused on whether a test and a technology is acceptable for newborn screening.
We do understand that pilot studies being planned for SCID may not include some of these components. So we discussed whether we could provide some additional education and guidance for the pilot studies to be able to include these key components. We discussed a grid of data points that could be communicated to different pilot studies as a plan for their studies and carry out these studies to make sure they're capturing the key data points that will be needed in consideration of the new condition.
And the subcommittee is taking this as an action item and will be discussing it electronically and on conference calls over the next few weeks. We realize that these pilot studies are a significant undertaking both financially and with precious samples, so we want to make sure that we guide the pilot studies in including all of the types of data that might be needed.
Thank you.
DR. HOWELL: Questions and comments to Dr. Brower. Ethan?
DR. HAUSMAN: Yes. The first question, only a question. Did we identify where "Counting Conditions" was published for where we could locate it?
DR. RINALDO: It was in the supplement to Pediatrics.
DR. HAUSMAN: Okay. Thank you.
DR. HOWELL: Questions or comments? Tony?

DR. GREGG: I was just going to make the point that the American College of Ob-Gyn Committee on Genetics has a draft that's sort of circulating right now to educate providers. The first draft, second draft, and third draft all received continuing concern over the definition of secondary targets, how best to educate in a couple of sentences what secondary targets really are. Are they on the launch pad to become part of the primary screen? Where do they really fit in this whole discussion?
The next thing that came up and continues to drag me down in finishing this now fourth or fifth draft is these metrics. Piero and I have had some email discussion, as well as discussion yesterday, about these metrics, positive predictive value, negative predictive value.
What I'm a little puzzled by is whether all the attention is directed to MS/MS or are we talking about newborn screening as a whole? Because patients and providers -- I mean, we're selling this as a newborn screening package, but we're not really addressing the specific aspects to CF screening, hemoglobinopathies as it relates to these metrics, some of the non-MS/MS aspects.
While the MS/MS aspects, I think, are probably driving some of the larger concerns just because there are so many tests and there will be so many potential false positives, I think we're going to need to have metrics that encompass the whole discussion, newborn screening, what are the possibilities, what are the metrics. And then for the groups individually as they're laid out in that table by the ACMG, the MS/MS group, what are the metrics, the non-MS/MS groups all individually? And I think that really needs to be looked at. How do you tell patients what's the likelihood that you're going to screen positive when all were considering, really, is MS/MS potentially in this discussion?
DR. HOWELL: Who would like to start in response to Tony's question?
I think it's fair to say that the discussion around secondary conditions has been considerable, and I think it basically derives from the fact that when you're looking for specific analytes to diagnose a condition, you without question have the ability to identify other conditions. And I think that's the issue that has been extremely difficult, at least I think so.
Who else would like to talk about that? Amy?
I happened to be at this committee yesterday, and this was a major discussion at that committee yesterday.
DR. BROWER: And you're right, Dr. Gregg. We also talked about cystic fibrosis with the different mutation panels being used, that the residual risk is really different depending on how many mutations the child was screened for. So, hopefully, with Dr. Farrell's efforts on this, the up side and some coordination between his efforts and ACMG, we'll better understand CF. But your point is well taken, and I think we understand that this is an area that we really need to focus on.
DR. HOWELL: We're doing pretty well on time, Madam Chairman. I wondered, Piero had a slide yesterday he showed at this meeting that addressed secondary conditions that I thought was very informative. Do you have that with you? You know, the one that's a very graphic demonstration of the issue of core conditions and secondary conditions and what, indeed, are the facts that are behind that. At least, you had that yesterday, and with luck, you've got that today and maybe you can show it.
Maybe while you're tooling up, we can hear from Dr. Green.
DR. GREEN: Thank you. Amy, thank you for a very succinct and accurate report.
But I think Tony's question about describing newborn screening to the obstetricians also brings up a point that we discussed yesterday at the meeting, and that is, that amongst Dr. Farrell's prodigious work around organizing CF screening was some sort of evaluation -- I'm not sure how that will happen -- of the appropriate mutations for which screening is the most informative. So there was discussion about seeing if those recommendations could be harmonized with the prenatal CF screening since I think it would be confusing for the public ultimately to have a mismatch of mutations.
DR. GREGG: No, I think that's a very important point.
DR. HOWELL: Thank you very much.
Dr. Hannon.
DR. HANNON: Two comments. First, on CF, the idea of the panel was to try and keep the mutational counting thing from getting into the same game we play with counting conditions. One particular manufacturer would say it's much better because they cover a bigger array of mutations to try to get a comprehensive panel which covers those mutations which are of clinical significance. So, I mean, that's the game that's trying to be hit before it gets started because you now have some manufacturers who have extensive panels of mutations and some that have few.
There is another issue about how many are actually captured by a particular screening lab, but we want to prevent the counting game from getting over into the manufacturing arena by identifying those that are

clinically significant and would like to enrol the CF Foundation in those decisions.
The second issue about secondary is that when Piero puts his paper up about what he sees as secondary, that's only mass spec. You've got the issues with galactosemia and other disorders where there are secondary conditions that are being excluded or added, and primarily for galactosemia, the polymerase and kinase are being dropped in favor of GALT for a lot of places. So, I mean, this is an issue beyond mass spec also.
I talked with Michele about a potential project with getting APHL involved to look at those disorders that are outside of mass spec in terms of the performance metrics, metrics that Piero has proposed, which I think are great. We need someone to get those disorders captured which are outside the panel that's captured by mass spec.
DR. HOWELL: I think that Harry's comments are correct. Obviously, we need screening for galactosemia. If you measure galactose, you're going to pick up kinase and polymerase, as well as the uretyltransferase. And if you do, obviously, the enzyme, you only get one of those.
The situation, however, has focused very heavily on mass spec at the current time. Piero had this chart yesterday, which I hadn't seen, that I thought was quite informative. That's the reason I've asked him to see if he can show that to the group.
The other thing that Amy mentioned that's important is that it's important for this group to know that there's only one manufacturer in the entire world that provides all the filter paper for newborn screening, which is, indeed, interesting when the entire screening program in the country is dependent on one manufacturer. So far, that's worked, but it certainly brings up a lot of interesting questions.
DR. RINALDO: This was a part of a presentation that I gave at the SIMD meeting a few weeks ago. It's called "The Imaginary Missing Wedge."
First, let me describe what this is. This is a plotting of the MS/MS conditions, listed for all the U.S. states. So here in a lighter color you see the primary targets. So there are 20 primary targets, and in a darker color, over 22 secondary targets. So there are a few states that actually say they are looking for all 42, and although there is actually quite a lot of consistency in testing for the primary targets, you see what I call the imaginary missing wedge. So all the states, if you want, are not -- again, it's not clear. That was part of a discussion yesterday. If you are looking for them or reporting them.
But the point is this is an imaginary missing wedge, and the reason is very simple. If you look at the uniform panel, here are all the conditions listed and the secondary target, and you ask a question, how many of the secondary targets are unrelated to the differential diagnosis of a condition included in the uniform panel, Dr. Gregg, the answer is very simple. Two. And that is really what people need to perhaps develop a better appreciation for, that all the others are linked to the differential diagnosis of a primary target.
And because it's just not feasible to make a differential diagnosis from the initial primary screening -- there are some anecdotal data. For example, the Netherlands seem to reserve the right to do some confirmatory testing and, if it's not a primary target, hide that information. It's probably something I don't think will work well here in the United States, but this is a model that in Europe is actually quite popular. That's a whole other story.
DR. HOWELL: And again, I think that in the evolution of the core panel and secondary panel, it was recognized all along you can't accurately diagnose the places on the core panel without at least considering those on the "secondary" panel. That's been very confusing and remains confusing. But I thought this graphic illustration was the fact that if you're running the core panel and so forth, it's hard to not come up with the others.
DR. THERRELL: Brad Therrell.
As the keeper of the national data, this is a little bit misleading, and that's why we volunteered to come back with a report to the committee next time because what that shows are the states that are willing to mandate those and to list on the website that they've mandated them. That's different from the graph you would get if you showed the states that are actually offering those conditions. So most states, in fact, offer all of those conditions, but they choose not to indicate that they mandate certain ones because of some legal responsibilities. And the lawyers are advising the programs that if they show that they're mandating those and then they don't pick one up because some of these are less likely to have all of them picked up, then they're exposing themselves to a legal liability that they don't need to do. That's why we think if we show this next time, it will be a little bit clearer as to what the programs are really doing.
DR. HOWELL: I think most of us would think that we should make decisions based on the best scientific and medical evidence and seek the advice of our lawyers to help keep us out of jail, but that's not a good

reason to not report something.
DR. RINALDO: Yes. This is, I think, perhaps a symptom of the confusion, that you have medical decisions made by lawyers.
DR. THERRELL: But it's not that they're not reporting them. It's that they're not mandating them. They're still reporting them. They're running them and reporting them. They're just not showing that they're mandated.
DR. HOWELL: They have very careful legal advice.
DR. RINALDO: I disagree because I've seen examples and tyrosine is the best example where you can find any combination. We have one primary target and two secondary targets, and I've seen states that either mandate or report tyrosinemia type I or II and now III. I've seen II and III but not I, and I think these are decisions made out of a scientific and medical context.
DR. HOWELL: So we can expect Dr. Gregg to have at least several more documents to review as you prepare that.
(Laughter.)
DR. HOWELL: But I'm serious. I think that coming up with some really thoughtful descriptions that are accurate about the secondary targets is very important and in the public interest and so forth.
Are there other questions or comments about Dr. Brower's report? The committee, like Denise's committee, had a very busy and productive time.
DR. SKEELS: Dr. Howell?
DR. HOWELL: Mike?
DR. SKEELS: Actually, I don't want anyone to leave with a misconception that when screening programs are just saying that they're mandating certain disorders, that this is being driven by sort of defensive, overly legal, narrow interpretation.
We work in a public policy context where quite a lot of decisions are made without purely rational, scientific thought. It's called the legislature. We go to them and we say, as a matter of public policy in my state, we're going to adopt administrative rules, or whatever the state's analog to that is, and we're going to screen for these as a minimum. That's exactly the way we put it. We say were going to look for these things as a stated purpose of our program, as a matter of public policy, to look for these. But we're quite open, and we say, but while looking for these along the way, we may find some other things that would be of value to the patient.
It's not as if we're pretending that we're not doing things that we are doing. We're doing what the public policy process dictates, which is to define in a formal way what we're looking for. I was sort of uncomfortable with the idea that we're just listening to our lawyers and doing what they say. It's not true at all.
DR. HOWELL: Thank you very much.
Any further comments and so forth?
(No response.)
DR. HOWELL: The Subcommittee on Education and Training, Dr. Hawkins' group.
DR. HAWKINS: We had a very good meeting yesterday and it was well attended. We, on one count, had over 20 people at our meeting.
Some of the issues that we've been talking about I'll address a little bit later, but I just want to start by reviewing, for everyone who may not be familiar with what we do, the charges of the Education and Training Subcommittee. Again, it's to review educating and training resources for health professionals, parents screening programs, and then go ahead and identify deficiencies and make recommendations for actions regarding these five groups that we mention at the top.
Kind of an update on the activities. Last meeting, we submitted a request to the committee, which we voted upon, and that recommendation actually was to develop and fund mechanisms to study the distribution of existing newborn screening, educational materials, and acquisition of knowledge about newborn screening by expectant parents in the context of the health care provider/patient relationship.
A letter was drafted and I guess was submitted to the Secretary after the last meeting. I'll just give you an update. First of all, that letter is under tab 5 in the notebook. I guess the letter has been submitted to the Secretary, but so far, we haven't heard any response back.
We had two conference calls since the last full committee meeting, two what I call very productive conference calls to kind of give us the next jumping off point, where we're going to go with the subcommittee after the last recommendation.
We also noticed some significant changes in membership of the committee. Some of the long-time

members have changed. Dr. Stephen Edwards stepped down from the AAP and Nancy Green has moved from the March of Dimes to Columbia University. Those are two voices on our subcommittee that added so much knowledge and we're going to miss them. Now we have two individuals here today, Dr. Ashton and Dr. Trotter, who were at the Education and Training Subcommittee yesterday. So we appreciate the input that you had yesterday at the subcommittee meeting. Also, we were notified that Gail Johannes will be retiring, and so she will no longer be serving on the E&T Subcommittee. We want to thank those that helped so far on this committee, and like I say, we appreciate what they've done.

Our current focus is still kind of going in the same direction. At the March conference call, our discussions were starting to be directed to broader issues involving communicating the newborn screening education materials, and particularly, we were looking at how these materials are developed in the context of different ethnicities and different cultural environments.

There were several questions that arose, especially at the March subcommittee conference call. Number one is, what newborn screening materials are available in different languages? Second, who's producing these materials? Are they being produced by the regional collaboratives? Are they being done nationally? Are they being done by the state? And what resources are there available as far as sharing those resources? How are these materials prepared? In essence, are these materials prepared with care, or are we just translating material blindly and putting out material that may not be completely accurate? And what are the considerations when preparing these educational materials?

That takes us into some things that we may not even consider, which brings us to what I'll talk about a little bit later, some of the individuals that spoke at the E&T meeting yesterday. But primarily we're looking at some of the ethnic and cultural issues. When we try to relay information to cultural groups, are we getting information that's accurate to them that they can use and they'll actually be willing to accept within their culture?

So the overall question that arose at that meeting was, could the regional collaboratives integrate their work in order to better disseminate this material that's produced in different languages? In other words, if we look at a regional collaborative maybe saying in the middle of the country, they may not have a lot of use for Chinese materials. If you think of a state somewhere, like North Dakota, versus a state like California, what type of material you may produce for your population is going to be totally different. In essence, California may have certain resources that they could share with another regional collaborative that would give them the benefit of having education material that may be arduous for them to prepare themselves.

So based on these discussions, we decided to invite some individuals to speak at our subcommittee. We had two individuals. One was Dr. Murray Brilliant. Dr. Brilliant is a professor of genetics in the Department of Pediatrics at the University of Arizona College of Medicine. There he serves on his research steering committee of the Department of Pediatrics and serves as the director of the genetics graduate program. Dr. Brilliant's research was kind of interesting in that he has been doing a lot of complex genetic studies and he's been looking at Native American populations when doing some of his studies. So he brought some insight -- I'll follow that up a little bit -- on some of the cultural aspects of genetic concepts in the native American cultures.

Our second speaker was Dr. Kristi Zonno. She's the Rhode Island Newborn Screening Program Coordinator and serves as the manager for the state blood spot and hearing screening program. Mrs. Zonno is also the state early hearing detection and intervention coordinator and the genetics contact within the Rhode Island Department of Health. She also served on the board of directors of the New England Regional Genetics Group and is the co-chair for the New England Public Health Genetics Education Collaborative.

So we invited these two individuals to come speak to us.

Mrs. Zonno's area that she covered at the meeting was the development of different education materials in different languages and kind of gave us a report on how they developed the materials in the New England district.

Just to briefly give you an overview of what they both talked about. Dr. Brilliant spoke on his experience in performing studies in Native Indian populations in Arizona, including the Navajo, the Hopi, and the Havasupai tribes. It was kind of interesting to hear him talk about how these groups relate genetic studies to their culture.

Right now, two populations, the Navajo and the Hopi, currently have moratoriums on performing genetic studies in their populations. There are several reasons for that. It's the way they view what has gone on in genetic studies. They have a negative perspective. They've been very sensitive to the repercussions of

things that have gone on in the genetic studies.
A good example is during the development of the Human Genome Project, both populations were under the impression that they needed to be in these studies because they were told that if they weren't studied for their diversity, that basically they had the possibility of becoming extinct. Now, we know we don't tend to talk about human beings becoming extinct because that is more or less kind of putting them in the category of an animal. So you can imagine being told that your type is going to disappear from this earth. So that would kind of make them step back and say, oh, well, maybe we don't want you to be studying us on a genetic basis.
A second one is during the genetic study in the Havasupai population from northern Arizona, they started doing some mitochondrial testing, and some of the results from their testing that they reported to these Native Indians was that actually their origin was from Asia. So based on that information, these Native Americans were not exactly happy with that, considering their religious background suggested that they arose from the Grand Canyon Basin. So you can imagine the sensitivity they've had by being told that where they have originated from their beliefs is now being challenged. So now there's some resistance to actually looking at them in a genetic way for doing studies.
Interesting enough, both native populations are currently part of the newborn screening program, and they do not consider newborn screening to be genetic because DNA is not involved. I remember at one of the first meetings we ever had here, I had a conversation with Piero that there is that impression in some communities that what is done with newborn screening is not really considered genetic unless they're tested by their DNA. And this is one situation where that situation has arisen where there's probably some miscommunication and not understanding exactly what genetics is. So if you were to relate to these Native American tribes exactly what testing is going on, what kind of resistance would they suddenly throw up as far as barriers to the newborn screening program?
So it's something to consider, as we go forward and we're developing education materials, that we understand these cultural barriers that we have to deal with. We tend to think that maybe this group in this room is the primary target, but we have to understand that there are other cultures and other ethnic groups that view the education, or especially genetics, in a different way than the way most people in this room may view it. So it's something to really consider, when you're developing this material, that you don't become offensive.
So this brings up the question, how do you educate a group of individuals who are so negative on genetic testing and then suddenly someone gives them material that says, hey, we're doing genetic testing on you and suddenly they throw up this barrier and they don't want to be included? I guess so far this hasn't occurred.
So, again, these are some of the questions that kind of were brought up from that issue. What will be the Native Americans' position when genetic testing becomes DNA-based? We've talked now about doing screening panels where we may have the future of doing a lot of DNA testing. Right now, if you look at some of the genetic platforms from companies like Affymetrix and Illumina, we're able to do a million polymorphisms at one time. So that's not going to be unheard of, that we may do genetic testing in the future completely on a DNA-basis.
What will be the reactions if educational materials consistently state that the newborn screening is a form of genetic testing? And how do you educate these diverse cultural groups on newborn screening without offending? And how do you persuade their continual participation in a program that they may throw up resistance to?
The second speaker we had was Kristi Zonno. Her talk was excellent as well. What Kristi did, she went through the process of how her regional collaborative is developing education materials in different languages.
Basically what they did in their process is they went around the regional group and they pulled, I guess, from different states and asked what are the top five languages that you would like to have material, and then they gathered these in the collaborative group, and then they created the material. Of course, they prepared the material in each language and they used a quality control testing to eliminate for spelling and language errors, which was really important when you started considering -- she showed examples of material that had actually been translated.
They didn't send it out to the community as a whole. They actually targeted the specific user group. In fact, when they got the comments back, the comments maybe were written on the material, but they were written in the language that the person spoke.
Then they had to have a translator translate that so they could go back and figure out what they did

wrong on the material. So it was an interesting quality control process they went through to make this material completely accurate.
Thus far, they've completed materials, of course, in English, Spanish, Portuguese, Vietnamese, Chinese, Khmer or Cambodian, and Arabic language.
Right now they're working on a number of different languages. I've got a couple of these with asterisks beside them, and I will discuss those in a minute. But right now they're working on Bosnian, French, Italian, Somali, Laotian, Polish, and Russian.
Like I say, there are two languages there with an asterisk beside them. One of them is simplified Chinese, and the topic came up yesterday, to show you how we may not know with the material we're developing, is what is the difference between Chinese and simplified Chinese. Evidently there is a tremendous difference between those two languages. Of course, as an American, I would have no clue what is the difference between those. But by developing the material for one Chinese group, it may not be applicable to another Chinese group. So it's very important to look at the language in context of maybe a specific dialect or specific group that you're targeting that you may not access using just one specific language.
Of course, this is the actual list that Kristi put up yesterday. She said right now they're also developing Haitian Creole. Immediately a couple hands went up in the group and said, well, wait a second, Haitian Creole is not a written language. It's a spoken language. In Haiti, they write French. So, in other words, once again there was the disconnect of not understanding, from a point of view, the exact group that you were trying to target. I don't know much about the Haitian Creole language, but evidently it's not a written language. So you really can't develop newborn screening material. You would develop for that specific population in French.
So they're going to show you in a broader view some of the difficulties with developing some of the material for targeting the individual cultural and ethnic groups.
Again, we also had material that was provided by Kathleen Valasquez from California. She provided a whole folder, and I wish we had copies of it. It was a big folder. We only had one copy of everything. But there was a lot of material that they had already translated in Chinese, Laotian, Korean, Spanish. So we were able to see some of that material.
Of course, the interesting note that came up yesterday is that the Spanish that may be spoken in California and Arizona is not the same Spanish that may be spoken in New York City. Again, you're trying to target your specific areas. What type of Spanish are you going to be writing your material in to target your specific population?
So there are several issues in developing NBS education material. First of all, of course, it involves more than simply just language translation. The material must reflect a relevant knowledge of the cultural- and ethnic-specific characteristics of each target group. Again, we just talked about the issues with the different Spanish dialects or like they had with the Haitian Creole.
The development of newborn screening education material is time consuming and costly. And duplication of time and expense is really unnecessary. We think the situation of California, which probably has one of the most diverse populations in the country, that probably a lot of the material that's being developed there could easily be used in other areas of the country, and it could simply be adapted.
Also, the newborn screening education material might undergo quality testing. That quality testing should involve finding relevant reviewers and have a feedback process that directly involves the target groups. In other words, just don't send it to a translator and have them translate it into Chinese or have it translated into Spanish. Give it to the people who are actually going to read it and let them test it in real-time and get it back to you with the actual comments.
Part of this issue also came up with what kind of pictures do you put on it. An example that I brought up yesterday is we saw some material with Wake Forest University where someone had put a picture of a Chinese family on there. One of the Chinese families that we worked with said, they're not Chinese. I can tell. They're Japanese. And I knew it was developed by one of the caucasians in our department. So, obviously, we have to understand that there are those barriers that we don't understand when developing material. We want to make sure that it's completely accurate, even right down to the pictures that are included in the material.
The newborn screening education material must relay a consistent national message, and I think that's something that should be important as the collaboratives and the states develop material. Are we relaying the same message to all the individuals that this group here today is actually advocating?
So in order to address these issues, we believe a coordinated development plan should be implemented to simplify and streamline the development of newborn screening education material in different

languages. So we came up with a recommendation that we'd like to bring up for discussion today. Mike Watson is in the back. And I apologize. I tried to find you this morning to show you this before. I didn't want you to be blind-sided, but I couldn't find you. I did find Brad this morning and was able to talk to him.

But this is the recommendation that we came up with yesterday. That the Education and Training Subcommittee recommends that the National Coordinating Center for the Regional Collaboratives work across and with all regions to create a national repository for newborn screening educational materials in multiple languages and multiple formats, paying close attention to cultural diversity and quality translation. Such a repository would eliminate the duplication of efforts by each region or state to maximize the efficiency, finances, and resources. The NCC should develop a committee, in coordination with the National Newborn Screening and Genetic Resource Center, that would develop guidelines for the translation of materials to be tested prior to deposit into this national repository.

Now, the goal of this national repository is not so much to force the areas to use this material, but is to supply material for them to use. Let's give a good example. A doctor is sitting in North Dakota and they have a family that's Laotian. And they have no material access. They can call up their region and say, I'd like to have some material for a Laotian. If they don't have that material, they can go to this repository. The information in this repository has already been refined. It's been edited, and they can actually get that information and get it back to the patient as soon as possible. So it would be an online resource.

So as guidelines for this repository, again, the repository should be created and maintained by the NCC, the regional collaboratives, and the NNSGRC. The repository should be maintained by Internet access. However, untested material would not be made public.

The committee formed by this agreement would institute rigorous quality testing guidelines to ensure the final quality of the deposited material. These guidelines should include testing in relevant target groups and should involve a feedback process. In other words, we're not trying to regulate how the material is produced in each region, just the material that would be deposited. The material that is deposited in this repository would have gone through a refined process that, if you're going to put your material there for access to the rest of the country, it has to meet these strict guidelines.

Probably one of the most important things is that it is tested in the relevant target groups and, of course, should involve that important feedback process.

All material deposited in the repository would be available to each regional collaborative for developing a regional-specific material. In other words, this is refined material. If you want to take that material and you want to develop your own specific material for your state or for your own region or even if you're in a doctor's office, you want to develop your own brochure, this would be refined material for you to access to develop your own education material.

The advantage to that is the key language translation and cultural-specific issues will already have been addressed.

This agreement would reduce the cost and time to produce quality multi-language newborn screening education material.

Also much of the material was already available. Some of the material is already refined and is already available. You look at areas like California and New York that have very diverse populations, some of this material is already ready to be deposited for everyone in this country to access.

And establishing the national guidelines for developing this material would create a more unifying message for the newborn screening program.

So I have just opened up a can of worms, I'm sure. So we will open the questions.

DR. HOWELL: I think that we, obviously, can have a few questions. Obviously, this committee doesn't have the ability to direct the National Coordinating Center or the newborn screening thing to do anything. But I would imagine, without knowing this, that the regional collaborative program that Dr. Watson has the coordinating center certainly has plans or at least has thoughts or something about developing educational material and so forth.

Mike, would you like to comment about that? You've had a great deal of time to plan this.

DR. WATSON: I guess no is not an option?

(Laughter.)

DR. WATSON: You know, it's an interesting problem. All of these questions that involve the regional collaboratives have, I think, an underlying issue in them, which is that, for the most part, most of the money is in the states. The states are charged with mandating what will be screened in newborn screening. As part of that process, they also develop educational materials. So in the regional

collaboratives, I think the same people often participate with the states in developing that material with them and for them.
Our problem is that we don't have the states playing well together, and I think that's probably the fundamental issue that we have to move towards for a number of things, everything from data collection activities, research involving newborn screening, educational materials. It's figuring out how to pull the states together so that they're not necessarily -- I think, you know, something for the Hispanic population in California probably works for Hispanic populations in other parts of the country. So figuring out how to pool our resources so that we're not duplicating efforts everywhere in the country is probably the best way to go.
That, I imagine, will be part of the meeting we have in September that sort of bridges HRSA's interests and NICHD's interests in figuring out how to get the states to function a bit more together so that we can collect national information about patient populations, give us a lot more information to make decisions on about newborn screening, not just about what's in it, but what might come into it. And as part of that, I think the educational materials will have to be put into place.
DR. HOWELL: But what I hear you saying is that, obviously, the states have a charge to develop educational material, and it would certainly be sensible for the collaborating center to at least have conversations to try to coordinate that.
DR. WATSON: Yes, I think so. I think Mike can answer the question. I think part of your charge, when you decide to screen for something, is to develop the supporting materials that will allow a screening program to move forward for your entire population. So I think it's a matter of figuring out how to get the various states that are moving on these things to sort of pool some of their resources and interests to develop materials.
DR. HOWELL: And I think at the same time, I would anticipate that Brad's center would collaborate in trying to make those things happen.
DR. WATSON: Brad I think already does. I think he collects all of these materials from all of the states already, as I understand it.
DR. THERRELL: Yes. We collect everything except the different languages. So we have all the English ones, and we pretty much know where all the different languages are. So when a doctor in North Dakota calls us and wants something for Vietnamese, we'll send them to California or to Massachusetts or whatever. So it wouldn't be that much of an effort for us to get the other materials and put them in our repository.
Now, the thing about having a group review them and makes sure it's up to snuff is a different issue. That's one where I think you get into some real issues with the states because even right now with the ACMG ACT sheets, not all states are using them because their advisory committees, in some instances, don't think they are as good as their own materials or something like that.
So I think it's a good idea to have this kind of repository. We've already moved in that direction partially. We can move more fully in that direction. In fact, we've just hired a new genetic counselor whose specific role is to work on educational materials.
DR. HOWELL: Mike had a comment I think.
DR. SKEELS: I was just going to respond very briefly. You're right. We are supposed to be providing culturally appropriate educational materials. Some states like Oregon have in statute that we're to conduct an educational program to go along with the other parts of the program.
I would say that the states do play well together in this regard sort of on a state-by-state basis, but there has been no national attempt to coordinate that or encourage it, and we will welcome that. I think it's a terrific idea.
DR. HOWELL: Harry?
DR. HANNON: Well, like many of us, I was in Minneapolis, Minnesota last week or week before last. I'm traveling so much I forget where I am when. But as always when I'm in a city, I try to tour the state lab, and I went to the lab in Minneapolis. I saw their educational material. What is in it that could create problems in exchanging materials is they have a list of about 54 disorders and are about a 9 font on the first page when you look at it. Here are all these disorders. I asked Mark. I said, when these are given to parents, what do you hear? And they said, oh, that's a lot of disorders, which sort of captures the aura of it.
But the other thing that was very interesting, which comes back to the comments that were made, is they have this little handmade pamphlet for the Amish population. They don't like to have pictures of people in them. So they have all these little Amish quilts, and they punch it and put a little ribbon through it. It's all

handmade for that population. So, I mean, this is a culturally sensitive undertaking that the folks do there that is very labor-intensive to put these together. They didn't want to give any away, but I managed to talk them out of one copy for Carol Bell because she's a big quilt fan. It had all these little illustrations of Amish quilts in it. So it was a very neat idea.
Thank you.
DR. HOWELL: Anne?
DR. COMEAU: It's true that I think there is room for national collaboration. Since 1999, we have nine languages on our website.
Two thoughts. One is that there are some standard messages that can go forward, and I think there have been materials developed for that as well. But when it comes to designing research studies and pilot studies, there may be human subjects review language that is required that is going to be state-specific. But in order to keep the cost down, I know what would be helpful would be a way to actually block out specific phrases from one language to another so that if you are trying to develop new materials and you're looking for a specific English phrase, you can find that phrase in the various languages because just knowing that if you're looking across nine languages, it's not always -- I'm going to use the term "chronological." But it's not always line for line that you can substitute lines. And if there were a way on a national level to take some of the available materials and really highlight a phrase so that you know that as a state, this is the phrase I want, I'm going to pull out that phrase, it would make the translation much more cost effective because translation -- I just couldn't believe the amount of money we had to spend to translate our 12-page brochure.
Does that make sense to the particular suggestion?
DR. HOWELL: That's an interesting idea.
MS. AU: Hi. I'm Sylvia Au from the Hawaii Department of Health. Coming from a state program, I want to say state programs do play well together in our region. State level education materials have to follow specific guidelines for that state. They have specific laws and information that you must include. California, for example, has a very extensive booklet that they have to give based on their state law. So we couldn't take California's booklet and use it in Hawaii because they have state law in their book that says you must include all of this. So there's no way that you could use it in another state. But you could take phrases, like Anne said, out of it.
The other thing is that in our region we had a research project where we did a lot of focus groups in our Western States Region, and we asked parents what they wanted for newborn screening education. We have a message library and a graphics library that's copyright-free. You can go in there and make your own education materials.
We also have a lot of information where we tested education materials, and we found interesting things such as parents, no matter what their ethnic background that we tested, didn't want pictures that showed specific ethnic backgrounds. They liked pictures where you really couldn't identify what ethnic background the person was, which surprised us as state programs because we always thought it would be nice to put pictures of diverse families.
The Alaska population had a beautiful painting that was done by a famous artist in Alaska. The parents were like we don't even know what that is, and we don't like that. So there are lots of things that we think are great, but the parents don't think it's great.
So I can share some of that information. It's all on our website for the education materials and the graphics library and the message library too.
DR. HOWELL: I would assume that none of the state brochures are copyrighted. I would certainly hope that they're not so that it would be possible for anybody to use anything that they see that's interesting in their brochure. But I may be wrong.
Piero.
DR. RINALDO: I just would like to add a comment that as you consider these foreign languages, I hope you realize that there is really no one Italian. I can speak with my family in a way that Dr. Pasquali wouldn't understand a word.
(Laughter.)
DR. RINALDO: Because this is a factor, I think, when people emigrate to this country so they can come from different parts, so you might identify them with a language that might not really be the language that you are using.
So I am just saying this to make a point that this material really should be of the greatest possible simplicity. I think one of the greatest things that happened in this committee when we had the

presentation -- I'm trying to remember the person that told us about the understanding of medical material.
DR. LLOYD-PURYEAR: Terry Davis.
DR. RINALDO: Yes. That was eye-opening for me because there we were touching with our own hands the fact that we can put together material in English and then we have large segments of our population that don't have a clue what we're saying.
So as we step in the territory of a foreign language, I think it only gets more complicated. So if this is done, it should really be done -- and I like what was said earlier. Anne, I think, said it -- to really convey very basic, fundamental messages and really try very hard not to get cute in details. It should be incredibly straightforward, simple, and then as a beginner of a dialogue rather than the answer to all the questions.
DR. HAWKINS: I think that's pretty much the direction we'd like to see it go in. It's not so much the states are putting their brochure on to force every other state. It's they're putting information. They have translated what this disease is in their language, and there may be 70 translations of what the disease is in those specific languages. You can specifically go in and you have this translation already available so you don't have to go out and ask someone to translate it for you.
In that respect, we could do every dialect that's in Italy. I mean, it's always possible. When you get things online -- yes, but you know what I'm talking about. When you keep it that simple and you make it simple, then you can direct it specifically. I just don't see any limitations to how many things you could put on there.
Dr. Trotter?
DR. HOWELL: Kathy?
MS. HARRIS: Very quickly. The MCHB has on their website a very simplified newborn screening brochure in English. It's very generic. It's available to all the states or to anybody who wants to use it and translate it. It's newborn screening information.
DR. HOWELL: Great. Thank you very much.
MS. HARRIS: Harry won't understand it because it's not in Southern.
(Laughter.)
DR. HOWELL: She's had too much snow in Albany this year. We'll forgive her.
(Laughter.)
DR. HOWELL: Thank you very much.
Tracy.
DR. TROTTER: I just want to expand on what Anne said and Sylvia said and we actually talked about in the committee meeting yesterday. The ultimate tool would be a modular translation of newborn screening, and you could then choose one from line A, one from line B, and one from line C, already translated phrases, and then create your own booklet. Everybody is going to create their own booklet. We understand that, but the cost of translation and the cost of making it accurate is what we're trying to decrease here.
DR. HOWELL: I think the bottom line is this committee obviously can't direct the National Coordinating Center, but I think that we certainly have conveyed to Dr. Watson and to Dr. Therrell the idea that this would be something that they will focus on and I'm sure they will be focusing on. And maybe we can hear back from them about their accomplishments and so forth.
The modular thing is very interesting, but relying on various areas of the country would, obviously, be very important. In my hometown, you would probably have to find someone to translate into English. So you might use some of those people to help with your Spanish tradition.
DR. TROTTER: Y'all can be added to almost anything.
(Laughter.)
DR. HOWELL: Absolutely. Thank you.
Are there any further comments? We need to move along. We've got a few things that we want to accomplish before we break in just a bit. There are a couple things that I would like to bring to your attention.
Number one is that under tab 6 we have the letter, the note, the cover letter, that would be provided to the person nominating. As you recall, we have approved the nomination form in anticipation that there will be small changes as it is used and so forth.
Yesterday Piero had recommended that there be a paragraph added to this that would make it very clear that for things to succeed in going through the committee, you really need to have a collegial effort

involving a spectrum of people, families, experts, the public health department. And he wrote the first sentence that's here as number one. We have number two and number three that are takeoffs on that. The second one is very similar to Piero's with a few enhancements, shall we say, of the English, translating from the Italian into the English. Look at that. They are basically the same with a few very thoughtful suggestions from the distinguished colleague to my left.
Then the third paragraph is a modification that is less specific.
Can we hear brief comments about these? I think the idea of inserting a paragraph is a very good one, and I think the question is how should the paragraph read. Piero?
DR. RINALDO: I would like to congratulate the author of the third one. I think it's short and sweet without getting in too many details. So personally I think the third is actually a nice thing without getting in too much details. So personally I think that's a better one.
DR. HOWELL: All right. The author of paragraph one has shifted his support to paragraph three.
Do we have any further comments? Mike is thumbs up on three. Any further comments?
DR. DOUGHERTY: Three is good.
DR. HOWELL: You like three?
DR. DOUGHERTY: Yes, but I was wondering if the letter needs a sentence saying that the contributors of the nomination form may be contacted in the future at some point to provide clarification.
DR. HOWELL: I think that would be implicit that that would be the thing.
So the bottom line is I see nods and thumbs up about paragraph three. So we will insert paragraph three. After the first paragraph, we will put that in. So that's good.
So the nomination form is ready to roll. This cover letter will go out with it. So that's great. Thank you very much.
Now, the second thing that we have to do is that we've had for some time in our materials the standard operating procedures of this committee, and we want to finalize that today and get that completely done. The standard operating procedures are under tab 12.
Let me comment before we go through that. Also yesterday you had handed out a substitute paragraph D about liaison representatives. On page 6 of the standard operating procedures, there's a paragraph D, "Liaison Representatives." Yesterday you were given a copy of a modification of that that was expanded that was a little more explicit about liaison representatives.
Can you put your hands on that substitute paragraph D? That's it. Does everybody have that?
DR. LLOYD-PURYEAR: They did.
DR. HOWELL: Well, I realize they did, but they don't. Who does not have it?
Let me go through it. I'll be quick. Okay?
Appointments of liaison representatives, primarily from professional organizations, are based upon written requests from organizations which document the commitment of the organization to providing expert input into this committee's decision-making process -- travel and per diem support of the representative will be paid the person as a liaison representative -- and strongly encouraging their membership to adopt recommendations of this committee.
The liaison representation suggested for the nomination to the committee is prepared and forwarded to the Executive Secretary of the committee, the Associate Administrator of Maternal and Child Health of HRSA for review and approval by this committee. So the nominations would come back to this committee.
Because of space and time limitations at this meeting -- and this has been discussed a good bit in the past -- liaison representatives must represent their organizations and show interest in the committee's work through active involvement and participation at committee meetings, have broad interests in relevant fields, pediatrics, newborn screening, genetics, other relevant expertise, and represent large constituencies relevant to the committee's need rather than small, albeit it important, constituencies.
For the biomedical industry, the entity must be national in scope and its products or services must be directly related to the committee charter. Industry must demonstrate active involvement with the committee interests and must demonstrate regular participation in the work of the committee.
Groups that represent more narrow interests or small constituencies, such as interest in a single disease, are invited to participate in this committee's activities on an ad hoc basis whenever issues of interest or concern are being discussed rather than as a liaison representative.
The committee shall limit the number of organizational representatives to no more than 11 -- and I would like to suggest we change that to 12 -- organizations or three-quarters of the total committee membership. The reason I have suggested that we change that 11 to 12 is because of the number of important critical national organizations that have come to our table. The 11 is somewhat arbitrary. If you take three-

quarters of the committee, it comes out to be 11 and a quarter. So it seems to me that limiting the number is important for practical reasons, et cetera.
But anyway, that is a substitute thing that's in the thing.
Can we have any comments about that? Yes.
DR. DOUGHERTY: The first sentence, the last phrase, "and strongly encouraging their membership to adopt committee recommendations." I'm not sure that that should be a requirement. If we want technical input, expert input, certainly we can get input from people who may eventually disagree with the recommendations and not encourage their organizations to go along with them. So I'm not sure whether there are any federal regulations on liaisons to committees, but it seems too limiting to me, that we only want to appoint people who are eventually going to agree with us.
DR. HOWELL: Ethan?
DR. HAUSMAN: The other, in concert with what Denise said, is FDA's functionality and our mandate is such that we review and regulate devices, medicines, foods, and biologics. So we wouldn't be under the umbrella of formally saying yea or nay, we like these, we're accepting them and incorporating them into our charter. It would not be the function of the organization. So we could not, in fact, do that. But FDA has a very deep and abiding commitment to the advisory committee's work, and we're very interested and excited to be involved with the committee now and in the future.
DR. HOWELL: Any further comments about that particular sentence?
DR. LLOYD-PURYEAR: Can I ask a question?
DR. HOWELL: Of course.
DR. LLOYD-PURYEAR: This document, by the way, was reviewed by our ethics and Office of General Counsel, and there are no regulations for representatives to advisory committees.
What if we had something strongly encouraging familiarity of their membership with the advisory committee's activities?
DR. RINALDO: Stay informed.
DR. LLOYD-PURYEAR: Pardon me?
DR. RINALDO: You can replace "adopt" with "stay informed." This is coming from a second language guy.
DR. HOWELL: To stay informed? To encourage their membership to be informed or stay informed about the --
DR. GREGG: Or report back to. We provide feedback back to our parent organization.
DR. HOWELL: We're not going to have any comments on the floor, Nancy, about this. This is committee business. Okay? Thank you.
DR. HAUSMAN: Rod, I think it may change the structure of the sentence, but as the institutional representative, the language is closer to we are committed to the advisory committee's ongoing mission and activities.
DR. LLOYD-PURYEAR: I'm sorry. Say that again.
DR. HAUSMAN: As a federal organization with a different kind of charter, we are, in fact, committed to the advisory committee's mission and ongoing activities. It's rough language as well.
DR. LLOYD-PURYEAR: I think given what you had already said before and Denise's concern, it's better to be less specific and more general in terms of -- you really can't expect what I wrote there, but you can expect familiarity with the advisory committee's activities and that there's a commitment by the liaison representative to serve that function to familiarize their constituencies about this committee.
DR. HOWELL: Peter has some comment.
DR. VAN DYCK: I think we have the sense of the commitment in the first part of the phrase, "document the commitment of the organization to providing input." "And strongly encouraging their membership to adopt the recommendations" should be wordsmithed to be "inform the organization of the activities of the committee."
DR. HOWELL: So if we made that, Peter, picking up on the "strongly encouraging their membership" to "stay informed" about the committee's activities --
DR. VAN DYCK: Well, we encourage the liaison to bring back the issues of the committee to the membership that they represent. I don't think we should wordsmith it right now, but maybe someone can in the next hour or two and we can adopt it at the business meeting.
DR. HOWELL: Diane, you have a comment?
DR. ASHTON: I think one area of concern is that some of the interested organizations represent industry, and that that probably needs to be part of the discussion because that really hasn't been clarified

previously.
DR. HOWELL: I'm not completely sure industry is in the document. What is your specific comment about industry?
DR. ASHTON: I think my understanding is that some of the liaison representatives that are interested may represent industry.
DR. HOWELL: Yes. In the document, we have a comment about industry as a potential representative on the committee.
DR. ASHTON: Okay, but I mean, has that been discussed having industry?
DR. HOWELL: Yes, it has been discussed. I think that there's a strong sense of the committee that it would be appropriate to have industry represented.
Yes?
DR. KAHN: Looking for my own representation in the document, I would recommend perhaps in the fifth to the bottom line in the first paragraph, the phrase "subspecialty expertise," if you just took out the word "sub" and made that "specialty expertise," I might find myself in that phrase. Otherwise, I'm having trouble.
DR. HOWELL: Okay, I think that's a good change. So "specialty expertise."
DR. GREGG: is it really clear that the committee is in favor of industry representation at the table?
DR. HOWELL: We can discuss that, yes. Any comments around the table?
(No response.)
DR. HOWELL: This has been in the document. I guess we haven't discussed it formally, but there's been certainly a discussion that industry is a significant part in the genetic testing world and it would be appropriate to have some degree. I think there's also been a feeling that the industry representation would not be a large part of the committee. That clearly is but, Piero?
DR. RINALDO: I think one thing that hasn't been discussed that I heard being mentioned is there's a rotating mechanism for industry sort of representatives. So before saying that we agree to it, I would like to know how exactly that will work.
DR. HOWELL: One of the discussions that's been presented individually, without any formal presentations to this committee, was that one of the issues that would come up with industry -- there are many groups that are very actively involved in genetic testing and newborn screening and so forth. And one of the questions has been, well, how would one conceivably have representation from such a broad group? And one possibility would be to have a rotating membership on the committee.
I might point out liaison members on the committee -- all the liaisons we're talking about -- are nonvoting members of this committee. Let's be clear that everyone understands that.
DR. LLOYD-PURYEAR: They're not members.
DR. HOWELL: They're liaisons to the committee and nonvoting.
But on the other hand, in discussing the thing, it's felt that it might be helpful to have this expertise at the table. But on the other hand, it would be appropriate to have some rotation so that you would have representation without a very large group or something of that nature.
But I'd be interested in comments from the members of the committee.
DR. SKEELS: I'm sorry. I just have sort of a procedural question. Is this the point in this meeting at which you want to talk about whether or not we want industry representatives? Or are you asking a more generic question?
DR. HOWELL: I think the question is should industry be represented, and if so, what might be a mechanism of having industry represented in a way that would be appropriate, but not a huge collection, yes.
DR. SKEELS: Yes. I don't have the answer. I think, as you just said, it's very important that industry's voice be heard. I'm not sure whether the liaison representative avenue is the best one or not. This is the only federal advisory committee I serve on, so I don't know how others handle this.
One question I would ask is what's the difference between being in the room and participating without any formal standing versus being a liaison representative? What does being a liaison representative confer to you that you don't already have by being here as a member of the public?
DR. HOWELL: Let's ask some of the experts on the federal world.
DR. LLOYD-PURYEAR: There are a great many federal advisory committees and many of them have at least one position at the table that serves to represent industry broadly. The Secretary's Advisory Committee on Genetic Testing had an industry representative. The National Vaccine Advisory Committee I think has always had an industry representative or two. They don't vote, but they're there to bring up

important issues that if you're not at the table, you don't often have an avenue to do that. So there is a difference between being at a table, even though you're not voting, just to bring information forward.
I don't know every single advisory committee that the government runs, so I don't know. Sometimes industry actually has a membership at the table, which I don't think is always appropriate.
DR. RINALDO: That goes back to my question because, again, I agree with Mike because let's say that we have industry representatives that are here. They consistently have come to this meeting. And one meeting, if the rotating mechanism -- that's what I would like to know is rotation. To sit at the table once and to leave that seat to somebody else the next time is really not a tangible difference and wouldn't change anything. So that's why I think we need to at least have not a discussion -- at least have an idea of how exactly this will work before we can make any discussion.
DR. HOWELL: Or would it work? I ask that question. I don't know.
Norm has a comment.
DR. KAHN: I'd like to share the experience of another group that I sit on. There's an organization called the National Task Force on Continuing Medical Education Providers/Industry Collaboration. It's a 45-member group. It's about 60 percent continuing medical education professionals and organizations and 40 percent industry. But it's deliberately designed for a collaborative discussion between those two communities. It works very well.
So I would speak in favor of having a position, a liaison representative, representing industry who would have the same rights and terms as any other liaison representative. I agree that there's the opportunity for others to participate from the floor in all of the subcommittees, but I think it is appropriate to have industry represented and that their representation should be in a seat that's the same as any other liaison.
DR. HOWELL: Would the rotational situation work and how would you see that working?
DR. KAHN: Well, I think I agree with Piero that rotating from meeting to meeting doesn't make a lot of sense to me. You don't have any continuity whatsoever in that regard. That's why I'm suggesting that a liaison seat, one of your 12, Dr. Howell, be specifically intended -- not required, but intended -- to be an industry representative and whatever the terms are that we assign -- perhaps we don't assign terms for the liaisons. Perhaps it's up to the liaison organization, in which case we might want to recommend a rotational term of two years, for example.
DR. HOWELL: Denise?
DR. DOUGHERTY: Well, I think we have this limit of 11 or 12 now, and I guess Piero's question about rotation made me think that just as there is in the statute that there has to be rotation among committee members, whether there should, in fact, be some language about rotation or reconsideration of committee members because we --
DR. LLOYD-PURYEAR: Committee representatives.
DR. DOUGHERTY: I mean liaison representatives or organization liaisons, whatever they're being called, because we may run out of room and there may be other organizations that might want to come on.
DR. HOWELL: Well, Denise has expanded the issue a bit. Members of the committee, as I think most people are aware, are appointed by the Secretary for limited terms. And you're suggesting that also the liaison memberships also be on some basis, so that periodically each of the persons that are in a liaison position would be reconsidered.
DR. GREGG: I'm fine with that sort of approach. The caution is, though, that if you are trying to provide a continuous stream of information back to your constituency, the minute you land another person in this seat, they're starting kind of from square one at some level in terms of what their running themes and comments have been working forward. In other words, there's a catch-up time period.
DR. DOUGHERTY: That's why I said be reconsidered or something like that so that there are some criteria here that say if you're not participating, providing expert input, you shouldn't be a liaison representative. So there may be every four years considering who's at the table as a liaison, not to say that they can't be reappointed.
DR. LLOYD-PURYEAR: Just to clarify. So, Denise, you're saying not rotating the individual, but rotating the organization itself.
DR. DOUGHERTY: Right.
DR. GREGG: So potentially AAFP is off the table next round. I'm just asking that question. That seems counterintuitive to the purpose, as far as I can tell.
DR. LLOYD-PURYEAR: I think the committee would think about what organizations -- say, AAFP never came to another meeting. Then you would question their presence. I think having that open to remove.
DR. GREGG: My question, though, about industry is industry is broad. Just that term. Is there some

process where a "industry representative" is invited, I mean, a specific individual?
And what I wonder about or worry about is competing interests that has a financial underpinning ultimately. I think that's probably what we're all somewhat worried about. So if you were going to ask somebody to be the industry representative and they were in the area of chromosomal microarray studies in prenatal specimens, there are competing methods for this. Which is the best lab? And if one person were sitting there, could they have undue influence with regard to the methodology?
DR. RINALDO: I believe, though, that there would be a clear situation of conflict of interest. So that will probably be picked up. I think it would be unwise for a company to try to influence.
DR. GREGG: Well, it's easy to say it would be unwise, but unless there's some other mechanism in place, it's possible. Once the statements are made and the dialogue begins, it's being done.
DR. HOWELL: I think your point is well made. I think there are two things. Let me again reiterate when it comes to voting, these persons don't vote. And the second thing is that everybody, when they come on the committee, a liaison, members or otherwise, do follow very clear conflict of interests. So if it's not clear to everybody what the conflict is, it should certainly be, and so forth.
Piero?
DR. RINALDO: My understanding of the way we have had the liaisons is that once a decision is made, it's up to the organization to name their representative. So I'm wondering there seems to be a consensus here that is unlikely to be more than one liaison from industry at any given time. So I would actually really punt to this group of people and say, you get together and decide who is going to be the representative and let them decide, because frankly, it could be a very tedious and contentious process here if we try to decide which one of all these potential candidates is the one we pick. I don't think you really can do that in a fair and objective way unless you use first come/first served.
So I would say perhaps these industries should find a way to talk and together nominate somebody. That I think will not have a problem of choosing, which is also I think a big problem.
DR. HOWELL: I think there are two steps. Number one is that I would like to hear from the voting members of the committee about their sense of having a single seat reserved for an industry representative. Now, the next thing would be the mechanics of filling that seat and so forth.
DR. RINALDO: You were thinking of more than one?
DR. HOWELL: No. I said I would like to hear from members of the committee about -- the thing that's been brought up on the table is a single person. I'd like to hear from the voting members of the committee on that issue.
Amy.
DR. BROWER: Maybe I won't vote, since I'm industry, on this.
DR. HOWELL: All right. I might point out, I think as you very well know, Dr. Brower, although she is a member of industry, was appointed to this committee not because she's a member of industry, but because of her expertise in the area, and so forth. But thank you very much.
I'm going to go over to the voting members, Tracy. Jim, what would your thoughts be about allocating one liaison membership position to industry?
DR. NEWTON: As was already brought up, I think you're going to get industry involvement just because of their expertise. It ought to be up to the committee where it seeks that expertise best, and I don't think you should necessarily designate that there needs to be any or a certain number of additional industry representatives. The committee should decide what its needs are at any given time.
DR. HOWELL: Greg, your thought?
DR. HAWKINS: Actually, he kind of made my point there too. I don't think a designated spot for industry should be made. We already have two industry representatives that serve on the full committee. I don't see that there's a problem with that so far, but still, if you start designating one for one specific -- that does limit you. What happens if there's no person for that spot? I think you need to leave it open to designate for your needs.
DR. HOWELL: I might point out there is currently no person who's a voting member of the committee who is appointed because of their relationship to industry.
DR. HAWKINS: Exactly.
DR. HOWELL: And that could or could not change in the future.
DR. HAWKINS: Right.
DR. HOWELL: So that's just by chance that a person is appointed because of their expertise and so forth happens to be in industry.
Mike?

DR. SKEELS: I agree with Piero it would be cleaner if there were an international association of industry newborn screening people and they could send a liaison and it was a collective. But that doesn't exist. I'm not sure that I favor adding a liaison representative from industry just because I think that although I'd like to hear their voice on specific issues, I'm not sure that it's necessary.
DR. LLOYD-PURYEAR: Currently we have three members of this committee who were appointed because they represented industry. They were appointed by the White House because they represented industry, I assume.
However, within our operating procedures, if you guys have read the financial conflict of interest portion, it will curb significantly the presence of industry as a member on this committee. So that raises the question of whether or not the committee thinks they should have a position as a liaison representative to allow the voice of industry at the table on this committee during deliberations.
DR. SKEELS: Well, I think anyone can be invited to join us at the table for any discussion. Correct? Whether they're a liaison or not. I mean, anyone could be invited by the chair to come up and enter a discussion on a selective basis, and I think that's a perfectly good role for somebody from industry. I'm just saying I don't feel that there's a need to add them as a liaison.
I have to admit I'm as concerned about the next step, which would be selecting an industry representative, as I am about whether or not we should have one. If we say yes and we add one, then we have started down a pretty interesting rabbit hole.
DR. RINALDO: I agree with Mike two days in a row now.
(Laughter.)
DR. RINALDO: I really think the real issue is the next step. What are we going to do? Have a search committee and have them give a seminar? I mean, it's just not really possible to do it in an objective and fair way.
So you said there is no such national or international body. Perhaps this could be the impetus to have one. If they can discuss among themselves of the interested industries how to select and rotate, then if that's limited to one, I have no objection to it.
DR. HOWELL: Jana.
MS. MONACO: I guess I was thinking in a more simplistic way as to looking at the letters, knowing that we have to think about adding someone and that there's space. At this point in time is there a problem with just reviewing who has requested a position on here because they are interested, they have a vested interest in what we're doing, rather than necessarily designating a slot and inviting just a potential person who may represent an industry or another organization and may not have a real significant interest, but because it's available and we create more problems for ourselves? But if we have people who are interested who have made an appearance consecutively at all the meetings and are familiar with the direction that we're moving with the committee, why not look at that approach, not necessarily isolating a position for whether it's a private organization or institute or an industry?
Because then you're overseeing more, thinking from a family perspective, those who are not in industry. Then you're starting to count slots, count seats, and I think that could just raise a lot of other issues.
DR. HOWELL: Amy has absented herself, so we're going to hear from Denise.
DR. DOUGHERTY: I agree with Jana. I would not save a single spot for industry. I'm not sure that this language specifically about industry in the liaison representative section is necessary. I'm sure industry knows of the interest here and the changes in the financial issues. So they would probably submit just along with everybody else, and then the decision would be, using these criteria, whether the group is selected or not.
I guess I would just add in the second paragraph groups that represent more narrow interests or small constituencies, e.g., local companies, because above you've said national scope.
DR. HOWELL: Right.
DR. DOUGHERTY: So I don't know if local companies and national scope -- that's probably not a good contrast, but something like that. So all organizations should have a national scope.
DR. HOWELL: We've had a discussion around the table. Can we have a motion about allocating a seat as a liaison member on this committee to industry? Would one of you like to make a motion on that? Piero?
DR. RINALDO: I move.
DR. HOWELL: What do you move?
DR. RINALDO: To allocate one seat for an industry representative but with the provision that will -- somehow we have to involve all these interested industries in the selection. Really, we shouldn't bog

down the committee with this process.
DR. GREGG: Can I just interject one point of fact? And that is, you just defined the role of the liaison is to report back to their constituency, and identifying one person at the table to "represent industry," define for me who their constituency then is. If you had somebody from Pediatrix sitting here, who is their constituency? Who do they report back to? Do they report back to people that design new tests? Do they report back to people that represent obstetric groups, pediatric groups? And how do they do that? So if the role of the liaison is to report back to their constituency, how does this person complete their obligation as a liaison member?
DR. HOWELL: Before we get any further discussion, does Piero's motion have a second?
DR. SKEELS: I'm not sure I understand it.
DR. HOWELL: Piero, do you want to make the motion again?
DR. RINALDO: The motion on the table is to agree to have one liaison added to the committee representing industry with the selection of such a liaison -- and I have to say that I'm digesting the point that Dr. Gregg made, which is a very, very valid one, but I still think at least let's see what happens. Again, the motion is that there will be a liaison seat and the selection will be so delegated to the industries who are interested in this process.
DR. HOWELL: Does that have a second?
DR. DOUGHERTY: I think that's two separate motions --
DR. HOWELL: Well, but does it have a second?
DR. DOUGHERTY: No.
DR. HOWELL: It does not have a second. So would someone else like to make another motion, a different motion? Jim?
DR. NEWTON: I would like to make a motion that the committee seek advice and expertise as needed from industry, but not have a designated liaison spot. That's the end of the motion. The rationale being I don't know how you pick that person and I don't want to be involved in the process of trying to pick a particular person to represent all and competing interests.
DR. HOWELL: Does Dr. Newton's motion have a second?
DR. HAWKINS: I'll second.
DR. HOWELL: It has a second. So any discussion of that motion?
(No response.)
DR. HOWELL: Can we vote on the motion? Oh, excuse me. Did you want to discuss something, Mike?
DR. SKEELS: Yes. I hate to go semantic on you, but I'm not sure what industry means in this case. Does that mean somebody who has a commercial interest in selling things for newborn screening, or does it mean anybody who's operating a reference laboratory that provides newborn screening services in the private sector? Can we just talk a little more about what you mean, what HRSA means, by industry? What do you mean, Jim?
DR. NEWTON: Well, I don't want in any way to imply a restriction on people in industry being part of this committee. What I'm saying is I don't even think we need that definition. People that provide valuable expertise to this committee can be utilized and nominated for membership on the committee without the committee trying to define what industry is, what that process should be of selecting a particular person for what is a very disparate group of interests.
DR. HAWKINS: I was just going to make the comment that if you do designate someone specifically, you're going to have industry competing for that spot. I mean, you're going to have letters and letters and people trying to get into that spot, and I think it creates an unhealthy competition.
I think what he's trying to say is we can have a liaison from industry at any time we decide we want. We pick them based on need. And if we find somebody from industry, that's great. If we find that we want a representative from some other place, that's great. But let's don't limit it to saying we always have to have someone from industry in that spot because we may not have the need for it or we may have the need for it. Let's keep it flexible so we can choose but not define that spot as just for an industry person.
DR. HOWELL: Do you have specific comments about industry, Mike?
DR. SKEELS: No. I've probably said enough. Just the idea of what is industry is troubling to me, but I'm ready to vote on the motion.
DR. HOWELL: Okay. We assume that we're thinking about industry in terms of a business of some sort. Anyway, the bottom line is, can we have a vote on the motion that there not be a seat allocated for a liaison member?
PARTICIPANT: Are we voting for it?

DR. HOWELL: For it, voting for the motion.
(Show of hands.)
DR. HOWELL: There are four people supporting that motion.
DR. LLOYD-PURYEAR: Five.
DR. HOWELL: I'm sorry.
MS. MONACO: Could you repeat the motion again?
DR. HOWELL: Dr. Newton, repeat the motion again.
DR. NEWTON: The motion is that the committee not specifically designate a liaison position for industry, but pick and choose expertise as it meets the committee's needs.
DR. HOWELL: And that was seconded by Dr. Hawkins.
Do you have any further questions?
(No response.)
DR. HOWELL: The vote again on the motion? For the motion.
(Show of hands.)
DR. LLOYD-PURYEAR: Six.
DR. HOWELL: That motion passes, so that we will not allocate a seat for the thing.
What about the quorum thing? There are nine people present. One is abstaining. We do have a quorum. I did not vote.
DR. LLOYD-PURYEAR: But I need to know how many are not voting.
DR. HOWELL: I did not vote and Amy did not vote.
DR. LLOYD-PURYEAR: But there are for, against, abstaining.
DR. HOWELL: No.
DR. LLOYD-PURYEAR: Then there are more votes than for.
DR. HOWELL: No.
DR. LLOYD-PURYEAR: You only asked for for. You didn't ask for other categories.
DR. RINALDO: Why don't you just ask in favor, against, and abstain?
DR. HOWELL: Can we please go again? Those people favoring the motion? And Jana voted and so forth.
(Show of hands.)
DR. HOWELL: There are six.
And there are two people -- you're against it, Piero? Against. Are you going to vote against it?
DR. RINALDO: I think there is the option to abstain.
DR. HOWELL: Okay. There are three people abstaining. So we're set. That is off.
And so let's proceed along. We have the potential of 12 seats. This is an interesting question, and I think the question of how you identify this input is very complicated, and I would think that in the future this will come back up again to think about some way to bring that.
Tracy?
DR. TROTTER: Just looking at this document, I want a clarification before you all vote on this from the liaison standpoint. Piero mentioned this, and I'm not sure it's true, reading the document, that the organizations that want to be liaisons are what is selected by the Executive Secretary and the Associate Director and the person is then picked by the organization.
DR. HOWELL: That's correct.
DR. TROTTER: So that person doesn't become then disapproved by someone or approved by someone.
DR. HOWELL: That's correct.
DR. TROTTER: Okay, thank you.
DR. HOWELL: For example, the American Academy of Pediatrics has been allocated a liaison position for obvious reasons as the other group here, and your organization, the academy, selects the person who attends.
DR. TROTTER: Thank you.
DR. HOWELL: And if that person is a poor person and doesn't attend, we'll communicate with the academy, and if it doesn't get better, that will be history.
(Laughter.)
DR. TROTTER: I'll pass that along.
DR. HOWELL: We have two letters in your folder that have been here for some time for organizations. Let me declare a profound conflict of interest right up front because I'm a member of both organizations, as is Piero. But you have a request from the American College of Medical Genetics and the Society for Inborn

Errors of Metabolism to request a liaison seat at the table. I don't have to go into it, but both of these groups are national groups. They're both actively involved, in one case, in the treatment of metabolic disease, and in the case of the college, very broadly in genetics and genetics policy and so forth.
So having commented about that, can we have further comments about these two requests for liaison memberships on the committee? Amy?
DR. BROWER: I think both SIMD --
DR. LLOYD-PURYEAR: There are actually four letters in the binder. There's SIMD, ACMG, a letter from Pediatrix, and a letter from PerkinElmer.
DR. HOWELL: Yes, we know that, but the thing is we've already allocated no seat to an industry.
DR. DOUGHERTY: No, no. We said no specific seat, but industry is eligible to nominate themselves to have some seat out of the 12.
DR. HOWELL: No.
DR. DOUGHERTY: Isn't that what we voted on?
DR. HOWELL: No. Goodness, no.
So there are two letters relevant to the remaining seats, and we've discussed those. And Amy is going to speak.
DR. BROWER: Thank you. I'm supportive of both SIMD and ACMG being liaison representatives to the committee. I think they both have well-defined missions, as well as a constituency that we want to have communication with, both communicating what we're doing as a committee and feedback on what we should be focusing on. So I'm excited that they both are willing to join the committee as representatives.
DR. HOWELL: Can we have any further comments from the few unconflicted people around the table? Jana.
MS. MONACO: I just wanted to say that I agree with Amy. As the committee further addresses the issues of nominating diseases or disorders to the panel, one of the issues is the treatment, what's available, how to treat these disorders and so forth, and I think representatives from both, especially SIMD, are an important voice here because these are the individuals who understand these diseases and disorders and can contribute quite a lot to making these selections and decisions.
DR. HOWELL: Any further comments? Jim?
DR. NEWTON: I just wanted to agree with that, but I wanted to clarify. I think what you said we're in agreement. What I meant to say in that previous motion was that there would be no designated spot for industry. It did not exclude the possibility that this committee might reach out to a particular group or person with expertise in a certain area that the committee needed.
DR. HOWELL: Yes. Yes, of course. I think that's implicit.
Any further comments?
DR. RINALDO: Going back to the point, I believe that is what has been done in the past. So nothing changes.
DR. HOWELL: Yes.
But can we have any further comments about the two? Jana and Amy have spoken about the liaison membership of SIMD and ACMG. Mike, do you have any comment?
DR. SKEELS: I agree with Amy. I'm just waiting for somebody to make a motion so I can vote.
DR. HOWELL: Make a motion, now that you're on the horn.
DR. SKEELS: I defer to my colleague from Nebraska.
DR. BROWER: I make a motion that we invite SIMD and ACMG to be liaison representatives to the committee.
DR. HOWELL: Is there a second?
PARTICIPANT: Second.
DR. HOWELL: Those in favor of that motion?
(Show of hands.)
DR. HOWELL: That's six. Is that correct?
Those abstaining? Piero and I are abstaining for obvious reasons.
Thank you very much. So we will get a letter off asking those auspicious groups to nominate important members.
Yes?
DR. BROWER: I just want to say one thing back to the industry. I think Tony's point is very well taken about communicating back to the constituency of industry, and I can take it as an action item to report back at the next committee meeting about professional organizations that represent industry that do play

that role of communicating across all industries related to newborn screening and maybe we can talk further about it.
DR. HOWELL: Let me interject a personal thing, and that is that I think it would be very important to have a strong voice of industry as a liaison situation. I think that if the industry side of the street can come up with a really clear mechanism of organizing that and so forth, I think that will create a very different environment for our discussion next time.
Denise.
DR. DOUGHERTY: Sorry. I still have a question. So if PerkinElmer and Pediatrix come to the committee and ask to be nominated, do we not have to vote on those self-nominations?
DR. LLOYD-PURYEAR: Yes, you do.
DR. DOUGHERTY: Okay. So I guess I'm wondering why we voted -- we voted on these two. By voting to accept these two, did we vote not to accept the other two? I'm just trying to make this a fair and transparent process and know what the rules are.
DR. LLOYD-PURYEAR: There's a request to be a representative. You have to vote.
DR. SKEELS: Sorry. This is a procedural question I think we need to resolve. If Joe Schmuck walks in off the street and nominates himself for the committee, do we have to vote on that, or can we just simply selectively vote to include those who we do choose and ignore the others? I mean, I just need to know that.
DR. LLOYD-PURYEAR: You have committee correspondence that you have to deal with.
DR. SKEELS: Well, one way of dealing with it is to send a letter that says, thanks, we'll consider this in the future. We don't have to vote up or down on everybody who nominates themselves.
DR. LLOYD-PURYEAR: This has to be a decision voiced by the committee. I don't act independently of the committee. So you have to say what it is you voted on, what you decided to do with these two other letters.
DR. HOWELL: In order to help Michele with her situation here, there was an earlier motion passed that would, at the current time, not allocate a liaison seat to industry on the committee. In view of the fact that these letters have formally come to HRSA, I think what Michele would like us to do would be -- we have a request from PerkinElmer and from Pediatrix for a liaison membership on this committee. Can we have a motion on that so that we'll clarify her records?
DR. SKEELS: Not to be difficult, but I thought that's what I was voting on when Jim brought it up. I thought that since those companies were mentioned by name during the discussion --
DR. LLOYD-PURYEAR: No, they weren't.
DR. SKEELS: -- that that's what we were voting on. Actually they were. And I thought that's what I was voting on. I'd be happy to vote again if somebody wants to make another motion.
DR. HOWELL: Let's make a very clean thing so there's no ambiguity. Would you like to make a motion, Jim, that would be specific to these two letters?
DR. NEWTON: Well, what I want to do is make a comment that if these two letters apply to an industry liaison position, I think it is clear that we've already acted on that. If they are seeking representation from the committee because they think that they, their organization, would individually add something to this committee, then in my thinking, you would have to consider that. But I don't think any -- I'm not trying to play favorites or anything like that. I don't think any one company can be a liaison for all companies.
DR. HOWELL: We don't have a position for a general liaison to the committee.
DR. NEWTON: Right.
DR. HOWELL: So that's not possible.
But would you like to make a motion so that we can clarify the fact that we've considered these particular things and have not approved them?
DR. NEWTON: I'm not sure what you want me to -- go ahead.
DR. DOUGHERTY: I would like to make a motion that we ask for more information from those two companies as to why they think they meet the criteria to be a liaison representative, given what we haven't voted on yet, but we are going to vote on, about appointing liaison representatives. We need more information.
DR. RINALDO: Let's not drag this forever. We're dragging this forever. I don't think it's necessary.
DR. DOUGHERTY: I don't feel like I can make an informed vote about whether those two companies, which I don't really know --
DR. HOWELL: Well, they're companies.
DR. DOUGHERTY: -- meet those criteria that we haven't voted on. I can abstain. I will abstain.

DR. HAWKINS: I do have one question. You say PerkinElmer is requesting a spot?
DR. HOWELL: Yes.
DR. HAWKINS: Is Peter Coggins still on the committee?
DR. LLOYD-PURYEAR: Peter Coggins is still on.
DR. HAWKINS: Then that would be two spots to PerkinElmer.
DR. HOWELL: I think we're becoming terribly bogged down. Michele is very concerned about the fact that we have not specifically declined the request of these two people, and it would be very helpful if someone would make a motion. We've implicitly done that because we've not had a liaison position for industry.
DR. RINALDO: I think just to put this to an end, I'll make a motion that we decline those two applications.
DR. HOWELL: Can we have a second?
PARTICIPANT: Second.
DR. HOWELL: We have a second.
Those in favor?
(Show of hands.)
DR. HOWELL: Are you not voting?
DR. BROWER: I'm abstaining.
DR. HOWELL: It carries. Thank you very much.
DR. LLOYD-PURYEAR: Wait. Three voted yes.
DR. HOWELL: No. I voted. Jim, you didn't vote?
DR. LLOYD-PURYEAR: So five?
DR. HOWELL: Yes.
DR. LLOYD-PURYEAR: Six?
DR. HOWELL: Six.
DR. LLOYD-PURYEAR: Six for.
How many abstained?
DR. HOWELL: Two.
DR. LLOYD-PURYEAR: Three?
DR. HOWELL: Three.
Thank you very much. We're going to have a brief break, and we're considerably behind time. So don't stay long.
(Recess.)
DR. HOWELL: We're going to start and we're going to hear some important things about the regional collaboratives and what they've been up to. Our first presenter is Dr. Piero Rinaldo who, as you know, is Professor of Laboratory Medicine at the Mayo Clinic, and he's going to talk about some of the efforts they've been working on to enhance quality in Region 4.
DR. RINALDO: Thank you.
This is a report about the activities of the Regional Collaborative Project, started in Region 4, which is physically in the Midwest, the Great Lakes Region, with the addition of Kentucky.
I realize that probably some of you have seen, prior to this presentation, the slides many times before. For others, this is new. So I'll really try to compromise and give enough information that could be, I hope, understood.
The first thing I want to say is that the defining characteristic of this project is that it really is based on active participation, active and frequent participation, that is, really defined on one end on timely submission of data -- and timely means at least once a month -- where we ask the participants to submit the percentiles of a normal population. And we encourage them to do it in a cumulative way, so starting from whenever they had data and keep adding to it. Their cutoff values, the most recent set. All the data, all their true positive cases according to local protocols, and that means all the amino acid and acylcarnitine data. And finally, their performance metrics.
As the process has evolved now, there are many other activities. We have a sample exchange project that I'll tell you a little bit about, and we have monthly conference calls. We have training courses, week-long training courses, and also face-to-face meetings of the working group.
To give you an idea of the current status of the project, this is a map of the United States showing in sort of a purple color all the states that currently are actively participating, and in green are shown some others that I think there is a chance of possible imminent addition.
Now, this project, as you can see, starting from Region 4 up here, has really now a standard to include states in all the other six regions. But this has also grown to include many participants that come from

outside the United States, and you can see here, from Canada, South America, Europe, Australia, and the Far East.
Now, to also put this in perspective, I'd like to show you -- this is a picture. I hope you can appreciate it. It was the very first meeting of the working group with representatives of six of the states in Region 4, and this is a group a couple weeks ago when we met in Minneapolis. It was a very productive meeting. It was just before the APHL meeting on newborn screening.
The active participation, as I mentioned before, is really all about standardized collection of newborn screening data. I repeat one more time. These are the things we are asking the participants to provide. Now, how this works. Well, the data are generated at the individual state level, and here you see the percentiles, the cutoff values, and the data of the true positives. All of these are posted now on our website. This is the home page, changed recently, and it is very efficient. Up here is the section that the participant was our project link on there. This is now live, and they ask for a user ID and password to access it and to protect the section where every state has a folder.
I'd just like to take the opportunity now to thank my buddy, Cindy Cameron, and her group at the Michigan Public Health Institute, who have been just fantastic in making this project happen. I just want to take the opportunity to say thank you to her for all their work.
This is a summary of our project. I have a quantitative mind, so I always like to see numbers and also to show you a little bit of difference. In essence, I can show you here now we are up to 71 participants, and you can see 38 in the U.S. What I think you see in this column is actually the delta, the difference since the end of 2006. So not only are we doing well, but I think we are picking up momentum and there is definitely an acceleration that at times feels most exponential. You can see we've gone up by a quarter in only five months and also in terms of international participants.
This is a number that I haven't updated since we met in Minneapolis. I think we now have at least 20 to 30 more cases waiting to be added to the database. Again, you see a growth of 30 percent. In the true positive database, now we are approaching 170,000 data points, and these are of individual values. We have also close to 8,000 percentile values from 37 contributors, and you see this is again a growth of double basically in five months. And the same is true for the cutoff values. Now we are about more than 2,000, 2,300. Again, you can see we're really growing at a significant pace, close to 50-60 percent.
Now, our goal, as you can see stated there, is a condition with more than 50 cases. One of the stated goals of this project is to collect the actual newborn screening data over at least 50 cases for each of the conditions included in the uniform panel and the secondary target. So we haven't added a new condition since December, but now we have four that are within striking distance. We have probably 800 MCADs and 500 PKUs, but I think we have exceeded the goal. The real challenge now is to achieve this goal of 50 cases whenever possible. That's why we feel -- at least I feel very strongly -- that this is actually the time to increase participation because for the really less common conditions, even the current size, even 71 participants, might now be able to achieve their goal.
DR. VAN DYCK: What do those two numbers mean?
DR. RINALDO: There are 20 conditions detectable by MS/MS in the uniform panel. We have now at least 50 cases for 14 of them. And there are 22 secondary targets, and we have at least 50 cases of 3 of them.
Now, the point is -- and that is really the philosophical -- the core of all this exercise is not just to collect data, but to do something with them. That is really where we use all these data to generate percentiles of all these markers and also disease ranges. I'll try to give you some examples how this sort of manipulation of the data generates what we call the tools of the project, of the deliverable. And that is really the point we emphasize, that the return, the frequent return for participation in the project, is getting updates of all these tools. These are monthly updates and now there is sort of broadcast email sent out to our participants. We used to attach all of the files. Now we just tell them, go and get them from the website because really we want to encourage familiarity with the website and people navigating it.
So the first example is what we call the cutoff ranges, and this is an important point because in many discussions, including when I talk to Steve Downs about the LOINC and the need to define a given number, there is a misconception that this is really a process of mandating some kind of magic numbers to people who perform newborn screening by MS/MS. And really, this couldn't be the farthest from the truth.
This is an example. I just use arginine, in part because it's one of those secondary targets, orphan, if you want secondary targets, that have no connection to a primary target. To explain what these graphs are, you'll have to take each of those sort of boxes at the bottom which really represent the distribution of values, and the two bars on the top reach to the 99th percentile, the bottom to the 1st percentile. The box

goes from the 10th to the 90th percentile.
Now, when we look at the normal population here, that is, what happened when we accumulate all the data from all participants. So the number you see there -- at least, there is a 99th percentile -- is really as the median of all the values submitted by participants.
So it's a fairly simple process. You compare the normal population with the disease population, and this is actually the variability in cutoff values. So the concept of target range or cutoff target range is very simple. You can see a highlight here. It's really the range of concentration between the 99th percentile of a normal population and the 5th percentile of the disease range, and the 5th rather than the 1st because we really would like to minimize the impact of some really unusual outliers that each and every one of us has experienced sometimes, and although you don't want to underestimate them, you also don't want them to have an undue effect and impact on the overall definition. So, it's a very objective, descriptive, if you will, process.
I use this to think of it as a thermometer. This is really a way where you can objectively say is your cutoff value within here as great. As you exceed the target range -- and, again, this is not a subjective decision, but rather is what is dictated by what happened in the normal population and what happened in the disease range. You might agree with me that the laboratory cutoff for arginine greater than 200, considering that is above the median of the disease range, might not be perhaps the best choice for that.
This is the same thing but for all. This is just one page, and we call it a score card. I realize it might be difficult to read from there, but it's just showing the distribution of values with the denominator for normal population, cutoffs, and disease range.
Now, whenever possible, like in this example of arginine that you see here, this is what we call the cutoff range, again defined for the interval between the 99th percentile of the normal population and the 5th percentile of the disease range. When you see a black background, it means that the overlap between these two is significant. So one of the two or both have to be overruled because either you will have very poor specificity or sensitivity.
This is just one of seven different pages. So we have similar pages for amino acids, amino acid ratios, acylcarnitine, acylcarnitine ratios. And you can see here again, paying attention to these columns, what proportions of these target ranges can be defined just based on the natural history of a disease and the gap with the normal population. But in many cases, we really have to intervene. This is a process of really very dynamic or constant adjustments and changes. That was one deliverable.
The second one is the plots, and the plots are the same thing. You already saw the one for arginine. This is an older version. Again, it's a graphic way to present the target range and cutoffs. You see this is just for phenylalanine. These graphs are the same. You see here we have a full scale with all the values, and here, just a highlight up to a smaller scale. So to really better appreciate the difference.
So these are practical tools. These are tools that operators of tandem mass specs or people responsible for the review interpretation of abnormal results are supposed to keep on the side on their desk, and they say, okay, I have a flag. And instead of really having it as a fairly abstract concept, you can say what this number is because one practical example -- the low-hanging fruit in this process is if I see sometimes patients benefit for a repeat blood spot when the initial value was at the 90th percentile of the disease range, unless there was a sample mixup -- really, that's what it is, and so frankly, the process could be expedited and improved.
So some people like myself like to see tables and numbers. However, we're a little overwhelmed by those seven tables, so we have now this. These are just the entire set for phenylalanine, for tyrosine on the right. These are all the plots for all the amino acids. Again, each of these, well, orange originally -- I don't know how they look from there. But all these sections here indicate what we call the target range for the cutoff of that particular analyte. And these are all the acylcarnitines.
These are updated constantly. Every time a case is added to the database, all participants receive a PDF summarizing the latest version of these once a month.
Now, the other thing that is relatively new and is actually probably trying to bring this process to the next level is what we call the comparison tools. This is an example. So what we do is we take all the data from individual laboratories. In this case, these are data from my own lab from Minnesota. So this is why it's not de-identified. So these are all the values.
And now it's answering a slightly different question. You say, how do you compare? When you're looking, put it side by side with all your peers. So we have a concept that whenever your value is between the 25th and the 75th percentile of all the values, we don't know if it's right or wrong, but we certainly can say that it's consistent with most of your colleagues and what similar laboratories are doing.

So we assign a color code based on if you are in this sort of safe zone, if you like, or you start deviating a little bit between the 10th and the 25th, you get a yellow color here. Or you go between the 1st and 10th percentile -- see, the color changes as you move to the periphery.
The main purpose here is really to give users a heads-up that somehow their number for a particular analyte is either the highest or the lowest of all your peers. Remember, here we have at this point, these are the data we prepared for the meeting in Minneapolis. We have 37 labs who did contribute at that time percentile values.
This is just a way to summarize it. Now, this is an individual tool that every laboratory received. We also provide -- and we did it at the meeting -- an anonymized table that summarized all these labs. In other words, based on your numbers that you have on the other form, you know who you are, but you don't know who the others are, and this is a very important point.
And then each and every one of these metrics can be plotted like this. For example, we tell the participants -- and, you know, not everybody is using the same number of markers. So the highest possible number is 62, but some use 35, 40. So as a really purely descriptive measure of what they're doing, we express in that other page what proportion, what percent of the values you're using is within that safe zone. So, for example, if the number is 45, okay, this is your lab. So from those numbers, there is a graph like this in the standing order, anonymized and, obviously, the labs change position every time in every graph. So you can get a sense of where you stand, again, in comparison to your peers.
This is anonymized, is objective, and is actually meant to be constructive. It's not a race. This is not about who is consistently here or who is behind. It's just to really point to individual laboratories where they might find opportunities to improve their analytical performance.
The same is done for the 99th percentile. Again, this is the same plot. And most importantly, that's in the end for your cutoffs. So in the case of cutoffs, it is a combination of two things. We use the same criterion of being in that safe zone between the 25th and the 75th percentile, but also we combine this with the target range as it comes from the disease ranges. The concept really here is quite simple. If you are in both processes in the middle, in the green zone -- so if your cutoff is within the range and your cutoff is within the mid-50 percentile, it has to be good.
So that's all we do. We combine the two and we say what number of the total use, and that's what it says here. I don't know if you can read it. These are the cutoff values that meet the goal of the project.
This is, again, a process that changes constantly. Yesterday Harry made the comment about the fact that as we sort of identify and possibly eliminate outliers, then the ranges will become narrower and narrower. Again, it's not like you never achieve perfection, but it's more about identifying things that could be improved.
This is from another lab, and I anonymized it. Again, the idea is to have these three tools side by side where you can see how you're performing on a specific analyte. Sometimes it's really interesting because here you see a normal distribution, but you can see that it's green here, it's green here, and then it's way shifted to the left or right. That means that the decision where to set a cutoff was not really driven by the analytical data, but rather by an external example. Let me give you two examples.
Again, isononamide. This is a lab that is all shifted to the left. That means that consistently their cutoffs tend to be lower than everybody else, with seven outliers. What does it mean? It means that this laboratory is very concerned with sensitivity and is willing to accept a higher degree of false positives. And what you normally see often is this happened in programs that have low volumes because this is not California, but if this were California or Texas or Florida or New York, they would drown in hundreds and hundreds of false positives, but because we may run at Mayo 10,000, 20,000 cases a year, it somewhat is manageable.
This is the opposite situation and this is, again, a trend where you see a shift to the right, meaning that this particular laboratory really is more concerned about the impact of false positives. So it's likely to be a high throughput, high volume operation. But here, the issue becomes if these cutoffs are shifted so significantly to the high end and with six outliers, meaning for six analytes these are the highest cutoffs of the entire project, there might be a risk of not detecting something.
So that is really what is new and was extensively discussed at the working group meeting in Minneapolis. The other thing we're really trying to accelerate now is a collection of performance metrics. This is included in the book. It's a paper, part of the issue of Mental Retardation and Developmental Disability Research Reviews -- it's a hard name to remember -- edited by Dr. Howell.
Again, here in the abstract, we make a point that for the purpose of the project, we have three, you may still call it, fairly arbitrary targets and that is to have a detection rate of 1 in 3,000 or higher, a positive

predictive value greater than 20 percent, and a false positive rate less than .3 percent.
Often and correctly, there is a lot of discussion about the definitions. So the definitions are the following. Detection rate of a newborn screening program is expressed as the number of neonates that on average need to be tested to detect one affected patient. The false positive rate of a newborn screening program is expressed as a proportion of positive tests in subjects proven by follow-up evaluation not to have one of the conditions targeted by a given screening program. And the positive predictive value of a test is the probability that the patient has a disease when restricted to those patients who tested positive.
In trying to simplify the process, we have what we call the performance metric calculator. This is a protected file where you can only enter the name of your state or lab, what period of time is covered, what volume, and you can just fill these four boxes really with the status and test and all the parameters will be calculated. We found it easy because it allows a quick and somewhat quality-proof transition to the main database.
Again, we do the same thing. These are the three parameters up to 20 participants. So this is anonymized and is telling you. So it's not the same lab being number 17 or 18. It changes over time. It gives you an opportunity, in a confidential way, to assess where you stand compared to your peers and also if you meet those targets.
I want to briefly tell you about our sample exchange program. This is really driven by Dr. Stephanie Mayfield, who is the director of the newborn screening laboratory in Kentucky. These are the targets of the program. We want to have 100 percent correlation of true positive cases with a threshold of at least 95 percent. We are shooting for having at least 90 percent of the primary analyte values within 20 percent of similar corresponding value.
Now we have a fairly simply system. Whenever one of the participant states has an abnormal sample, in a round-robin fashion and strictly in alphabetical order, we'll send a punch to the next laboratory. And then they both report to Dr. Mayfield. Now, Dr. Mayfield is the only person -- and her staff -- who knows who is the sender and who is the receiver. Everybody else only sees the statistics, and the same is true for worst performance metric. Somebody has to know, but I'll defend it with my life, if necessary, who the individual numbers are.
We want to have 100 percent active participation, and now we are really looking at ways to increase participation. This is just a snapshot of where we stand. Again, when we met as a working group, as of May 3rd, we had overall exchanged 138 cases, and 119 have been completed. We have a 97 percent correlation.
Actually it goes back to a point that Dr. Hannon made earlier. This is actually a way to somewhat refine and focus the challenges that come from CDC or from others because you can say that you can find out an actual value when you spike specimens that is really challenging the range of cutoffs. So so far, we have three discrepancies where there was a disagreement between the sender and submitter, about 3 out of 138. So one was a VLCAD. One was a glutigus hemotype 1, and the third was a maternal carnitine uptake defect.
We are now more organized. We had a number of people going around not necessarily just coming to Mayo but actually going and visiting each other. We are now trying to do it in a more organized way. So this is the agenda of the week-long training sessions. The next one will be at the end of June, and you can see -- I don't know if you can read it, but basically most of the time is actually spent on reviewing actual data. So the people that come go for a full immersion process of reviewing data, data, data, and second tier tests. We also have discussions of the tools that you have just seen as they come from individual laboratories.
So we are planning, now with the support of the grant, to have maybe six or seven a year, but it also depends on demand and the idea is to keep it fairly small. So this is actually a larger group than I thought but I think is manageable.
Now we have received notification that the application is official, I presume. I look at Cindy who says okay. So it looks like there will be a sequel. So we have five more years to go.
What we really want to do, starting from now, is more of the same. We want to develop and implement clinically validated cutoff values and postanalytical tools, continue the training, collecting performance metrics, all the interaction we have had, continue the clinical validation of second tier tests, continue all the other activities.
What will be really very different and new and exciting, frankly, is the development of a customized software to manage the collection analysis reporting on newborn screening data. And these are the operating principles. We want to have a Web-based access, password-protected system to allow even a

large number of users to go online and to log in and use this simultaneously.
Now, the key difference from the past is it will be a peripheral data submission. Right now, everything comes, is posted, and I or somebody working with me, but mostly myself, we extract it, enter it in the database, and generate the tools. We're really also thinking of long-term sustainability of this process. That it really should be changed. So the participants should enter their data. And beside the automation of administrative function, we really want to have on demand user-driven production of project tools, in other words, the incentive to enter data. Then you can immediately print out an updated report to see how your cutoffs have changed, if your distribution -- if the percentile has changed, has improved. So that really gives us a means to give immediate feedback to the users as they want, as they please.
So easy generation of customized reports. That is particularly the comparison tools where you compare your own data versus everybody else, and also have the flexibility to add a new condition and markers with potential applicability beyond MS/MS and to query the database perhaps to generate novel reports. So we'll start probably next week.
That's all my report.
DR. HOWELL: Thank you very much, Piero.
Are there questions or comments about all this effort that we have going on in Region 4? Ken?
DR. PASS: Thank you.
Piero, that's a very nice piece of work. Thank you for all your efforts.
A couple of questions, maybe just personal questions, or you characterize them afterwards.
Number one, does your data set include data from private laboratories?
DR. RINALDO: Private laboratories meaning?
DR. PASS: Newborn screening laboratories.
DR. RINALDO: Do you define us as a private lab? Yes. Do you define ARUP as a private lab? Yes.
DR. PASS: And others.
DR. RINALDO: Where are you trying to go?
DR. PASS: I'm just asking you. Does Pediatrix submit data?
DR. RINALDO: No.
DR. PASS: Question number two. Have you considered using multiples of the mean rather than percentiles?
DR. RINALDO: Absolutely. Actually we had a very lovely discussion in Minneapolis, and definitely that's something we have to look at. The good news is there are at least three participants who are quite experienced with the use. I should have mentioned it, but we really want to -- because the way the database is set up, it's actually fairly easy to convert all these absolute values into multiple (inaudible). So yes, we are going there.
DR. PASS: Good.
The final question. In my new role as a researcher and an assay developer, I've come to recognize even more so how precious those newborn specimens, the Guthrie spot specimen, is in terms of a positive control. I just wanted to ask you what type of attention did you give to the use of those specimens in developing new assays versus comparing performance among states.
DR. RINALDO: The idea is that if people are willing to share a bunch of their cases, the likelihood is they will receive in return a number they will never be able to test and analyze on their own. And besides, it's not a finite supply. We continue to find cases not for the rare diseases -- if you're talking about developing an assay for SCID or Krabbe or ALD, sure, those are precious and perhaps they should be used wisely. You're really supporting the people who have, really, an ongoing pilot study. Eventually you will run out of a particular sample. My philosophy is okay. There will be more.
DR. PASS: Thanks.
DR. HOWELL: Bill?
MR. SLIMAK: Just a point of clarity. There's always been confusion on whether Pediatrix supplies data or not. The reality is that that data belongs to the states, and I can't unilaterally give that. You can check with Brad. He has to go to each of the entities. They give approval. I format it, and I electronically send it. But to be very clear, in the testing I do, it's somewhat a misnomer that Pediatrix doesn't supply data. That data belongs to the states.
DR. RINALDO: So would you be willing to provide me with a name and contact of the people who have the authority?
MR. SLIMAK: Yes. I'll email those to you.
DR. RINALDO: I'll expect to see it in the next few days.

MR. SLIMAK: Because you can use Brad's data as an example. He's contacted each of the individual entities. They've given approval. We format it. We send it back to the entity. They approve it, and then we send it to Brad.
DR. HOWELL: I think that would be tremendous because, obviously, you have a very large number that you handle, and that would be helpful. Thank you very much, Bill.
DR. GREGG: Can I just ask for one quick clarification?
DR. HOWELL: Quick.
DR. GREGG: You went through the effort to define detection rate, and detection rate is traditionally sensitivity. But it seems like it's a slightly different nuance to detection rate the way you're defining it here. Can you just comment briefly about how you might have altered a bit from traditional thinking of screening tests some of these definitions?
DR. RINALDO: Not briefly. Perhaps we can do it later.
DR. GREGG: Well, I think it's important, though.
DR. RINALDO: Sure.
DR. HOWELL: Thank you very much.
We started late because we ran into the coffee break. So we're going to be running a little bit late, but we're delighted to have Dr. Pasquali from Utah, who is going to talk about what's happening with laboratory QA.
DR. PASQUALI: Well, thank you very much for inviting me to present this project.
The background for this project is we have discussed this for two days. So newborn screening by tandem mass spectrometry has been implemented in most states. Of course, there have been challenges with cutoffs, interpretation of results, ratio, and so on. And these have been beautifully addressed by the collaborative project with Region 4.
Now, there are still some unresolved issues on how to deal with profiles that are a little bit more unusual. They are borderline/abnormal, and they can be due to iatrogenic effects. They can be due to hyperalimentation. They can be due to medication. Or they are, again, an unusual profile for metabolic disorders.
So I have seen, by talking to people, there are different ways of handling these. So you have some instances in which physicians admit the patient with an abnormal result, an abnormal newborn screening result, until confirmatory tests have been done. And then you have the other extreme where they say, yes, this is very urgent, but just get the test done within 72 hours. So there is a mixed, not uniform -- not a consensus on how to handle some of these issues.
So what is the goal of this project? The goal is to improve recognition of these abnormal patterns. Decrease the number of the unnecessary confirmatory tests that are done on these infants. When it's possible, promote the use of second tier tests that will help clarify whether there is an abnormal profile due to a metabolic disorder or not. And ultimately, decrease the number of false positives and also false negatives that can derive from these tests.
How will we do this? One thing that I think is very important is we're going to start with our region, which is Region 6, and we will encourage all of our states to participate in the collaborative project of Region 4 and attend the training sessions. Then sending educational challenges. So these will be blood spots from real patients either with metabolic disorders or clinical conditions that will result in abnormal profiles. And then compiling a complete report that will address not just the analytical part of the testing, but also will be a more complete assessment of the analytical and follow-up and clinical aspect.
There are already existing programs that address blood spots and evaluation of a program. One is the CDC proficiency testing which is extremely important for the quantitative assessment of several of the analytes included in the newborn screening.
There is another program, which I don't know how many are aware of. This is run by a European organization, ERNDIM, and they provide the blood spots for a qualitative assessment. The problem with that program is that most of these blood spots are not from children, but they are from adults. Most of the time, the patients are already on therapy. So this does not really reflect what you will see in a newborn blood spot.
So, again, this is our project. We'll evaluate, again, the whole program. But we'll approach this considering the newborn screening, again, is not a test but it's a whole program. That includes the laboratory, the follow-up, the clinical part, education, and ultimately evaluation of the whole program. All of these are components of the newborn screening program.
Which diseases do we want to target with this approach? We want to start with the tandem mass specs.

The metabolic disorders detected by tandem mass spectrometry -- we can include -- and I'll give you an example of -- we want to include the endocrine disorders such as CAH, when you have either a primary screen or a second tier test which can be performed by tandem mass spec. We will include again not diseases but clinical patients who are on hyperalimentation, antibiotics, special diets, or other medications. And then we can expand these to other disorders in the future. But for now, just the targeting of tandem mass spectrometry.

The educational challenges will involve -- we will have a review panel which is composed by biochemical geneticists, laboratory and clinical based. Again, metabolic physicians needs to be involved in this because they are ultimately the recipient of these results. The CDC will be involved in this process because of their long-time experience in handling programs such as this.

And we will look at the markers used, second tier tests used, if applicable, significance of this finding, recommendations for the follow-up. What kind of confirmatory test? Is there the need for a metabolic referral? And what kind of urgency? So do you say, yes, this particular profile needs to have immediate attention, meaning before the end of the day, this baby needs to be seen by someone, or it can wait a little bit longer. And who is involved usually in the review of these data? Is it the technical supervisor? Is it the medical director? Do you have a metabolic consultant, or do you have a combination of these?

We will collect all of these forms, and the report that we will send back will include the clinical description of the patient, exactly what was the presentation of the patient, were there abnormal metabolites present in the sample, explanation of this abnormality. Why do you have this specific analyte elevated in this particular disorder? So basically if one can collect all of these evaluation forms, it will be like biochemical genetics 101 kind of class.

We will discuss the importance of second tier tests and recommendations for follow-up and the lessons learned from different cases.

So we will include in the evaluation form also in the discussion about the abnormal metabolites some of the graphs from Region 4, what Dr. Rinaldo has presented. We can use it for the recommendation for follow-up, also the ACT sheet that the ACMG has developed. I think that this will be a way to put together all of the resources that have been developed so far and putting them together and use them, not seeing them one at a time, but really looking at the whole picture.

So this is an example of a baby, low birth weight, who was initiated on medication before collecting the newborn screening sample. The steroid profile by tandem mass spec showed normal 17-hydroxyprogesterone, androstenedione, and the cortisol was low. But despite the normal 17-hydroxyprogesterone, the ratio, 17-OPH plus androstenedione divided by cortisol, was clearly abnormal and allowed the identification of this child who had, indeed, CAH, a 21-hydroxylase deficiency. This is the steroid profile that has been developed and described by Dr. Rinaldo's group a few years back.

So how will we distribute all the information? By electronic mail. It seems to be the best way to distribute information, these evaluation forms. It will be important to meet with the participants at least once a year to discuss these educational challenges. And results can be discussed also during the regional meetings. Now, tracking the performance over time will determine also the impact of the training sessions and these educational challenges, again, on the performance.

What are the challenges? Obtaining blood from patients. So we need to have many centers involved in collecting several numbers of cases. We need the participation of NICUs to identify all these factors that affect the newborn screening results. And we need, of course, consent forms that can be shared with other states. And as part of the project, we will develop a general consent form, again, a kind of basic consent form that can be used, hopefully, by more than one state and also can assist with IRB submission.

Tracking of data will be very important to develop some metrics to evaluate the results and compare them over time. We can integrate these again with the Region 4 database, plus we have many participant laboratories.

As you can see, we're going to start with our region, and in our region, one way or another, all of the states have adopted tandem mass spectrometry.

The enrollment, again, although it will start as a regional effort, will be open to every laboratory, and there will no cost to participate. The only requirement will be to analyze two to three sets of blood spots twice a year, fill out the results form and mail the results and attend one meeting per year to discuss these results.

So in summary, we believe that this project will improve the quality of screening, will increase awareness and education about metabolic disorders, and complement the activities of Region 4 collaborative project

and the existing proficiency testing that's currently run. We've seen that in our state, when we have adopted this educational session with our follow-up program and so on, it's been very successful.
DR. HOWELL: Thank you very much, Dr. Pasquali.
Are there questions or comments?
One of the things that comes to mind is that the National Institute of Child Health and Human Development has a very longstanding neonatal research network, and perhaps in trying to identify neonates with special issues, working in collaboration might work.
Of course, Bill Slimak had just commented, but obviously, Pediatrix also has a very large neonatal network that might also be able to help you in getting appropriate samples of infants who are getting special treatments that would affect newborn screening.
Thank you very much.
DR. PASQUALI: Thank you.
DR. HOWELL: We're going to conclude this morning's session by asking Emil Wigode, who is Director of Federal Affairs for the March of Dimes, to give us a federal legislation update. I think before he even starts, you can look at tab 14 and see that there's a great deal of activity in areas related to this committee on Capitol Hill.
Emil?
MR. WIGODE: Thank you, and I know I'm standing between you and lunch. So I'll try to be brief but rich in content.
I guess just to start with, for the March of Dimes, federal activity on newborn screening is a priority, but all of our chapters at the state level -- it's a foundation-wide advocacy priority, and they are working on getting all the states up to at least the 29 core conditions. So I just wanted to say that up front. We're not just focused on the federal legislation at the March of Dimes.
I thought I'd start with just a quick update on appropriations and funding issues. The fiscal year 2007 appropriations process actually wrapped up about four or five months into fiscal year 2007. I think basically we ended up with level funding with most of the agencies that deal with newborn screening. The MCH block grant, which most of HRSA's newborn screening activities come out of, was level-funded. NICHD was level-funded in '07, and a lot of the programs at CDC were also level-funded. So it was kind of a wash this last year.
In '08, the process has just gotten underway, and we're working with several members of Congress to increase specifically HRSA's budget for newborn screening from about $6 million in 2007. We're requesting a $3 million increase on that. I'll just pass out -- on the Senate side, just recently, we had 15 Senators that signed on to a letter to appropriators requesting that increase. So that's gone to the Appropriations Committee. And we're also, on the House side, working with several members of the actual subcommittee that decides this funding on getting that increase. So that's a priority for us this year.
And I think just to talk for a minute about the overall budget environment, which is going to be kind of what drives whether we're able to get this increase or not, the House and Senate passed their budget resolution yesterday, which is their overall blueprint for kind of the fiscal year. On the domestic discretionary funding side, they provided overall a $23 billion increase over 2007, and that's for non-defense activities. So keep in mind that's not just health care. That's education, environment, a whole host of issues, and it will be up to the Appropriations Committees to allocate that additional money amongst the different bills during the appropriations process. So we're hoping that the health funding bill gets a significant portion of that.
Just keep in mind too that with that budget resolution, that does not go to the President. He does not get to veto or sign that. It's just a resolution in Congress, and the OMB Director has actually publicly stated that because the budget resolution is $21 billion above what the President's budget was, that he will recommend that the President veto several appropriations bills that go above the President's level. So it's going to be, I think, a long process to actually get some of these funding increases and just to get overall some extra money in this years appropriations bills.
Also, during the appropriations process, of interest for the committee is Secretary Leavitt testified before the House Appropriations Committee and was asked specifically by Representative Lucille Roybal-Allard from California about the status of the letter that this committee submitted to the Secretary a while back on asking him to facilitate the adoption of the 29 core conditions. His response at that hearing was that he had not received the letter, but would look into it and would get back in writing to the committee. They have not gotten back to the committee in writing yet, but we're hopeful that that will happen soon. We may get a response out of the Secretary on that letter and recommendation.

On the authorization side, in your folders there are several bills. I wanted to just focus on two that are specifically related to newborn screening.
The first is the Newborn Screening Saves Lives Act, and I know you've heard about this bill before. Senator Dodd and Senator Hatch have reintroduced it in the Senate, and in the House, Lucille Roybal-Allard from California and Mike Simpson from Idaho have introduced a counterpart. That bill basically authorizes several grant programs around education and training for health care professionals, education for parents and families, follow-up care. It also has a grant program that would provide assistance to states to help improve their screening programs.
It would also reauthorize this committee for another five years, and within that reauthorization, I think there are some changes to kind of reflect better what the committee is doing right now. So that would be added to the codification of this committee.
It would also require CDC to ensure the quality of laboratories. Right now, that's a voluntary program. It would make that a requirement.
It would also require CDC to develop a national contingency plan for newborn screening in the event of public health emergencies or other emergencies like we saw with Katrina.
The other newborn screening bill is the SHINE Act, which Senator Clinton has introduced in the previous Congress and is planning to reintroduce this session. Right now, there is not a House counterpart. Just to highlight a few of those provisions, it would authorize an Internet clearinghouse for educational materials. Again, it has several grant programs that would help states increase their capacity and also study the benefits of screening for additional disorders beyond the core 29. It would also require the development of guidelines for states to report newborn screening data.
Both the Dodd Newborn Screening Saves Lives Act and the Clinton bill, the Senate Health, Education, Labor, and Pensions Committee -- both bills are under their jurisdiction. The committee leadership is very interested in moving a newborn screening bill in the next month or so. So they are right now encouraging Senator Dodd and Senator Clinton's staff to sit down and come up with a consensus newborn screening bill. So we're hopeful that will happen and we'll actually see it move out of committee in the June time frame.
On the House side, I wouldn't say there's any imminent movement. Our strategy right now has been to -- we've gotten a little more receptive response on the Senate side. So we're kind of focused on getting it out of committee in the Senate, get it out of the Senate, and then hopefully get the House to move on it. So that's kind of the status of things. I know there was some interest last meeting on Senator Obama's genetics bill. The one update I would just say to that is one provision from his bill that would require an IOM study on safety and quality of genetic tests was actually included as an amendment to the recent FDA reform bill that passed the Senate. So that provision from the Obama bill is currently in play, and the House I know, over the next month or so, is looking at doing their version of the FDA reform bill. And then it will go to conference committee.
So if anyone has any questions.
DR. HOWELL: Thank you very much.
Are there questions of Mr. Wigode?
(No response.)
DR. HOWELL: You're optimistic that the joint effort with the Dodd/Kennedy thing will, indeed, move through in June?
MR. WIGODE: Yes. We're getting a pretty good response that it will go through committee in either June or July, and then we'll see from there.
DR. HOWELL: If there are no questions or comments, thank you very much.
We'll now break for lunch. Why don't we come back at 10 after 1:00 and we'll have a nice full hour? We've got a lot of folks who have signed up to comment. So let's get back promptly at 1 o'clock because we're expecting a lot of wisdom.
(Whereupon, at 12:10 p.m., the meeting was recessed for lunch, to reconvene at 1:10 p.m.)

AFTERNOON SESSION (1:12 p.m.)
DR. HOWELL: Ladies and gentlemen, we are still having a few people that have not yet come and some people have had to leave. But we're going to start with our public commentators. We have a considerable number of persons who are going to speak this afternoon. So we're going to have to stay quite strictly within our guidelines.

I have one slight change in the schedule, and that is, I'm going to ask Kathleen Huntington to speak in the second space because of problems with travel arrangements. So I hope you all will find that appropriate. And Ms. Claudine Williams will not be speaking this afternoon, but other than that, the public commentators are as you see it.
I'd first like to all on Paula Brazeal, who is President of the United Leukodystrophy Foundation. We'll have four minutes to speak.
MS. BRAZEAL: I'll try to be very quick and brief.
I previously addressed this committee in June of last year, and at that time, we were discussing the application process. At that time, I appealed to the group of the necessity and the critical need for newborn screening for ALD and shared my family history of losing two sons, a brother, an uncle, and the many carriers in my family history. So I won't bore you with that today.
However, I was enthused by the presentations here. They were wonderful, so different from last June. I could see, on behalf of this committee, the change in the enthusiasm. The level has escalated in enthusiasm for accomplishing what we're all trying to do as a team.
Having said that, there were some other things that I observed. During the presentation, I heard the repetition of current nomination draft, fall-back loops, conceptual framework, road maps, issues, elements, components, white papers, and I'm not going to go on, but this was a continual repetition.
But then I went to a subcommittee and at the subcommittee, the first one I went to, I had to check out after an hour and a half. So that one consisted of the current nomination draft, the fall-back loops, conceptual frameworks, road maps, issues, elements, components, white papers, and an issue that we needed to form a description and define all of the above. So I didn't see a lot of progress there, although it's been very entertaining because this morning, Mr. Chairman, you made a comment and I found it very interesting. You suggested that people think outside the box. Thank you very much.
Yesterday in a subcommittee meeting, another member of the committee expressed a concern that we're going to do all this and we won't have a mechanism in place for follow-up treatments because people might think outside the box. So I really think we need to get on the same page and move forward.
I'm committed to following the guidelines for an application for newborn screening. We have a team ready. I would ask that we have a time frame, a commitment from this committee as to when we will see this. So we have made every attempt to meet the challenges that have come from what you have given us so far. I realize that you're striving for perfection and I admire that, but we need to move on and see what works. If we don't complete the first step, we'll never reach the rest.
I realize I have a lot more, but I don't want to be barred from coming back.
DR. LLOYD-PURYEAR: Your comments can be put into the minutes in their entirety.
DR. HOWELL: If you have other written comments, they can go into the document and so forth.
MS. BRAZEAL: Okay.
DR. HOWELL: Thank you very much.
MS. BRAZEAL: But I will be back because I will be watching. And can you answer my question?
DR. HOWELL: Well, let me make a few comments, and I'm not going to comment after each thing. But, number one, the committee has officially approved the nomination form which will be available after this meeting. So that is done.
MS. BRAZEAL: It will be on the website?
DR. HOWELL: Well, I don't know where it will be. Michele will do that. It will be somewhere, the website and so forth.
But the other thing is that the evidence-based group has been established. The form will clearly be tweaked as they work on it. But that's out there and that's done. So you need to go home and get busy.
MS. BRAZEAL: We will.
DR. HOWELL: Thank you.
Kathleen Huntington from the Genetic Metabolic Dieticians International I've asked to speak next because of some travel plans.
MS. HUNTINGTON: Thank you, Mr. Chairman and members of the committee.
I'm a clinical dietician and member of the Genetic Metabolic Dieticians International. It's a new professional group that was formed to address the needs of our particular profession in serving our particular patient group, which is primarily patients who have been identified and diagnosed through newborn screening.
We support the ongoing efforts of the Secretary's advisory committee to refine, improve, and expand newborn screening.

We have a unique position to understand the health care delivery to these types of patients because we're in the front lines of designing treatment, implementation, and adherence to therapy.
Basically most of the tandem mass spec disorders are managed through medical food, and approximately 25,000 are probably on medical food in the United States. Despite the fact that this is the cornerstone of therapy for these disorders, medical food is not covered by insurance. The average cost for therapy for all the disorders is around $5,000 a year. If you take an individual who is not treated, who is like a retarded individual, PKU, the monthly cost for supervised nursing care is $3,000 to $5,000 a month. $5,000 a year; $3,000-$5,000 a month. So you could actually treat 12 people with the same funds, what it would cost somebody to care for them in a nursing care facility. So, obviously, there's an advantage for treatment.
But states, in responding to this problem with insurance care coverage, have passed state mandates, but it's a chaotic array of different kinds of laws and regulations that don't treat all disorders or don't provide the same kinds of medical foods for the same type of amino acidopathies. There's a whole array of things that are different.
Oregon passed a law in 1997, and we took our cue from how to describe what medical foods are from the Orphan Drug Act of 1988, which says a food which is formulated to be consumed or administered 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 on the basis of recognized scientific principles are established by medical evaluation.
That's a long, drawn-out phrase, but our clinic distributes all the medical foods that are needed by our patients. And we make a point of making sure that packaging is labeled in similar language so everything that goes out to all our patients has this type of language on it as part of the label, which really helps with coverage.
We also worked with Blue Cross/Blue Shield to get a HCPCS code set up to reference medical foods, and that eliminated the chaos that goes on when you're trying to figure out what the heck medical food is in an insurance claims division. So that really streamlined the whole process and we are able to bill insurance companies and we get very good reimbursement.
So dieticians like myself, patient families can just detail -- very frustrating details of how they have fought insurance companies. But anecdotal information is not enough. We are involved in a survey of our professional group to look at what the status of state coverage is, and we would like to share these results that we come up with with the committee and to collaborate on an effort to make sure that health care coverage is guaranteed. To that end, I hope that you will agree.
DR. HOWELL: Thank you very much.
MS. HUNTINGTON: Do I turn this in to this individual?
DR. HOWELL: Yes, by all means, if you'll give it to Jill, that will be great.
Our next person is Ms. Micki Gartzke, who is a parent and Director of Education and Awareness of Hunter's Hope Foundation. I didn't see Micki. I thought she had flown the coop.
MS. GARTZKE: I was tempted.
(Laughter.)
MS. GARTZKE: First of all, good afternoon to everybody, Dr. van Dyck, Dr. Puryear, Dr. Howell, members of the committee.
I was struck yesterday, Dr. Howell, when you noted that we are at the 10th meeting of this committee, which means you all have welcomed me to provide public comments 10 times. I've been at every meeting. I've provided public comments at every meeting.
The number 10 got stuck in my head ever since yesterday when you brought it up, and I thought of parents who, when they have their newborn babies, they get excited when they see 10 fingers and 10 toes and what that brings to your heart. I've been focusing kind of on that in the last day or so.
And then the other number 10 that's been sticking in my head is that my daughter would be 10 if she were still with us. So I've been a little emotional.
And then I got frustrated with a lot of what I heard this morning. My comments, for sure, would have put me over four minutes, so you're just getting like four bullet points this afternoon, but I'd be happy to submit the written comments.
My comments are around the nomination process, and I am thrilled and applaud you for finalizing that form. The Krabbe Disease Team is ready and we will submit a form to nominate Krabbe disease with all the proper expertise, and I'm looking forward to being able to access the form and make that nomination.
As you heard yesterday, Dr. Therrell gave some brief statistics on the success of the New York program started last year for Krabbe disease. He highlighted that they had identified two children at high risk and

two children at low risk, and I also know that they have identified one child with the early infantile onset who has been transplanted and is about to go outpatient and doing very well in the transplant process. That's a huge milestone. That has never happened in the world before, that a child was able to receive treatment for this disease without already coming from a family who had lost a child. So we're very excited to be able to share that news and make a nomination within the same short period of time.
When I was reading the minutes from last time to prepare for this meeting, a comment that Dr. Duke made that Dr. van Dyck read stressed the importance of making sure that the parents' voices are heard. And we will have many opportunities today to hear from more voices, but I just want to thank you for giving me the opportunity to have my voice heard for 10 times now.
Thank you.
DR. HOWELL: Thank you very much, Micki, and let me emphasize one other thing that I think you know, and that is, all the committees and the subcommittee meetings are open to everybody, and we particularly welcome parents and so forth to come and comment at those meetings.
Our next spokesperson is Ms. Jill Levy-Fisch, parent and President of Save Babies Through Screening Foundation.
Jill?
MS. LEVY-FISCH: I think I'm a lot shorter than Micki.
Good afternoon, everybody. Thank you for the opportunity to speak again today.
And I will reiterate what Micki said. It's hard to believe that it's been 10 meetings and 10 times that I've been here. It's been a long and interesting road.
First of all, I want to say how proud I am of the New York State program and what's being done in regard to newborn screening for Krabbe disease. It's really incredible to think that even one life has been saved by this program, and if it is even one life, I consider it to be a huge success.
In April, I attended the expert meeting for long-term follow-up, and what was accomplished that day I think will really help us to redefine the system, both public and private. Ultimately, long-term follow-up should take a developmental, lifetime perspective.
The focus of the information that was presented that day was on ages 0 through 18. However, we really should be extending that to 21 years of age as there are many different transition periods in the life of an affected individual such as puberty, even managing one's own health care in a college setting, and transitioning into adulthood.
Lifetime follow-up, however, is essential in order to provide the greatest possible benefit to those affected, and at the same time, that knowledge will provide crucial information that we need to save those born in the future. There's much to be learned from those we're treating now.
I'm extremely glad to see that we are this close to beginning the nomination process. It's been a long road and I appreciate the work that the committee has done to get us to this point. This is a pivotal time in the world of newborn screening. With the testing currently available and the hundreds of tests that will soon be knocking on our door, the fact is that thousands of lives will be saved as a result of this process.
As you know, I a member of the Subcommittee on Treatment and Follow-Up. One of the issues being addressed by a subcommittee workgroup is that of reimbursement and coverage of metabolic foods and formulas, and we heard some of that earlier. Families continue to suffer tremendous financial difficulties due to the lack of coverage and reimbursement. Government programs, such as WIC, are problems in some states, and when you speak to families, you really see how this issue extends beyond the private insurers, although the insurers themselves are causing tremendous problems.
I really do hope that the committee will act expeditiously once recommendations are made by the subcommittee. Circumstances are now so dire that we actually have parents who are divorcing in a desperate attempt to qualify for financial assistance. This clearly indicates to me that the system currently in place is broken and really needs to be fixed.
That's what I have to say for today. I really do appreciate all the opportunities I've had to speak, and I thank you.
DR. HOWELL: Thank you very much, Jill.
Our next speaker is Andrea Williams, Executive Director of the Children's Sickle Cell Foundation, Incorporated.
MS. WILLIAMS: Good afternoon. To the advisory committee, the work that you do is important.
I just want you to know that I've heard the committee reference genetic diseases and heritable disorders as being rare diseases. It is my intent to remind the committee that sickle cell disease is not rare. Approximately 1 in 400 African Americans have sickle cell disease and 1 in 12 with sickle cell trait. These

carriers are at risk for having a child with sickle cell disease.
Proper attention to carrier diagnosis and follow-up genetic counseling is a vital extension to the work of newborn screening. Every child that tests positive for sickle cell trait has at least one parent that also has sickle cell trait, possibly two. Should both be carriers, they are at a 25 percent risk of having a child with sickle cell disease. Education of these families is an important factor that will empower the families to help them understand what sickle cell disease is and how they may be at risk for having a child with sickle cell disease.
Education of the providers to view sickle cell trait as a diagnosis requiring an action plan with referral of parents for genetic counseling is an obvious next step toward the education for trait carriers.
Thank you.
DR. HOWELL: Thank you very much, Ms. Williams.
Our next spokesperson is Dr. Carol Greene, who is on the board of directors of SIMD.
DR. GREENE: Also short.
Mr. Chairman, members of the committee, thank you once again for the opportunity to speak, and like a couple of the previous speakers, I've been here for all of the meetings.
Once again the SIMD wishes to express appreciation for the dedication of the members of the Secretary's advisory committee and for the effects your work has already had on the status of newborn screening. The improvement in the number of states mandating and actually implementing the recommended newborn screening panel is, in no small part, a result of this committee's efforts.
As the professional organization of clinicians and scientists focused on inborn errors of metabolism, we are in a position to recognize the life-saving impact this has on families. We're also in a position to see how the expansion of newborn screening highlights the need to assure that detection of disease by newborn screening results in improved health and well-being to the affected newborns and their families.
We, therefore, appreciate the opportunity last month to participate in the meeting that was just mentioned to consider long-term follow-up and treatment issues. As you know, these are critical issues for our membership and for the families we serve, and in the statement to the committee today, we wish to highlight two points.
First, we have spoken to the committee before on the need for support for ongoing research and continuous improvement in screening follow-up and treatment. In particular, today we want to share a new SIMD policy statement, which I will be sending in electronically, focused on improving objective outcome data of new treatment. This one is very short. I can read it in its entirety.
"Current developments and understanding of human metabolism and genetics are providing exciting therapeutic options for treatment of inherited metabolic disorders. At the same time, we increasingly appreciate the complexity and variable expression of inherited metabolic disorders. Therefore, the SIMD membership strongly recommends that therapies introduced for clinical use should be implemented in the context of ongoing collaborative efforts towards collection of objective outcomes data."
Second, we have also spoken to this committee at previous meetings about the need to assure lifelong provision of the treatments that are essential to protect the health and well-being of those with inborn errors of metabolism, including those found to have these medical conditions as a result of screening.
In particular, we wish to join others in highlighting today the need to assure the access to medical foods that are needed to treat metabolic disorders, and we will be sending the committee a copy of our recent policy statement on that issue. I think the main point there is we highlight a little bit of the history and point out that we feel that these medical foods should be covered in the same way and to the same extent as medications that are essential for life, like insulin for diabetic and digoxin for somebody in heart failure, because they have the same implications.
So we recognize these are complex issues and that a great deal of work in partnership with many stakeholders is required for success, and as always, the SIMD is eager to work with this committee to achieve our mutual goals. And in that light -- and I know it's not done until you find out whether the next levels up approve, but we very much appreciate the vote from the committee to consider having the SIMD at the table.
So thank you very much.
DR. HOWELL: Thank you very much. I'm not aware that anyone has to approve the actions of this committee, but we'll see. I'm sure someone will have to. But anyway, we're not aware of that, and so we think it's a done deal.
Our next speaker is Dr. David Whiteman, who is the Medical Director of Shire Human Genetic Therapies. Dr. Whiteman?

DR. WHITEMAN: Thank you, Dr. Howell and members of the committee. This is my first time speaking here, and I appreciate the opportunity.
I came here originally to address you on the issue of the expansion of the core panel of newborn screening, and now I find that it's my turn to congratulate you on having completed the nomination form process and the development of the Evidence-Based Medicine Subcommittee.
As you know, I'm the Medical Director of Shire Human Genetic Therapies and my main interest in newborn screening, therefore, links to lysosomal storage diseases in particular and to Hunter's syndrome especially. Dr. Ron Scott's group has recently concluded their resolution of the difficult problems they were having with newborn screening technology or the implementation of their new technology for mucopolysaccharidosis 2 and we certainly intend to submit a nomination for Hunter's syndrome as a condition to be considered, along with the other lysosomal storage diseases with the support of the family organizations, the clinicians who treat such patients, and obviously, ourselves.
The second thing I'd like to address and perhaps is relevant to that is some of the comments about the relationships with industry from this morning. I apologize for arriving here halfway through the discussion that Dr. Rinaldo eventually had to terminate.
But I am struck, having come to this meeting for the first time, at a lack of industry representation. "Industry" is a broad word. It includes people who manufacture devices, develop screening tests, in some cases implement them, either provide or support therapies, develop software for follow-up, manage information and so on and so forth. Those are things that many of the people who are represented at this table also do. Everybody in some way or sense is attempting to serve the needs of the families and the patients.
One industry representative would certainly not suffice to represent all that effort, but I do think it's important you give some consideration to either representation or some communication, if you will not accept representation, with industry in moving forward.
I echo the comments of Ms. Brazeal and others concerning some of the language that we've heard today. I think there's clearly an emphasis on excellence here, but I think there's also an emphasis on process that may be somewhat overstated. For those of you who may have heard various news bites today, perhaps I can best express my concern about that by echoing one of our Senators who, in regard to another very important national issue, said today, please do not let perfection stand in the way of the good. Perhaps in our situation, we should substitute "the very good."
But I do think that you should be aware, if you are not already, of the urgency that families feel around these issues, the urgency that those of us who treat patients feel around these issues, and the importance of early identification.
Thank you for the opportunity to speak to you.
DR. HOWELL: Thank you very much, Dr. Whiteman.
Our next speaker is Mr. Spencer Perlman, who is the Government Relations Director of the Families of Spinal Muscular Atrophy.
MR. PERLMAN: Good afternoon. Dr. Howell and members of the advisory committee, thank you for the opportunity to testify today.
As Dr. Howell already said, my name is Spencer Perlman and I am the Government Affairs Director for Families of SMA, the largest international organization dedicated solely to eradicating SMA by promoting and supporting research, helping families cope with SMA through informational programs and support, and educating the public and professional community about SMA.
I'm testifying this afternoon as a representative not just of FSMA, but of the entire SMA community, including the Spinal Muscular Atrophy Foundation and Fight SMA, regarding the committee's nomination and evaluation process for candidate conditions on the uniform newborn screening panel.
Specifically, I am here to urge the committee, as it develops the nomination and evaluation process for candidate conditions, to permit the addition of disorders to the universal newborn screening panel that do not presently possess a demonstrated treatment or cure. The SMA community represents a unified front in strongly urging the advisory committee not to preclude an external evidence review group from considering the case for universal newborn screening of a disorder solely due to the lack of a presently available treatment or cure. The SMA community and other similarly situated communities should be allowed to make the case during the nomination and evaluation process without this historical bias.
Newborn screening can play a vital role in the development and treatment or cure and in improving the quality of life of the infants afflicted by deadly and disabling disorders such as SMA. As you know, SMA is the leading genetic disorder -- leading genetic killer, I should say, of children under the age of 2. It is also

a relatively common rare disorder, occurring in about 1 of every 6,000 births, with 1 in 40 people in the general population being carriers of the disease. Approximately 50 to 70 percent of affected children suffer from type 1 SMA, the most severe form. More than 95 percent of these children die in infancy or require extensive respiratory support by their second birthday.

Newborn screening is an issue that is of paramount importance within the SMA community. In fact, the FSMA website section devoted to newborn screening is one of the most heavily traversed and visited portions of the website. SMA families, as well as investigators and clinicians within the SMA community, recognize that newborn screening holds great promise in assisting the efforts to identify a treatment or cure for this deadly disease.

There have been several exciting research breakthroughs in SMA research for the past five years, and this research, along with clinical trials now in progress and drug discovery programs that are moving forward rapidly, could benefit from identifying affected individuals at birth and hold tremendous promise in developing a treatment or cure for SMA.

Sixteen leading SMA investigators and clinicians from across the United States and Canada have signed a letter to the committee expressing their belief that these research efforts will be significantly enhanced if presymptomatic SMA-afflicted children could be identified through newborn screening. I have copies of the letter for each member of the committee, if they are interested in seeing it, and I respectfully request the letter be placed in the record of these proceedings, along with my oral testimony.

I'll just briefly summarize the letter. There are several reasons that SMA research, clinical trials, and drug development can benefit from identifying affected individuals at birth, even though no current treatment exists.

Number one, natural history data indicates that there's only a small opportunity for intervention in the most common and severe form of SMA type 1. Dr. Kathryn Swoboda of the University of Utah School of Medicine has found type 1 infants, demonstrating normal distal innervation during the presymptomatic phase of the disease, suffer rapid loss of motor units in the first three months and severe denervation with the loss of more than 95 percent of units by 6 months of age.

Number two, preliminary data in human and mice models indicate that presymptomatic drug intervention is more effective than postsymptomatic.

Number three, presymptomatic enrollment in the clinical trials may greatly enhance the chance of identifying an effective drug intervention for SMA, particularly for type 1 SMA infants. Clinical trials in symptomatic patients with end-stage denervation and contractors may actually disprove the efficacy of therapies which, when administered early, might truly benefit this population. Additional studies regarding presymptomatic drug intervention can occur only if an adequate population of presymptomatic type 1 SMA infants is identified for participation in clinical trials.

In addition to the benefits to research, diagnosis of SMA at birth has several other benefits, and I'll go quickly.

One, it will allow patients to obtain proactive treatment earlier in the disease progression with regard to nutrition, physical therapy, and respiratory care, which will lead to a better quality of life for SMA-afflicted children, reduce respiratory morbidity, and extend lifespan.

Number two, the natural history of SMA appears to be changing due to more proactive care and improved clinical treatment, and earlier intervention through newborn screening could enhance these results further to the benefit of SMA patients.

Number three, a delay in diagnosis has significant economic and medical consequences. Identifying SMA-afflicted individuals at birth eliminates the pain and cost of unnecessary testing that otherwise would take place in attempting to diagnose the affected patient.

And finally, newborn screening will provide parents with earlier genetic counseling before they are likely to have a second affected child which, sadly, frequently occurs when diagnosis is delayed.

In addition to the aforementioned items, the case for implementing universal newborn screening for SMA is made more convincing by the fact that the technology currently exists and has been recently updated by Dr. Tom Prior of Ohio State University. The assay has greater than 95 percent sensitivity and 99 percent specificity.

In conclusion, the SMA community strongly urges the advisory committee to state explicitly that the existence of a treatment or cure is not a determinant factor in whether a disorder is eligible for inclusion in the uniform newborn screening panel.

I thank the committee for the opportunity to testify.

DR. HOWELL: Thank you very much, Mr. Perlman.

Our next presenter is Ms. Laura Breitenucher, who is an associate with the Winning Strategies on behalf of the Spinal Muscular Atrophy Foundation.
MS. BREITENUCHER: I'm with the SMA Foundation with Spencer. We're together.
DR. HOWELL: So Mr. Perlman's comments have covered your wisdom also?
MS. BREITENUCHER: Yes.
DR. HOWELL: All right, thank you very much.
Our next presenter is Ms. Kimberly Symonds, Executive Director of the Wilson Disease Association.
MS. SYMONDS: Thank you, Mr. Chairman, members of the committee. This is my first time before you and I thank you for this privilege and honor.
I'm here to tell you about the importance of the extended panel to include Wilson disease. Wilson disease is an accumulation of copper in the liver and brain, and it is estimated it affects 1 in 30,000. However, we believe that it is much more common due to the number of cases that are missed or misdiagnosed. Although this is rare, if we are able to help one family from losing their child because of a delay in diagnosis or a missed diagnosis, this is worth it.
I remember a story. It happened last year. It was a 16-year-old girl. She went to the pediatrician's on a Friday. She was presenting with jaundice. Monday her parents admitted her to the hospital. Tuesday she was on the transplant list, and she died on Thursday from Wilson disease. It was undetected. Her parents said if they had only known, they would have been able to treat her and she would still be with them today.
The problem with Wilson disease is there's no easy way to obtain the proper diagnosis. Currently it can take up to 10 years before a person receives accurate diagnosis. During this time, the copper continues to accumulate and much damage is done to the liver and body as a whole.
Another problem is we mimic many other disorders, hepatitis, Parkinson's, Tourette's, ADHD, autism. It is often a diagnostic odyssey which only delays the process and denies the patient proper life-saving medication.
With the addition of Wilson disease to the newborn screening panel, families will know there's a problem from the very beginning. When will the child's life begin to present with Wilson disease? No one knows. But at least they can maintain proper testing to ensure that the child's body remains healthy and copper does not build up. Chances are they will be able to manage the disease with a reduced copper diet and zinc acetate.
Additionally, if these Wilson disease children are caught early, they will avoid the toxic chelating medications that newly individuals currently must take. With early detection, the child has a much better chance of a healthy life, which is what we are all seeking.
We urge the committee to review Wilson disease for inclusion in the uniform newborn screening panel. We believe Wilson disease is a strong candidate because we have effective treatments and therapies. We are working with Mayo Clinic on a newborn screening pilot study for Wilson disease in Minnesota, and we are clearly moving in the right direction with that study.
As with many diseases, early detection is the key to prevent lifelong physical and mental difficulties. With Wilson disease it is no different.
As for our application, it will be revised and submitted as soon as our scientists tell us we can.
Thank you.
DR. HOWELL: Thank you very much, Ms. Symonds.
Our final person commenting today is Mr. Bill Slimak, who is Vice President of Operations of the Pediatrix Medical Group.
MR. SLIMAK: Good afternoon and I thank you for the opportunity to speak before you. I will do two things that people will not expect me to do. One, I will be short, and secondly, I will be unemotional.
What I want to do is provide some clarity on kind of the definition of industry. I think what got overlooked this morning was that the group that was being nominated was not Pediatrix Screening, but Pediatrix Medical Group. Pediatrix Medical Group is a national practice of neonatologists. We're some 900 neonatologists dealing in about 220 hospitals in the United States. We also have specialty practices in pediatric cardiology and we also have a smaller perinatal practice. And we operate in some 43 states in the United States, also Puerto Rico, and we also have some practices in Mexico.
As part of that, there is Pediatrix University, which is a Web-based educational system where both internal and external physicians, mainly pediatricians and neonatologists, look for continuing education. We also have pediatric research. Because of the number of babies we touch, we have a huge warehouse of clinical data. Over the next couple years, you will see a lot of involvement of the lab and that clinical

data. At the Minnesota meeting, you saw two papers by Don Chase, one on TPN and some of the studies we've done there, and then the second one was on a new application of T4 on tandem mass. We will continue to do that.
As part of Pediatrix Medical Group, there's additionally the hospital-based hearing screening program which operates in many hospitals, and then finally, there's Pediatrix Screening, which is obviously the group you know most.
Those three parts of Pediatrix Medical Group touch approximately 1 million of the 4 million babies that are born every year.
The point I'm making here is if you broaden the definition of industry to include Pediatrix Medical Group, as you broaden that definition, you will start touching more and more people at the table.
Secondly, as you broaden that definition, it will be almost impossible to come up with one representative that can look at all the different facets of what this group calls industry. You have clinical laboratories operating in the CLIA world. You have reagent manufacturers operating in the FDA world. You have pharmaceutical houses that provide pharmaceutical treatments that operate in a different FDA world. There is no natural place for that group to come together. It just won't happen. We all deal in different organizations. We deal in different regulatory structures.
Now, that said, I will continue to come to this meeting. I will continue to try to have an impact on what we do and how we do it. I will continue to stress the advocacy that the Medical Group has for making sure that the newborns in the United States get the most comprehensive screening and clinical service available.
Thank you.
DR. HOWELL: Thank you very much, Bill, and we'll look forward to seeing you, obviously, at the future meetings.
Having said that, this group has been very expeditious this afternoon, and in spite of the fact that we had 11 commentators, we're actually slightly ahead of schedule.
That brings us finally to the area of committee business. I wonder if the committee members, sparse though they may be at this point in time, have any additional -- we obviously do not have a quorum. So the question is, are there additional items that should come before the committee this afternoon? Amy, Denise, Jana?
DR. DOUGHERTY: I had a little medical episode this year while the policies and procedures were going back and forth. So I was wondering what the status is. Has the committee approved the policies and procedures, or where does that stand?
DR. LLOYD-PURYEAR: Well, we obviously can't have a vote now. That one section on liaison representatives needs to be done. The other section -- we have never approved them formally. So I don't want to wait until September, though. So I'm going to be working via electronic mail to refine this.
DR. HOWELL: We certainly have discussed them, but I think Michele is correct. We've not formally approved them. But we clearly are prepared to do that and certainly should do that very soon, I would think.
Is there any other business? Amy?
DR. BROWER: Just as we were thinking about the pilot studies, one thing I was wondering if the committee could get an understanding of how long states keep their cards and how that practice varies across the different states, just thinking about resources as we develop new assays.
DR. THERRELL: We've actually published a paper that outlines what the current practices are. It's in the Pediatric supplement, and we update it from time to time on our website as well.
DR. HOWELL: Was your question broader, and that is, to make the suggestion to the states about what would be an appropriate -- you're telling us what the states currently do.
DR. THERRELL: Yes.
DR. HOWELL: Was your question broader and might make a suggestion that the states try to save them at least a certain period of time or something of that nature?
DR. BROWER: Yes, to enable the analysis of the positive cases. I'm just thinking if there's any linkage into the 4,000 positive cases that Piero now has in his database, and as they identify positive cases, if there could be a mechanism to save those cards that represent positive cases.
DR. HOWELL: Have you discussed that with your group or anything along the way?
DR. RINALDO: No, but this certainly can be addressed. I believe that the practice is now -- I doubt that no true positives are discarded. Some states have rules that require destruction of the cards, but specimens can be kept for the purpose of educational quality control and quality assurance. So I presume that these

samples are kept.
DR. THERRELL: Yes. Most states do retain their positive cases in some way just for that kind of thing, for future studies. It's the negatives that there's a question about, and the general consensus is if you keep them longer than six months, then you've extended past the period of quality assurance into the research realm.
DR. HOWELL: Any further issues?
Suggestions for the agenda for next time can be forwarded to Michele, as usual, before the agenda is constructed.
Any other business before the committee? Michele?
The September meeting is scheduled. Your calendars come to Michele for next year, and as soon as they're studied, as far as who's available and who's not, those will get out.
So if there are no further discussions and so forth, I suggest that we adjourn, and since there are not enough people to have a motion that it be officially approved, let's just go home.
(Laughter.)
DR. HOWELL: Thank you very much.
(Whereupon, at 1:58 p.m., the meeting was adjourned.)