DEPARTMENT OF HEALTH AND HUMAN SERVICES
HEALTH RESOURCES AND SERVICES ADMINISTRATION
Meeting of the Advisory Committee on Heritable Disorders in Newborns and Children

Thursday, September 24, 2009, 11:45 a.m.

Bethesda Marriott
5151 Pooks Hill Road
Bethesda, Maryland

PROCEEDINGS

[11:45 a.m.]

DR. HOWELL: Let's find our seats so we can stay on schedule. We're -- we understand that we had a very successful series of meetings. You'd better sit down or put on a bulletproof vest, back there. We are -- I understand that we had a series of -- a very successful subcommittee meeting. And so, we're going to start with Gerry, but Gerry's not -- where is Gerry?

DR. VOCKLEY: I'm here.

DR. HOWELL: Oh, you're here. Okay.

DR. PURYEAR: I just have one announcement. Please, committee members and representatives, remove your cell phones and BlackBerrys from the table. They interfere with the output of the sound. Thank you.

DR. HOWELL: Gerry, you're going to report --

DR. VOCKLEY: I am.

DR. HOWELL: -- from that site?

DR. VOCKLEY: I am. I'm --

DR. HOWELL: Great.

DR. VOCKLEY: -- trying to figure out how to

push this button and flip my papers at the same time, because nothing is organized, of course, since we just finished the meeting. We did, in fact, have a fairly wide-ranging discussion, and set, I think, some agendas for the coming meetings. We updated some of our ongoing projects. So, we've heard from Harry Hannon on the routine second screen study, which for -- as you know, for many months to couple of years, had been relatively -- oh, you're going to hold it, okay -- was relatively stalled. But, now we have six States that have gotten IRB approval, some of whom are already starting to enter data, which -- and that this will cover about a half a million births per year, for 5 years -- on the retrospective study of newborns receiving second -- routine second screens. So, we think we probably won't have much data available at the next meeting, but potentially in -- oh boy, look at people arguing now -- hold -- push my buttons.

VOICE: That's right.

DR. VOCKLEY: It's just like back home.

VOICE: We've been wanting to push your buttons for years.

DR. VOCKLEY: Just like back home. And so, that's moving forward very nicely. Bob Vogt gave us an update on the CDC's efforts to make reagents for newborn screening available and so four of the five Genzyme-produced lysosomal storage disease enzyme substrates for tandem MS have now been validated, and are being made available, while the fifth one is -- which was -- oh, I can't figure it -- oh, the CRB-A substrate is not quite ready to go yet. We also were reminded of a study that's about ready to get started in Minnesota comparing the antigen-based multiplex-B technology in comparison to MS/MS enzyme assays for those diseases, and comparison to a traditional fluorometry enzyme assay. And so, hopefully we'll actually have some comparative data on those techniques. However, most of the meeting was spent on trying to sort of establish -- with the recognition that the SCID application that we talked about, or that

we evaluated at the last meeting and made recommendations on, represents the vanguard of a new set of diseases that are going to have a molecular-based test as the primary screening, rather than the reflex -- or rather than the second-tier follow-up. And so, we really started a discussion today looking at the implications of that to the operations of this committee and policies related to newborn screening. And I think there was a general consensus that -- I can do this now, Ron, I'm done with my papers -- that -- thank you -- which this really represents some significant challenges for us, and potentially -- I don't want to say so much a paradigm shift, but recognizing the -- how those issues play into newborn screening. The technologies are, to some extent, less mature than tandem MS was when it was implemented as a newborn screening platform. They're more variable. And the idea that we have functional follow-up tests for those primary testing is -- breaks down when we get to DNA tests, because, in theory, we can test any gene, and we don't have follow-up functional testing to let us

know what "mutations" in many of those genes means. So, we really felt that we needed to focus, in the coming months and over presumably the next series of meetings, on how best the subcommittee can bring these problems to the attention of the full committee, and how we can best -- let me back that up a second. We're not going to be able to stay on top of all technologies. We're a limited group of individuals coming together once every few months, and we're just not going to be able to drive that way. What we hope we can do, and what we think we should be trying to do, is to set a -- refresh the goals of what these sorts of technologies ought to be achieving, relative to newborn screening, and then be able to make sure that, as new tests come forward using these technologies, that we have some platform to fall back on that is actually relatively technology-independent. That said, we are going to have some ongoing discussions on technology, and we had Michelle Caggana, from New York State, give us a very, very nice overview on those technologies that are sort of in practice now

and look like they're going to be, forward. So, more of a history and current status. So, we hope that we'll have some very interesting electronic communications in the next several weeks, and identify a platform of questions that we would like to address, going forward, as we talk about integration, implementation, movement from academic laboratories to large State laboratories with developmental budgets, to State laboratories that are -- don't have a lot of money and are worried about just how they're going to implement testing. It, I think, promises to be a very interesting discussion, and as we move forward I think we'll have some new insights as to how to implement all of this, or how to consider it as we look into implementation of single tests. So, I think that's it.

DR. HOWELL: Are there comments or questions of Gerry?

[No response.]

DR. HOWELL: Thanks very much, Gerry. We'll go ahead now to the next one, the Subcommittee on Education and Training, and it's Jana

and Tracy. And I gather Tracy is going to speak, is that correct?

DR. TROTTER: Yes, if I can get this going here. Okay. Well, we also had a wide-ranging and very satisfying committee meeting. The -- just to remind you who the members are, we had an equal, if not greater number, of guests as well, who provided us with a lot of information and help, and we thank them, once again, for their input. The first update that most of you are aware of is that a newborn screening clearinghouse collaborative has been granted, and it is a HRSA project, through the genetic services branch, with NNSGRC and the Genetic Alliance. And if you looked at the announcement, the obvious is to the increased awareness of newborn screening to all stakeholders -- and we'll come back to that as our final recommendation, a global recommendation from the education subcommittee, later; provide a central linkage for data resource sharing and some point-of-service access for both providers and the

consumers; and to help integrate the electronic health technologies for -- as this starts coming onboard in the near future. We received updates from basically all of these organizations, in one fashion or another, most of which are going to be included in my comments today, and the rest will be available to us in our minutes, as well. The -- back to an old slide you've seen before, from an article, that a number of people in this room were authors of, suggesting that the advancing volume and complexity of newborn screening leaves the primary-care physician with increased responsibility, and therefore needs to have increased educational efforts, so that we can effectively deal with the system of newborn screening and make that system work for everybody. To that end, our subcommittee is -- felt like we would partner with numerous organizations whose goals are the same as ours. From that perspective, I just mention a few of them here on this slide, you know, and some of the ways we thought we could create

this educational message and try to make it more generic than specific, such as responding to the out-of-range result that literally all practitioners who care for newborns will be dealing with in the world of expanded newborn screening, on a fairly common basis. Things that we talked about yesterday in the Long-Term Follow-Up Committee: coordination of evaluations, coordination of care, providing a true medical home for these children with special needs, and the ongoing education of the -- all the players involved. And we sort of feel like we can serve in an advisory capacity to a lot of groups who are currently involved in that, and have done so, in an attempt to avoid duplication and enhance collaboration. And I'm very pleased with how that has gone in the last year. I mentioned, last time we met, that we had specifically become involved with a meeting that Greg Farrow and the National Human Genome Research Institute had put together in -- last June -- in January we were made aware of it -- entitled Developing a Blueprint for Primary Care Physician Education In Genomic Education,

which certainly sounded like it was right up our alley. So, we sort of horned our way into that meeting and added, tacked on, an afternoon. So, the general meeting went for a day and a half, and the second day, in the afternoon, we had what we termed a Maternal Child Health Roundtable, which included about 30 participants from pediatrics, family physicians, ACOG, and beyond, was very well attended, with people who are both interested and people who have -- are at a level in their respective organizations to make decisions. And we have -- Alex Kemper has worked with a few of us to produce a report on that particular part of the meeting, that we would look forward to publishing soon, if we get the -- some approval from this committee. So, just to go over some of the specific things we talked about: What are the knowledge areas that all of the representatives of the primary care world felt that they needed to know, or that they felt uncomfortable with or needed expansion? They are probably not a surprise to anybody in this room as to what those things are. And I won't go through all of them here. But, it -- you know, it -- the range was sort of all the basics, from documenting a good family history, knowing what your resources are, how to respond to genetic -- the new era of genetic testing, and what do you say about genetic tests, and how do you interpret them, that type of thing. The barriers were talked about for some period of time, because we know they're there. We know there's a lack of time in an average primary care interaction with a patient to deal with some of these things, that there's an increasing drain on the time of those people doing full-time genetics, in terms of this exploding information. And, quite frankly, there was a lack of enthusiasm, which was pretty palpable in the room. A lot of it was a lack of what I term "genetic literacy," just the ability to talk about the issues and the language made people not very confident about what they're doing, and when they lack confidence and they lack certainty about what they do, they don't do it very much. And they all felt that this was an area that they needed to improve. And there was, surprisingly, a level of

concern, mostly people my age, who sort of still thought about genetics as, "Deals with rare diseases that occur rarely, and therefore I rarely have to deal with it." Yeah, I know. And it was generational. And there were some of the younger members who said, "No, this is -- affects every patient who walks in, in some way." And this sort of movement towards the genetics of common diseases, becoming more and more apparent. But, I think there is still a barrier out there that relates to that whole situation. We talked about a number of educational interventions that would be helpful, starting obviously in medical school and residency, because if you don't start there, you're probably not going to get it done. Trying to get [inaudible] involved into board examinations, into [inaudible], into quality improvement programs. Those were all received fairly well, in that everybody's looking for that type of thing. It is something that tends to be well received by practitioners, in terms of doing, especially, case-based-type approach to those types of problems, and I've noted some other ones here, as well.

And then a brainstorm of Michele's, which we embraced, is the thought of something called a "learning collaborative" -- or, at least that's what we called it, "a learning collaborative." Based in much of -- based in many mentoring-type programs, and in some ways back to the genetics in primary care program, which was more of a teacher-to-teacher thing, the idea would be to pair physicians in primary care, from busy primary care practices, with experts in genetics and genomic medicine, which could be geneticists or genetic counselors or combinations thereof; to have those physicians attend a meeting where we define the opportunities for how to incorporate genetics into their primary-care practice; develop specific projects for those pairs or groups, which could be maybe one-on-two, or one-on-three, even; and participate throughout the year in -- with a conference-call-type approach; meet again at the end of the year to share those results; and then create a system to formally evaluate the project in a way that we hope can create some energy towards incorporating more and more of this type of learning, from a genetics perspective, into the

primary-care program. And Michele has termed this the Genetics in Primary Care Training Institute, so -- as the title [inaudible]. We discussed that at length today. People were very excited about it, from many disciplines. Lots of great ideas, as a matter of fact, because this, sort of, not been fleshed out, in terms of the specific ideas, but I received a lot of good thoughts today. So, we would look to this committee, recommend strongly that some program like this be brought forward -- funded, in other words -- and that we can pursue this. So, some of the next steps, just to reiterate: residency training programs -- Alex is involved in some [inaudible] with the regional collaborative that may well prove a template for this in the future. We're trying to partnership with board of -- American -- Board of Pediatrics, specifically to [inaudible] to that -- again, the development of these learning collaboratives. And then, hopefully, a follow-up meeting of this entire group that met for 2 days in June at the NIH, because I think it was an exciting meeting, with a lot of people who were very

interested. The -- you know, the final recommendation, if you will, from the Education and Training Subcommittee to the committee in general, which is, of course, preaching to the choir, is this -- the perception that the need for public awareness, at a very basic level of newborn screening is -- we've gotten way behind. Newborn screening's gone quickly, and expanded quickly, and the public awareness has not. I think we saw some of that last night at the Blood Spot meeting. And if we don't have everybody on board that this is something good, then the next step is going to be very difficult. That is, unfortunately, going to probably require a immense amount of resources, both dollar wise and energy wise, but I suspect that people in this room are the folks who can make that happen. Thank you.

DR. HOWELL: Thank you very much. Are there questions of Tracy about his report? Tracy, I would -- the -- obviously, the details of the learning collaborative has not been

fleshed out, but could you make -- could you formulate a motion for this committee, as far as looking at developing such an effort?

DR. TROTTER: I would be happy to. Do you want me to write something up and bring it to you at some point at this -- today or tomorrow? I could do it right now.

DR. HOWELL: I like that.

DR. TROTTER: Okay. Yeah, I would like to make a motion that the committee supports the effort of a learning collaborative for genetics in primary care, and that we move forward in -- over the next 6 months in, hopefully, finding some funding and mechanism to do that project.

DR. HOWELL: Is there a second to that motion? Those favoring that motion? It appears to be unanimous. Any [inaudible] -- excellent, and so forth. And I would be fairly confident that funds may be discovered to support that, so that we'll look forward to seeing that move ahead.

DR. TROTTER: Thank you.

DR. HOWELL: Thanks very much for that -- you obviously had a very meaty meeting today, and so forth. And now we go to Coleen, with the Subcommittee on Follow-up and Treatment.

DR. VOCKLEY: Can I just make a comment about that learning collaborative idea?

DR. HOWELL: Yeah. Please.

DR. VOCKLEY: The only thing is for the group to consider some family input in that, in the sense that you're developing something that is going to be a service for families. In some of the learning collaboratives we've done, we've had family members as part of the team. So, I would just mention that.

DR. HOWELL: The chairman of that working group is nodding that he understands. Thanks. Coleen?

DR. BOYLE: Okay. Thank you. I'll be brief. I have just one slide summarizing the work of the subcommittee, but the slide is in no way a reflection -- the brevity of the slide is in no way a reflection of the work of the subcommittee.

We also had a very active subcommittee meeting this morning. We also had a special meeting yesterday on one of the topic areas, which I'll discuss. And as you all know, we have been focusing most of the energies of the subcommittee on trying to define what "long-term follow-up" is, since that's -- that was the -- sort of the piece of the newborn screening system that was the least well defined and developed at the time this committee became chartered. And I think we've made substantial progress in that area, but I think we have a lot left to do, as a reflection of what I'm going to tell you. You all know that we did have a -- sort of the first, sort of, the grounding paper that was coauthored by the subcommittee, and Alex Kemper took the lead on, in terms of defining what "long-term follow-up" was. In the context of that effort, we also spent a lot of energies trying to define: Who are the major players in the sectors involved in long-term follow-up, and what are their principal roles and responsibilities? And we now have a document that has

been developed over the last, probably, year, that attempts to do that, and fleshing out what the -- the major roles and responsibilities of those various sectors. And the primary sectors we were looking at are the public health sector, both the national and the State level; the provider sector, both the primary and the specialty-care aspects of that; and then obviously, the family -- the child and the family as a separate sector. So, that was shared this morning in our subcommittee, that draft statement. We all agreed that it needed a little bit more tweaking, which we're going to go back and do. And hopefully we'll be able to share it with the full advisory committee once we get buy-in from the subcommittee on our next -- at our next meeting, whenever that is. January? Is that when our next meeting is? Yes, okay. So, that's the status on that. So, in the context -- again, thinking about long-term follow-up -- if you could follow, down here on the second bullet -- I don't have a pointer -- yeah, here we go. On the last -- actually, our last

in-person meeting, in January, we started to think about, sort of, the next steps on long-term follow-up. And this was really trying to develop, sort of, these quality measures, to measure the success of long-term follow-up, as a sort of a public health and a healthcare provider assurance function. And we brought together a number of folks, including the grantees, from CDC, NIH, and HRSA that are involved in long-term follow-up, to start looking at what was being collected from a data perspective, and whether or not we could define some common data elements or sort of a common data set. And we felt that, after that meeting, that was probably too ambitious, and it was also putting the cart before the horse. So, we took a step back and said, "Oh, what we really need to be doing is what -- defining what those overarching questions are." Sort of, what are the quality measure there, in terms of trying to understand and monitor long-term follow-up? So, we have spent a lot of time over the last -- actually, since January -- putting together a small group who actually has come up with a matrix that looks

at the -- sort of, the major questions that need to be addressed, and using the framework of the Kemper article, in terms of the major components of long-term follow-up; namely, the -- excuse me -- care coordination, evidence-based treatment, continuous quality improvement, sort of, ongoing monitoring and surveillance aspect, and then the research -- or the new -- the clinical, as well as the clinical trial research of the new knowledge discovery. Obviously, this is all a continuous process. And then we framed that within the context of the different sectors. And yesterday we had a very lively meeting, where we basically took each of those -- sort of, that draft document, and tried to refine it by that different sector. So, I think we've gotten to a point where there was consensus, sort of, across the sectors, in terms of what the major questions were. I think we need to do a little bit more work on that, which we hope we will do, in the context of, sort of, our ongoing calls. And Chris Kus has agreed to, sort of, try to shepherd that forward. So, I do feel like we

are making some very concrete progress. As you all know, our -- another agenda item for our committee has been the whole issue of medical food and the issue of coverage for -- insurance coverage for medical foods. And Dr. Howell gave a brief summary of the updates on the letter that the subcommittee had developed, and the advisory committee had adopted, and went forward to the Secretary. But, in that context, we were -- also had been doing a survey, in three of the regional centers, trying to get a better sense of this problem at the local level. And Mary Kay Kenney, from HRSA, did a very nice job -- I don't know if she's here -- sort of giving us a preliminary overview of the analysis from that data. We're still collecting additional information, but the hope was that we'd actually have something that we could present back to the full committee again at our next meeting. And then the last item I have here -- in our discussions yesterday, as well as this morning -- again, I thought we had some very good discussions -- some of the short-term follow-up issues sort of came

up, and some of -- I should say, the -- some of the challenges with short-term follow-up came up. And I guess it became clear to a number of us that the advisory committee could be very instrumental in perhaps providing some policy guidance around these short-term issues -- or, recommendations. And one of them that we had discussed was the -- perhaps it would help short-term follow-up, in terms of a data reporting perspective, if newborn screening conditions were a reportable condition at a State level. That might help facilitate the reporting and collection of that information, and the -- really, the key components that are captured under short-term follow-up. So that's -- that was one issue that we talked about. The other issue was the fact that, many States, the linkage with vital records doesn't happen on a routine or real-time basis, and the fact that children, you know, are -- may, in fact, be lost through that process, and that that just seems like a little bit of a no-brainer, but, obviously, to facilitate that from happening at a State level is very challenging. So again, what could our -- us -- this

advisory committee do to help facilitate that happening in a ongoing and, you know, most advantageously, a real-time basis? We thought that that might be something that the subcommittee could give some thought to. So, we did get a volunteer. I had asked for a volunteer to help shepherd that -- these issues along. And there may be other, sort of, very tangible activities or issues that the advisory committee could really help, sort of, take on or move and address. So we do have a volunteer there, and I'm delighted with that. So, that's the update.

DR. HOWELL: Any questions of Coleen about her committee's work? Thank you very much, Coleen. We'll expect -- so you have -- you're going to have a couple of very specific reports for the committee in January.

DR. BOYLE: Yes.

DR. HOWELL: So we'll look -- we'll look forward to seeing those, and so forth. We're now going to have an update from Ms.

Christine Brown on the draft letter -- legislation on medical foods that's currently being sponsored by Senator John Kerry. I mentioned that briefly this morning. I would like to welcome Ms. Brown, who is executive director of the National PKU Alliance. This alliance is a national nonprofit organization that works to improve the lives of individuals and families associated with phenylketonuria through research, support, education, and advocacy, while working toward a cure. Ms. Brown has an extensive career in coalition-building, fundraising, advocacy, and she is, importantly, the mother of two children with phenylketonuria. Ms. Brown?

MS. BROWN: Thank you very much, and thank you for the opportunity to give an update to the committee. I just have a few slides to share with you as I give you an update on our advocacy efforts. The National PKU Alliance was actually formed last year, officially, by parents, grandparents, and adults living with PKU across the country, and our mission is to improve the lives of individuals and

families with PKU. I'm doing this by raising money for research, offering support to families, providing education on the disease, as well as advocacy, while ultimately seeking a cure. We are actually a coalition of State and regional PKU organizations, so each of the organizations that you see above, there, has a seat on our board of directors. Right now, we -- to be a member organization, you have to have your 501(c) (3) nonprofit status from the government; and so, we also have some other organizations that are not listed here, that, once they have that status, they will be members, as well. So, if I put together all of our member organizations and those that are waiting for their status, we actually currently cover 38 of the 50 States. This past summer, with everything happening very quickly on healthcare reform -- actually, this past spring -- we made a decision to actually send our advocacy chair, Kelly McDonald out of Texas, to Capitol Hill for the summer. And we started this out by looking at -- as healthcare reform discussions were

happening, we wanted to make sure that inborn errors of metabolism were not left out of the discussions, you know, during this time in Congress as things were moving rapidly forward. And so, Kelly spent 6 weeks here this summer. We gathered healthcare stories from around the country, from families dealing with PKU, in terms of the difficulty that they were having getting coverage for both medical food and also for the modified low protein foods. And in addition to that, we also used the letter that this subcommittee formed in April to HHS, and this was just an incredible way for us to provide education to Members of Congress. Over the summer, we actually had a chance -- we visited with all 100 Senate offices, and right now we're up to, I think, about 230 House of Representative offices, and all of them have received copies of your three-page letter. And it's just been a wonderful way for us to provide some legitimacy to our work, and to really be able to use this as a document that very succinctly shows, you know, what the problem is, and then also your

recommendation for what the solution is. As Dr. Howell has stated, Senator John Kerry announced, actually earlier this month, that he agreed to draft legislation to federally mandate insurance companies to cover medical foods and modified low protein foods for PKU as well as 29 other inborn errors of metabolism. And we are so pleased that -- Dr. Howell, that you're working with his office, as well as others, in the drafting of that legislation. One of the things that we've been doing is, we've been embarking on some advocacy campaigns connecting PKU families with their Senators and with their Representatives. And just to give you an example, last week we had more than 900 e-mails sent out to Members of Congress from parents, from grandparents, from adults, from family members, from clinicians, et cetera, about the importance of covering the medical foods. We are also embarking on a coordinating campaign of phone calls, e-mails, in-district meetings, and also -- excuse me -- letters to the editor that will be appearing, as well, as we move this campaign

forward; also, working in partnership, obviously, with other rare-disease organizations and other IEMs. And one of the things that we also are currently looking for are, if any of you, as practitioners, have specific cases that you could share with us on denials that have happened with your patients, either in Medicaid or Medicare, for medical foods. One of the other things that we've been working on is some separate meetings that we've had with CMS to show specific examples of where there's been denials in coverage. So, I would really like to thank you. These are actually my two children with PKU. My first is actually, you know, drinking his formula on the beach this summer, and the other one -- I don't have a picture of Connor drinking his formula. But, your letter has really made just a huge difference to PKU families across the country. You know, it's been just absolutely incredible for us to be able to use that letter as one of our talking points; for families to also hand that letter over to their Senator or to their Representative in in-district

meetings that they've had. And again, I really think that it's given our cause, as a patient advocacy organization and as a mother, real legitimacy, in terms of that this is an issue and it is a serious problem. I mean, I was on the Hill yesterday, and I brought with -- my can of Phenex-2, I brought my medical letter, and I brought pictures of my kids, and that's how I talk about my story with my own Senators and with my own congressional representative. And, you know, I do realize that we have a fight ahead, that this is just the beginning. And that, you know, working together, you know, in a coalition, that's what we really need to do to advance the cause for all children and adults with IEMs. And lastly, you know, I think the National PKU Alliance -- we're just seeing so many things happen. There's just been an explosion, we think, in research, in new treatment options, things coming down the pike, this opportunity with the legislation. And I think there's a real feeling among the PKU community that this is -- very exciting time, it's a very -- you know, time of innovation that this community has not

seen for a very long time. And we really, I think, have the energy and the passion and the knowledge to really change the history of PKU as we know it. So, thank you, again, for this letter. It's really just -- it's helped us so much in our work.

DR. HOWELL: Thank you very much. Are there any questions of Ms. Brown? Jena?

DR. MONACO: Yes. As a parent, I truly value those efforts. I wanted to know, does the legislation that's being drafted address the issue of self-insured companies not having to follow mandates like this?

MS. BROWN: We hope so. Again, we haven't seen any of the draft wording yet for the legislation. I do know that we're not expected to see that for another 3 weeks, because Senator Kerry's office is dealing with other healthcare reform issues. You know, I do know that was a large part of the letter that you sent, and obviously that's what we want. But, you know, once we have that information, have that draft legislation, we'll be sharing it, you know, among the

rare-disease and IEM community.

DR. HOWELL: The document that I have seen from his office is an outline, at this point, that they're using to draft the document. And the outline contains most of the -- well, I think, all of the things that were on our letter, and some other things. And so, we would anticipate that that will happen. And so forth. I think that, obviously, the committee has worked with this a lot, and thought about it, and I think we appreciate, tremendously, your efforts, because I think that the Secretary of HHS cannot, obviously, enact legislation. And so, I think, to accomplish some of the things that we wanted to see happen will have to be a legislative issue, I think. And so, I think that that's wonderful, and we appreciate your efforts on behalf of the committee, and I think the committee is very appreciative of your kind comments for their work. Any other comments?

[No response.]

DR. HOWELL: Thank you very much. And we'll,

obviously, keep the folks posted, and so forth, as we move forward.
It is lunchtime, and we have a relatively short lunch, because we're going to start off at 1:15 with a presentation from the Office of the National Coordinator of Health Information Technology. So, we'll need to eat briskly and be back promptly so that we can have that presentation. So, thank you very much.

[Lunch recess.]

DR. HOWELL: We need to resume, to stay on schedule. And I want to remind you, again, to remove your BlackBerrys. I've never understood the technicality, but, when they get near the microphone, they cause grief. Our agenda, that you have, indicates that we'll hear from Dr. Charles Friedman, who is deputy national coordinator of Health Information Technology in the Office of the Secretary for Health and Human Services. Unfortunately, Dr. Friedman is unable to join us today, but we're very pleased to have in his safe --

in his place, his colleague Ginger Price. Ms. Price is the lead for the Nationwide Health Information Network project in the Department of Health and Human Services, the Office of the National Coordinator for Health Information Technology. Since August in 2008, the Health -- the National Health Information Network has moved from a trial implementation phase, showcasing interoperability demonstrations in forums to a limited production pilot phase, where Federal and private sector --

[Announcement over the public address system.]

DR. HOWELL: Well, that's very helpful. [Laughter.]

DR. HOWELL: And so, Federal and private-sector partnerships are securely sending health information across the network. So, let me welcome Ginger Price, who's the deputy director of the Office of the National Coordinator for Health Information Technology. Ms. Price. And these microphones are quite curious, in

that you have to keep your finger on the little button all the time. It keeps your finger quite busy.

DR. PRICE: Isn't that interesting. Isn't technology wonderful? Thank you very much. On behalf of the Office of the National Coordinator, I bring you greetings. I'm not 100-percent sure; should I be working a presentation from this? Okay. Please forgive me, because it's not appearing on the Desktop.

[Inaudible]

DR. PRICE: No, they're not. So let me just find it.

DR. HOWELL: I wonder if we could bring Ms. Price a handheld microphone, because I think it would be far easier to use than to deal with your weary finger.

[Pause.]

DR. PRICE: Thank you very much. Today I'm going to talk with you about a few things, some of which I know very well, and some of which I know less well. But, I will attempt to walk

you through some of the overview of the ARRA activities that are going on in ONC that you will be interested in and, hopefully, leave you with some information where you can go for regular updates and to find out more. If you have questions that I am not able to answer, please ask them anyway. I'll be glad to take them back and refer them to the program. After we discuss meaningful use and State Grant Program, I will move on the Nationwide Health Information Network and be able to give you an overview and take your questions on that. So, as most of you know, I'm sure, the challenge for health IT right now is one of changing fundamentally how we collect, organize, and use health information within the healthcare environment, both within the EHR realm, and also within the health information exchange realm. And achieving that and using it in a meaningful way on a day-to-day basis, so that over time we will be able to affect outcomes and actually be using that data, not just to install the technology, but to use the technology, is very important.

In the summer of this year, the HIT policy committee provided final recommendations to the CMS regarding the definition of "meaningful use." And CMS is drafting that "meaningful use" Notice of Proposed Rulemaking, and these should be finalized in 2010. There are some implications for healthcare reform concerning this. As things go on, they will become more and more constrained. We'll learn more and more about "meaningful use" -- what happened -- get the feedback. So, for 2011 the "meaningful use" criteria is that we will capture and be able to share data. For 2013, we will advance care processes with decision support. And for 2015, the goal is to actually show and measure improved outcomes. Most of you have probably seen this. This is the June 16, 2009, Meaningful-Use Matrix. I will, at the end of this, give you -- well, it's not that much of an eye-chart. I thought that you might be interested in this; that we actually do have the discrete measures for some of these. These will be refined over time with feedback from the community. So, here's the timeline for the next 12

months. This is a suggested timeline, courtesy of the HIT Policy Committee, that in Q3 they will develop the process for updating the meaningful-use objectives and, hopefully, tag the 2011 measures relevant to specialties; and in the fourth quarter of this year, conduct informational hearings to inform the 2013 and 2015 criteria development. I think we have a calendar for this on the Web site. And if you go to www.healthit.hhs.gov, there are hotlinks on the right-hand side, and also down the left-hand navigation, places where you can go, and this information is constantly updated. In the first quarter of 2010, the 2013 and 2015 criteria will be updated; and in the second quarter, the -- we will work with the Standards Committee to ascertain the availability of those standards. And then, in the third quarter, we find the 2013 meaningful-use criteria, and, in the fourth quarter, assess the industry preparedness for meeting those 2011 and initial 2013 meaningful-use criteria. As you can see, this is a very ambitious and far-reaching agenda that the Health IT Policy Committee

has set out for themselves. The informational hearing on meaningful-use criteria for 2013-'15 will be held in October; and at that time; the gaps in meaningful-use, appropriate measures, will be discussed, also the criteria for specialists; so that the use of measures relevant to specialists, the participation in national registry, and the development of new measures will be discussed there, in that open hearing. And feedback and new ideas from provider organizations for 2013-2015 will also be sought at that time. As you can see, the -- they are addressing the entire spectrum of physician practices, from the spectrum of hospitals and safety net providers, as well. Some considerations concerning the phasing of "meaningful use" is that they want the -- to tie this to enabling the health reform. The focus on the outcomes, not the software, although, in adoption, the software is a very important part of this, because it needs to be useable or no one will achieve meaningful use.

The feasibility -- we want to balance the urgency of health reform with the time needed to implement HIT, so that we do get a good adoption rate. The Committee itself is very sensitive to the under-resourced practices. So, small practices, community health centers in rural settings, are very important considerations in their deliberations. But also, health IT is essential to achieving health reform in all settings. So, experience supports the finding that "meaningful use" isn't easy and it requires ongoing help to implement and maximize the use. And HITECH recognized that, as well. So, there are two important grant programs, totally approximating $1.2 billion of ONC's $2 billion dollars in discretionary funds to assist and support the ongoing implementation of health IT that supports "meaningful use." Those programs are the State Health Information Exchange Cooperative Agreement Program and also the Health Information Technology Extension Program. I will not discuss the Health Information Technology Extension Program today, but that is -- but

that is a program whereby developing at the regional levels, there will be assistance to help people achieve "meaningful use." So, in order to keep up to date, there is a health IT recovery portion, in the left-hand navigation on healthit.hhs.gov. And you can keep up to date with everything that's happening at that place. So, a little bit about the State Health Information Exchange Cooperative Agreement Program. We have put out funding opportunities into the community. They are focused at State-designated entities who will form either collaborations or the State will identify someone to receive these funds for the State, and to develop and advance the mechanisms for sharing across the health system that are implied and required by those funding opportunities. So, there's about $564 million that will be awarded to support efforts. And we want to achieve widespread and sustainable health information exchange within and among States through the meaningful use of electronic health records. So, this is a -- this is a very interesting

combination of things, where health information exchange and health electronic records are important, together. The Centers for Medicare and Medicaid Services will issue proposed criteria for "meaningful use" by the end of 2009, and this will guide these efforts. So, to help potential applicants, they put out a grants primer. So, all of the funding opportunities and the links to government wide Web sites that talk about this, and how it will be achieved, are out there, hung off of this Web site. And ONC is also initiating a series of section 3013 State Cooperative Agreements Program technical assistance calls. I think they've had two, so far. And these provide resources and answer questions for those interested in responding to this funding opportunity. During that first call, the NHIN was one of the subjects that was most requested for people to hear about, to find out: What is it, how does it figure in to these opportunities, and where do I find out more information about it and see if this is something that

I want to propose in my proposal? So, the NHIN is basically a network-of-networks concept, where the -- what were the old geographically-oriented RHIOs and other health information organizations can exchange information with integrated delivery networks, with community health centers, with registries and repositories, Federal agencies, whoever would want to abide by those standards and conventions and exchange information over the NHIN. So, the Internet -- everybody has looked at the Internet, since its advent, as a great way to be able to share information, and they wanted to share health information. However, that presented two critical challenges; the Internet is very open, and we needed to be sure that patient privacy, security, and trust could be established and maintained, and also that information exchange could be interoperable between systems, so that information generated in one system could be transmitted across a nationwide network, and it would mean the same thing on the other side of the exchange. The NHIN has been designed to

address those challenges. So, in order to assure that we can have this privacy, security, and trust, there are several elements to this. One is a very light, physical infrastructure, so that we can have a registry that knows all of the NHIN participants, and it knows that they are members in good standing, and it also has the ability to remove those from the registry, in case there is some kind of a breach or something happens and they are no longer considered a member in good standing. This will be the purview of a governance entity of some sort who will be able to adjudge whether they are -- have the qualifications to become a member, and also when they need to be -- we hope that that never happens, but -- removed from that network. We also have Web services built, to be sure that patient preferences can be adhered to. We have a consumer preferences service, where the Health Information Exchange Organization asks that consumer how they would like to have their information handled, whether they would like to have it exchanged over the NHIN or whether, at this time, they would prefer not

to. Those are honored at the point of origin and also can be looked at the other side. There are audit logs which do take this into account and where this can be audited. We also need assurance that transmission across the Internet is secure. And we do that in several different ways. The NHIN uses a digital certificate and also an encryption algorithm to be sure that all information exchanged over the Internet, where it goes from one side to the other side, is totally encrypted and safe. In terms of interoperability, the NHIN includes a set of technical protocols, industry standards, and very specific implementation guides that enable those NHIN participants to read and understand the health information that's exchanged, with minimal or no point-to-point coordination. In order to do this, we take the interoperability standards that HITSP puts out, and then we constrain them further to be sure that both parties on each side can only interpret the information one way. We put those out, and then they can be instantiated in "gateways," we call it, that go

between the integrated delivery network, for instance, and the RHIO, and can be understood on either side of that. So, basically, the NHIN provides common legal framework for information sharing. In order to come on to the network, people will be required to sign a data-use and reciprocal-support agreement that governs how they will react within this exchange. There can be other data-use agreements that will be in place -- say, at the community health center level, at the integrated delivery network level -- but does not govern the exchange across this network. Also, the common infrastructure necessary for network security and connectivity, again, in several ways that we accomplish this, both within the Web services themselves, within the encryption, and also by issuing a digital certificate that each holder must own before it can exchange information across the network. And, we have the specifications, which ensure that the content can be understood on both sides of this, and also that the content -- the transport and the acknowledgement can be done.

This is basically how the NHIN is configured. The NHIN itself is the little starfish-looking thing between all of the gateways. The gateways are the instantiation of the specifications that ensure that everybody, no matter what they look like on the back end of this -- they can have their own architectures -- but this very light, common architecture and physical network ensures that we can understand, amongst all of this. Now, we see here that the NHIN has always considered that we will have other entities on here. Today, mostly we have people exchanging a C32 document, which is a summary of care -- has information in it, and this enables both people on each side to have a certain level of information. But, as you can see, there are other networks that we will be wanting to bring on. I kind of call these "entity groups." So, when PHRs would come on, we would need to look at the NHIN and relook at the services to see, Do they need something different? How does this need to be changed? Does this change the trust fabric? What do we have to do so that they can

come on and become a part of the overall network? So, some of the principles for the NHIN: Needs to be highly distributed, so patient information is retained at the local health information exchange level or in the local integrated delivery network or, in the case of VA or DOD, within their local systems. And there's the principle of local autonomy, where each of the health information organizations -- and that would be, for instance, VA, DOD, Indian Health Service, Kaiser Permanente -- they make their own determinations with release to patient information. Once they have done that, and they put it in, we are the secure transport which gets it from one place to the other, and in a form that can be understood on the other side. We focus only on interorganizational health exchange at this point. At the beginning, the NHIN was really looking to see, Can we find a standard that we can drive down into the lowest level of health information exchange? And, that really was not possible at that time. We may get to that someday, where these standards can be driven down at -- to a

lower level. But, really we started out to focus on interorganizational health exchange. Can VA exchange with DOD? Not going down into the inter-DOD level or the inter-VA level. Using the public Internet: We wanted to go as light as we could. We did not want to build, you know, spaghetti of -- all across the country, where people had a proprietary network. We wanted to reuse what was already out there, to make it cheap, light, and very flexible. So, we started out with a set of protocols and standards, which are basically from Web services, which -- and content profiles -- which we can ride on the Internet, but create, basically, a virtual private network on top of that Internet, so that we can be private, secure, but still run on, basically, the public infrastructure. The NHIN -- we wanted it to be platform-neutral. So, it's adopted a stack of Web services that can be implemented using many operating systems and programming languages. Some of you may know, we started off with -- coming up with prototype architectures. There were four of them. Then we

refined that by going into trial implementations. And we had nine contractors who really implemented this nine different ways. The Federal Health Architecture Group worked with the Feds to come up with one gateway which could be reused by all of the Federal agencies. And that is called "CONNECT," and that has been released into open source and is being used today, not only by the Federal agencies, but also by some private entities. The NHIN Cooperative is a group of private health information organizations, State-level health information organizations, provider organizations and IDNs, and Federal entities. And all of these have come together, some through contract, some through grant, some through understandings with the Federal Government, where we had something we called the "Federal Consortium," and they all came together to develop the trust fabric, the organizational understandings of how the Federal Government could exchange health information securely and -- you know, all of the rules of engagements between the private and the public health information organizations.

Where we are now: We have come out of the trial implementations, which were highly successful and, really, a proof of concept for this, and immediately were challenged by organizations that wanted to move into what we're calling "limited production pilots." MedVirginia and Social Security Administration wanted to go into limited production, and they did that in February of 2009. The trial implementations were over in December of 2008. So, you can see, this is not a very large amount of time for someone to go into production. Other organizations that we are working with now in implementation phases are planning to demonstrate health information exchange in the limited production environment, including Kaiser Permanente, The Department of Veterans Affairs, and they plan to go into a live production mode to exchange information in December. The Department of Defense plans on joining in January. The Centers for Disease Control and Prevention are actively working on a demonstration, and Social Security has released an RFP on the street which

they will be starting to award in January. And there are $24 million of ARRA dollars that are going into an NHIN-based exchange of information, where Social Security will get information from these organizations to make eligibility determinations. They have automated that. It is -- it is very, very impressive what they have done. They have cut the time down from some 73 days, waiting for disability determination, to in the neighborhood of 30. And we hope to see that really pick up, this next year, both in volume and also being able to shave even some time off of that. So, the next phase, we will start the formal process of onboarding pilot partners, according to the rules of engagement, into this trusted community. We will have a setup where will perform conformance testing and interoperability testing. "Conformance," being conformance to the NHIN specifications; and "interoperability," meaning, "Now that I'm conformant, can I actually get information from me to you, whether it's across the street or across the country?" We will -- upon completion of testing and also the vetting of the character and qualifications of

the organization, we will issue them a digital certificate and add them into the NHIN service registry. The service registry is the -- is the -- contains all of the organizations which, not only have past conformance testing and interoperability testing, but are ready to exchange information with each other. The specifications can be used by organizations who do not wish to join the NHIN. It is entirely possible to do that. The benefits that the stakeholders are telling us will accrue from actually joining the NHIN is, they will not have to do a point-to-point data-use agreement, which will really make it very, very much more scalable and able to share with a wider variety of people, and in a less stringent manner. So, I thought you all might be interested in a few of the things that are coming up here. As I say, in our first foray into this, we working from the AHIC use cases and instantiating those in the NHIN. Now that we have a whole new vista ahead of us with "meaningful use," and a whole 'nother group of people who want to come to the table, new features are being

asked for, and a lot of these have to do with public health, and these have been put in. We have business cases for them, we have sponsors for them, and we are in the process of evaluating these and seeing into which release of the NHIN specifications we can include them. So, we are responding to these requests, and we will take them to the NHIN technical board, who will evaluate and tell us how to go on this. But, I think that this is incredibly wonderful, to see us moving from a trial implementation phase of doing just predetermined work to seeing people see the utility of this and telling us what they need to do to be able to exchange information. So, going forward, we're going to showcase demonstrations and network operational capabilities in early 2010. I'm looking for sometime in January for us to really be able to start operating these in greater measure. So, if you're interested about more on the NHIN, please go healthit.hhs.gov and click on the Nationwide Health Information Network or join the

LISTSERV. And, if there are any questions, NHIN@hhs.gov, and we will get back to you.

DR. HOWELL: Thank you very much, Ms. Price. I have one question, and that is -- in response to the public request for comments about the documents, this group -- our committee -- had sent a note to you about two issues. One is that there was no newborn screening measures included in any of the discussion, and nor were there any specific pediatric measures. And do you -- could you comment about those, or where those might be and whether anything is moving in that area?

DR. PRICE: Yes, but, first of all, may I ask you a question? Because, I did not know that there was something submitted -- so, where would I be looking for this submission?

DR. HOWELL: I'll ask Dr. Puryear, who is a submitter.

DR. PRICE: Well, I'll -- let me get with you after this. No, there are no requests underway, and we can certainly provide you with a way to do that.

DR. PURYEAR: This was a previous request for

comment, probably a couple of months ago.

DR. PRICE: And the request for comment was from?

DR. PURYEAR: You guys.

DR. PRICE: The NHIN?

DR. PURYEAR: Yes.

DR. PRICE: Really?

DR. PURYEAR: On the "meaningful use."

DR. PRICE: Oh. Got it. Here's what I will do. Because the NHIN -- it was not specifically on the Meaningful-Use Committee, coming up with that -- I am taking a note and I will go back and check with them.

DR. PURYEAR: I can certainly submit the committee's comments to you, also.

DR. PRICE: That would be great. Thank you.

DR. HOWELL: Good.

DR PURYEAR: Thank you.

DR. HOWELL: Excellent. Thank you very much.

DR. PRICE: Things are moving fast. It's hard to coordinate, sometimes.

DR. HOWELL: Excellent. The -- are there questions or comments from

anyone on the Committee or anybody in the audience who would have a question of Ms. Price?

VOICE: [Inaudible.]

DR. HOWELL: Can you come -- Lisa, can you come up to a microphone, since this is being recorded?

DR. FEUCHTBAUM: Lisa Feuchtbaum, with the California Department of Public Health, Genetics Disease Screening Program. It seems to me a natural forum for unfolding some of these linkages, if you will -- because that's really what they are -- would be within State -- within State databases run -- for example, linking vital statistic records with -- in California, it's Medi-Cal or Medicaid data files or -- we have something called OSHPD, which is an outpatient services database for hospitals. And within States, as State employees, it would be great if we can just get access. It seems so natural that we should be able to access through, you know, the digital certificate and with all the agreements -- get access to data within -- get -- we should be able to get access to data within our own Department of Health Services. And so, that would be

applicable for any State. I mean, I'm thinking from the California perspective. But, currently you have to jump through lots of hoops to get access to data that you would think you naturally should have access to, being all part of the same Department of Health Services. As well, there's disability data through different programs that serve disabled; there's education databases. There's just all these great databases, and it seems that there should be a way to facilitate the linkage for people who have legitimate uses of that data. Thank you.

DR. HOWELL: Is that possible, to link data within a given department? Is there any reason you -- that your group couldn't do that?

DR. PRICE: Yeah. [Laughter.]

DR. PRICE: Let me tell you what some of the challenges will be with doing that. Now -- and I'm going to take this back, and I think that we should sit down and discuss -- you know, as the State grants

happen. But, some of the challenges for the NHIN have been: If you're going to make something nationwide, there are differing -- and you get to the edge of a certain area -- there are different rules, for how you deal with data and how you request data and how you handle data, that are very State-specific. So, there is a lot of sharing and policy work that needs to be done. This is -- I am very proud of the NHIN team that -- for working 2 years to get the data-use and reciprocal-support agreement, that really normalizes -- between States -- so that we're able to just share that summary record. So, I can see this in my mind, and I think that it is something that we should bring up and talk about, but I would need to do a lot more analysis of what the different databases are. And, you know, hopefully, over time, it definitely should be true, if we can work out the policy and issues and get the standards in place.

DR. HOWELL: Thank you very much. It just seems like an extremely important and very ambitious

project that you've got. Are there further questions or comments for Ms. Price?

[No response.]

DR. HOWELL: Thank you very much -- I don't see any hands, and so forth, and --

DR. PRICE: Thank you.

DR. HOWELL: -- for coming and joining --

VOICE: [Inaudible]

DR. HOWELL: -- joining us today. Is there someone on the phone?

VOICE: Hello?

DR. HOWELL: Hello?

VOICE: Ned?

DR. HOWELL: Ned, is that you?

[No response.]

DR. HOWELL: Well, it's a voice in the dark. [Laughter.]

DR. HOWELL: The -- we'll move on to our next presentation.

VOICE: Hello?

VOICE: Hello, Ned?

DR. CALONGE: Yeah, I'm on the line; but I was muted, so that wasn't me.

VOICE: Oh.

DR. HOWELL: Okay. All right. You were accused falsely, but we're delighted you're there, and so forth. [Laughter.]

DR. HOWELL: The -- we'll move on to our next session, which is --

VOICE: So, somebody should be muted that's not.

DR. HOWELL: Someone is -- we're going ahead with Dr. Zuckerman's presentation. And he's going to tell us about the progress of implementing the newborn screening use case and the companion resource guide since he last presented to the Committee in February. Dr. Zuckerman has been a member of the Commission for Certification of Healthcare Information Technology, Interoperability Work Group since its creation, and is co-chair of the new Interoperability Workgroup this year. And he is working aggressively and vigorously in this area and he's going to tell us about what's --

where he is with his various projects, today. Alan?

DR. ZUCKERMAN: Okay. Thank you. And again, I'm speaking to you primarily from my role -- I think you need to switch the presentation -- yes -- as a contractor with -- I'm sorry -- as a role as a contractor with the Office of the National Coordinator and Personalized Health Group Initiative. This is a very good bridge from the last presentation, because Ms. Price mentioned this legacy of use cases that were approved by the AHIC and which are now going forward as this last phase of the initial development of standards for the Nationwide Health Information Network. During this transition, after the passage of the Recovery Act, the HITECH -- which contained the HITECH Act, there was an interruption of work at HITSP to translate prior work into the new framework. And work has resumed now on the newborn screening use case, which is now on track to be completed in January of 2010, and which will be put forward as one of those standards to be approved by the Health Information Technology Standards Committee. And also, measures

will need to be developed to assess meaningful use of EHR. At the same time, the Association of Public Health Laboratories, Public Health Informatics Institute, completed their work on an implementation guide for newborn screening, that's now been approved. It's important to remember that the Health Information Standards Panel is not a new standards development organization, but they harmonize and integrate and give guidance on the use of existing standards. So, having base standards from other organizations like HL7 and the work that APHL did, lays the foundation for their recommendations. Also, integrating the Healthcare Enterprise that runs the Connectathon at HIMSS, has also issued a white paper on newborn screening. And I just learned, at the lunch break, that they're moving forward on programs to get vendors to implement projects in newborn screening, newborn discharge, and in the capture of hearing-screening results. I'll be telling you a little bit about the Requirements Design Standards Selection document that

was just issued this past Monday, which is why it's not in your briefing book, but is easily downloaded from the HITSP.org Web site, that I hope you'll comment on. And the next phase in the development of the use case will be a process called "inspection testing" of the draft interoperability specification. I think it's also important to return to the presentation that Clem McDonald gave at your last meeting about the development of coding and terminology, and to realize that the deliberations of the HIT Policy Committee are now creating an anticipated rapid movement towards the use of SNOMED and LOINC coding, which will be of particular significance for newborn screening. And, as you'll be hearing from representative from NLM, that Web site went live last week, and I hope that all of you will be working with that. I'm also going to give you some information about a project we've done to take a look at the data that's captured on the filter paper used to collect the newborn screening specimen, which forms the lab test ordering information that's part of the use case, and raise some considerations of activities which you can

be engaged in between now and your next meeting. The RDSS document, which, again, is available on the Web site, essentially is the first milestone in bringing the use case into reality, and it provides specific solutions for each aspect of the original use case. It doesn't allow redefining the scope of the use case that was approved last December, but for every event, every action for those events, a solution is proposed. And among those events are things like obtaining consent for newborn screening, potentially obtaining consent for retention of residual dried blood spots, the ordering of the tests in various reporting back to clinicians, as well as to public health. So, in that document are decisions about how to move forward on implementing the use case -- selection of particular standards, selection of coding. The RDSS will be open for public comment through October 16, so we don't have a great deal of time, but there are opportunities to comment on the standards and on the coding methods that have been selected. And most of the RDSS cross-references other existing work and documents. So, rather than say the

newborn screening is a unique and different entity, they refer to reuse of material from immunizations from maternal and child health use cases, reuse of material on the ordering and reporting of other laboratory tests that will need to be modified and extended for newborn screening. So, it's important that we look at the RDSS to see that the key unique features of newborn screening have been identified. And among the things to look at is: What does the ordering process for newborn screening involve? What data is captured at the time a newborn screening specimen is obtained? Because that's going to lay the foundation for a lot of the long-term follow-up work which will follow. There's also been a lot of interest in defining how effective we've been at combining hearing screening with other forms of newborn screening, and whether there needs to be provision for separate documents and information exchanges to capture the ordering and reporting of hearing screening, or whether this can occur in conjunction with metabolic screening, as it does in about a third of the States.

And it's also important to take a look at the requirements for newborn lab reports. And as we've discussed at previous meetings, newborn screening is unusual compared to other lab tests, in that one both reports what the laboratory actually measures, but you're also reporting a great deal of genetic test interpretation against target disorders. And different States may interpret result values differently. And there will be an effort in the final interoperability specification to accommodate State-to-State variability and to adequately report both the interpretation of the condition screened for, as well as the raw data that those interpretations are based on, with opportunities to suppress excessive data that will be a problem for clinicians. Of even greater importance in the RDSS, is the actual draft interoperability specification itself, which is now on track to be completed by October 30. So, there are only a few weeks remaining to come up with this document. But, inspection testing and public comments will continue through December 4th. And it's very important to understand what

"inspection testing" means. This doesn't mean actually implementing the use case; it means sitting down on paper, and looking at what is going in individual newborn screening programs, and seeing if the mechanisms and codes and appropriate data fields are there to carry and transmit that data, and to accommodate variabilities in methods and procedures that are currently in use in the States, but also, to think forward over the next 5 or 10 years, new approaches to newborn screening that may require a new form of information exchanges. And one of the fallout from the HITECH Act is that what it comes out in these specifications will eventually carry the force of regulation, so that the standards that are selected now aren't going to be totally voluntary, because, not only will there be incentives for hospitals and physicians and their offices to adopt certified EHRs, that are using these, but there will also be other restrictions on the way States implement systems and the way that Federal funds, such as grant funds, can be used. So, it's really important for people to inspect this

interoperability specification, see that it meets your needs and that it wouldn't create barriers in the future if this moves forward to come under the various regulations. It will be revised every 2 years, but the first round is proposed to go forward as an interim final resolution on standards in December. And again, as I said, much of this will make reuse of material from other use cases, such as existing EHR lab use cases, and work that's been done on the personalized health care use case for reporting of other types of genetic testing. And one of the unknowns that has been resolved in the last few months is the selection of SNOMED and LOINC and the additional incentives that are going to go with that. So, there will be a migration from ICD-9-CM to SNOMED-coded problem lists, although that will take some time, and the use of ICD-10 for billing and certain other statistical reporting will continue in parallel. But, there's now no longer a question that by 2015 the problem lists and EHRs, both in the hospital and ambulatory setting, are going to use

SNOMED codes to describe problems. And this makes the work that you'll hear about at the National Library of Medicine all the more important -- all the more important for this Advisory Committee to look closely at that, because we can no longer complain about lumping, or the inability to locate cases because it's not being coded on documents. It's going to take time to implement, and there will be a period of transition. But, eventually SNOMED-coded problem lists will be in use. In the same way, LOINC codes are going to be used to report the laboratory measures. And a special set of LOINC codes have been developed to report genetic test interpretation as well as the identification of alleles and even the recording of gene sequences. And again, it's important that we make sure that these new documents are going correctly. HL7 balloted a special implementation guide for genetic testing, reporting on their lab messages back last May, and this creates a foundation for how newborn screening results of the present and the future will be accommodated within the current framework of electronic

lab reporting. The people at the National Library of Medicine are counting on you to be their clinical experts, to make requests from them, and to make corrections to the data which will be referenced in these HITSP documents. And the final area I want to turn to is that of the test order data fields. With the help of Brad Therrell at the Newborn Screening and Genetics Resource Center, we're able to take a look at filter paper forms from 50 States and D.C., and to look at the kinds of information which States appear to be capturing. Now, this still needs to be verified further, but cluster analysis reveals three categories of fields, and we'll take look at some of those. The goal is not to get every State to capture the same data, but to make sure that the standards which are going to be promulgated can accommodate the variability of what States actually do. To take a look at the graphs I'm going to show you, you need to appreciate a method we've used for this that you may want to apply to other data,

where on the X-axis we're plotting out the number of States using a particular data point, but on the Y-axis we plot out the number of children to which this applies, by multiplying the number of States collecting the data by the number of newborns in that State. And these slides, which were developed by some of the staff at ONC from Deloitte, I think, present a very nice way of looking at data. In the upper-left corner, you see how there's a scatter plot of fields which are used, some in only a single State, some in nearly all of the States. We're now going to explode that top cluster of the data elements used in almost all the fields. And you see how some of the fields are used for large numbers of infants; some may be used in a large number of States, but relatively few infants; and some fields, such as birth date are not even universal, and that's because one of the States doesn't enter certain data directly on the filter paper, but has it in other data sources. But, when you take a look at the ordering of the dates -- and all these slides are in the briefing book -- you can see that there is a reasonable

clustering of information that's unusual compared to other laboratory tests, but essential for follow-up. So, there's a great deal of urgency in capturing transfusion data, capturing information about the mother, to facilitate follow-up, and efforts to resolve some of the name problems. When we look at the less frequently collected data, we see the diversity of information, that only a few States may capture the mother's age, that some States require Social Security numbers or Medicaid numbers. And by looking at this data, we're making an effort to be sure that all of the kinds of data that States are capturing for their own needs are going to be incorporated into the standards that are going to be put forward for adoption by the HIT Standards Panel. And, here again, we have a larger list of the variety of less frequently used fields. The infrequent fields, we want to still have general purpose fields into which a State could add any additional coded data element. This is an approach which we also may want to undertake with some of the data elements that are coming out of the Long-Term Follow-Up Committee.

And, in closing, I just want to raise a few points of decision for the Advisory Committee today. As I said, public comments on the requirements design will be open through October 16th, and I hope as many of you as possible will take a look at what has been included, and particularly some of the areas such as consents and other things we might not normally think of in electronic health exchange. The inspection testing phase will be extremely important to get people to actually sit down on paper and see, "Can I do what I'm doing today on paper using the electronic standards that are proposed?" Among the requests that have come out from HITSP is a need to number all the laboratories. And again, many of the newborn screening laboratories do not have CLIA numbers; and so, we need some advice on whether we need to create a whole new newborn screening laboratory number, or if there are certification -- other laboratory identifiers that can fill this role, so that standards that were developed for general labs in hospitals and other settings can be applied to

newborn screening. By the time of your next meeting, on January 21st, we should have a final interoperability specification, and I hope that you will put taking action on that on your agenda at your next meeting. And following my presentation, we're going to move on to hear from the staff at the National Library of Medicine about their newborn screening code site. And again, the Advisory Committee should participate in ongoing interaction with the National Library of Medicine to be sure that the codes in their site adequately meet your needs, because HITSP has chosen to use their site and their work by reference, rather than putting a fixed list of codes or tests into the specifications. So, as NLM revises its database every 6 months, the standards, in effect, will change. Thank you. And again, I'm particularly eager to get responses on some of these five points, here.

DR. HOWELL: Thank you, Alan. I wonder if members of the committee have any specific comments for Alan. Does the Committee want to respond to any of

the questions that he's posed here, or individually?

DR. BOYLE: I have a general comment -- and maybe, thought -- because it seems like there is a tremendous amount happening in this area, and I'm wondering if the Committee might want to consider a workgroup or subcommittee that takes a more deliberative review and interaction with all of the -- that's happening within the -- in regard to standards, electronic information. I mean, it's a little daunting to me, hearing all of these talks, to see whether or not -- and particularly since there is a use case in work for newborn screening, I think it would serve us well to be more engaged in this.

DR. RINALDO: I'm meditating about the third point. So, are you saying there are, in the U.S., State newborn screening laboratories who do not have a clear number?

DR. ZUCKERMAN: Many of them do. And some of them apparently don't. So, it's important that, as we come to final specifications, that that not be a requirement.

DR. RINALDO: Is Jelili here? Can he raise

his hand?

VOICE: [Inaudible.]

DR. RINALDO: Because that would be extremely worrisome to me.

DR. ZUCKERMAN: We just need to make sure this one of several areas which need to be reconciled in the standard, that when we borrow something from another use case, that we're able to still meet all of the requirements.

VOICE: Alan, can you talk a little bit about well coordinated this effort has been with the previous ONC in the Nationwide Health Information Network discussions around interoperability, as well? Are they closely linked? Are we -- can we be reassured of that?

DR. ZUCKERMAN: I think that you can be comfortable that everything that HITSP is doing is very closely linked to work that's been previously recognized, and that, rather than open a debate on which version of HL7 we should use for newborn screening lab report, decisions that were made in developing the NHIN are going to more forward. And these are going to apply to long-term follow-up, as well. There is a quality reporting document architecture that's been developed, that could be used to collect quality measures for newborn screening. There is now a laboratory ordering standard that is moving forward. Many other pieces of the problem are going to come forward. I think the other area which the Advisory Committee should think about are those request for measures under "meaningful use." And I see at least nine of the meaningful use criteria as being particularly relevant, such as capturing orders, incorporating lab test results into an EHR. But, it also deals with access to patient-specific educational resources, providing patients with timely access to their health information, providing patients with electronic copies of their information, and exchanging key clinical test results among providers. And so, I see these as being ripe for one of those specialty-specific measures, and that newborn screening could become a way in which practices and hospitals could show that they're making meaningful use of their HER. Because these capabilities are going to be built

into the products -- both commercial products and the recertification path for open source and in-house products that people will be using under our [inaudible].

DR. HOWELL: Can we have some comments about Coleen's suggestion of having a group work on this in some depth? Piero, do you have any comments about that? The -- could we have some suggestions of who might serve on that group other that you and Coleen? [Laughter.]

DR. RINALDO: Thank you for a reminder to keep my mouth shut. [Laughter.]

DR. HOWELL: The -- why don't we start with Coleen and Piero, and then add members as you see fit, and so forth. And Alan can certainly be an outside consultant to the group, and so forth. But, can you give a little thought to that, and come back and tell us what you're -- how you're going to manage this program? Okay? Outstanding, and

so forth. We're always pleased when you have a comment. But, you're obviously very, very interested in this activity, with your work in region four and so forth, so I think that would make -- and does anybody on the Committee have a key interest in joining this distinguished group?

[No response.]

DR. HOWELL: Well, they will probably enlist some additional help. Alan, thank you very much. Are there any other things that you would like us to comment on at the time -- but, we'll work through this new active, small committee.

VOICE: I think that you -- you just need to adjust your frame of reference, and not look for newborn screening as a discrete component of meaningful use, but look for the capabilities that can be measured and addressed through effective newborn screening. And so, I think that will be a key part of identifying how to fit the matrix, because the matrix that was agreed on last summer is intended to go forward through 2015, and the part that's lesser is how the specific measures will be attached. It's at the level of the measures that newborn screening will enter the matrix, not at the level of special capabilities that are unique to newborn screening.

DR. HOWELL: Thank you very much. We'll now move to a discussion of newborn screening codes and terminologies, and an approach to a standard report payload. And we're pleased to have Dr. Kin Wah Fung, who is a scientist at Lister Hill Center for Biomedical Communications at the National Library of Medicine. Dr. Fung's area of research is health data standards, medical terminologies, and their effective use in the clinical environment. And, today you're going to discuss with us NLM's work on standardizing newborn screening codes and terminology. Dr. Fung?

DR. FUNG: Hi. Good afternoon. My name is Kin Wah Fung, and I'm from the Lister Center of the National Library of Medicine. I work with Dr. McDonald on this project, and Clem would very much want to be here today, but due to

a previous engagement, he has to be somewhere else, and he does send his apologies. So, here's what I'm going to talk about today. I'm going to start with some goals of this project, and then I'll go straight into describing what we have done so far, in terms of standardization of the newborn screening data content, and also standardization of the messaging formats. And I'll also show you what our new Web site looks like. And then I'll finish by talking about some of the work that remains. So, all this work about standardizing is to promote and facilitate the use of electronic health data standards to record and transmit newborn screening test results. And the reason for doing this are because that you can have several benefits by transmitting data electronically. First of all, the reports can be transmitted much more quickly if they are done electronically; and secondly, when data is transmitted electronically, it is much easier to track the infants with positive test results and to make sure that they are properly followed up. And also,

standardizing the content of the newborn screening results will very much encourage and enable the use and comparison -- basically, the pooling of results from different laboratories and centers. And last, but not least, if we get enough data, it's very likely that this will give rise to some ideas to improve the newborn screening process in the future. For the test results to be able to be transmitted electronically in a standard form, two things have to happen. The first thing is that there should be standardized codes for the contents being transmitted; namely, the test names, the analytes, the conditions being screened and also other categorical answers. The second important component of this project is to standardize the messaging format, which is like a container to hold what is being transmitted. So, as much as possible, we would like to adhere to national and international coding standards when we standardize the content of the data being transmitted. And coding standards that we recommend to use, as mentioned by Dr. Zuckerman, are LOINC and

SNOMED CT, and ICD-9 and 10-CM are also the other codes that we would -- and -- use. And also, there are some additional codes for enzymes and OMIM. And I'll talk about these coding systems one by one, in case you may not be very familiar with what they are. So, LOINC stands for Logical Observation Identifiers Names and Codes. It was originally developed by the Regenstrief Institute in Indianapolis, which is where Clem used to work; and he's one of the founding -- one of the founders, actually, of the LOINC standard. And this effort is fully funded and supported by the National Library of Medicine. What LOINC does is, it provides a set of universal codes for identifying measurements. What I mean by "measurement" is -- well, one obvious example is, like, a laboratory test; it would be a measurement. LOINC also covers other measurements, as well, such as, maybe, an X-ray procedure, a chest X-ray, or MRI. There would be a LOINC code for that. And also, LOINC covers clinical measurements, as well. So, the idea of giving codes to these measurements is that this information can be

transmitted unambiguously in an electronic message, like in an HL7 message. And I'll talk about HL7 a little bit later on. The LOINC standard is widely used in both the U.S. and internationally. And LOINC is free to everybody for -- free for everybody to use. There's no cost involved, and there's just a very simple license. So, to prove that LOINC is used internationally, here are some examples of translation of LOINC concepts into other languages. Here's the translation of the name "glucose" into eight languages, including Portuguese, Estonian, French, German, Italian, Korean, and, even simplified Chinese. So, here is the LOINC site. If you're interested, you can go and take a look. And you can download everything from there. And LOINC also provides a program called RELMA, which is very useful. If individual labs wants to map the test codes to LOINC, This is a program that will help them to do so. Next, I'll talk about SNOMED CT a little bit. SNOMED stands for Systematized Nomenclature of Medicine Clinical Terms. SNOMED was originally developed by the

College of American Pathologists, maybe 40, 50 years ago. And the original coverage is only for veterinary medicine. And very shortly afterwards, it was expanded to cover human medicine, as well. So, in the year 2007, the ownership of SNOMED CT was transferred to an international organization called the IHTSDO, the International Health Terminologies Standards Development Organization. And now there are 12 members of this organization, which includes the U.S., Canada, U.K., Australia, Netherlands, Sweden, and Spain. And the number is still growing. So, SNOMED CT has rapidly become the emergent international clinical terminology standard. One thing to note about SNOMED CT is size; it's the most comprehensive clinical terminology that's available. It has over 300,000 concepts -- not only concepts; it also has a very rich network of relationships between these concepts. And these relationships are very useful if one is to perform computation or reason -- or inference with these concepts. And its multilingual terminology is being translated into Spanish, German, French; and part of it

is also translated to Chinese. And SNOMED CT is available free of charge for use in IHTSDO member countries, the U.S. included. And in, also, low-income countries, as defined by the World Bank, and for any qualified research projects in any country. ICD-9-CM, I believe most people would have heard of it. It is the International Classification of Diseases, the 9th Revision, Clinical Modification. And ICD-9-CM is the official system of assigning codes to diagnosis associated with hospital utilization and public health reporting in the U.S. And one very important function of ICD-9-CM codes in the U.S. is that it's used for reimbursement and is one of the HIPAA code sets. Since there's a planned transition from ICD-9-CM to 10-CM by 2013, so we have included, also, the ICD-10-CM codes in this project. So, there are some other code standards that we have used here. One of them is the enzyme codes, which is a list of recommended names for enzymes, recommended by these two bodies. And the enzyme codes

also are freely available for use. The OMIM codes stand for the Online Mendelian Inheritance in Man. This is a very comprehensive and authoritative collection of human genes and genetic phenotypes, and their names and codes. So, last, but not least, I would like to mention the UMLS. The UMLS is not -- the Unified Medical Language System, in itself, is not a single coding terminology; it is actually a conglomeration of many biomedical terminologies. It is developed by the National Library of Medicine over 20 years ago. And it consists of a huge Metathesaurus which incorporates over 100 biomedical terminologies; classifications and coding systems and the like. And it contains over 1.5 million concepts in biomedicine. And the one special thing about the UMLS is that the content of the UMLS are organized by meaning, so that all the terms from these different terminologies, if they consider to mean the same thing, they will all be grouped together and given a common and permanent identifier, called a "unique concept identifier or CUI. And the UMLS acts as a bridge between different coding standards.

So, what we have done is, we collect the lists of tests, analyze conditions, and also the correct categorical answers; and some of them are already mapped to standard coding systems. And for those items that do not have standard code attached to it, we will try to fill in the gaps, if we can find any codes in the standard coding systems that were within the concept. And, at the end of it, we will also add the UMLS concept unique identifier to all the entities. And we publish this list on our new Web site, the newbornscreeningcodes.nlm.nih.gov, and later on I'll do a brief -- I'll show you some screenshots from our Web site. Now, we publish this list, together with the guidance and rationale for their use, as advised by the AHIC Committee on Newborn Screening. And we also added other useful links on our Web site. And what we plan to do in the future is, of course, we have to maintain this list, as, invariably, there will be changes made to them, and we need to update them over time. So, next I would like to shift to talk about messaging standard. So, we'd like to encourage the use

of HL7 as the standard for reporting newborn screening results. And we would like to do this by facilitating the development of a standard specification for the payload part of the message that use these codes and approaches as proposed by the AHIC committee. So, next I'm going to talk about HL7 a little bit, in case you might not be very familiar with HL7. The Health Level 7 is an international messaging standard for the healthcare domain. And it -- currently it has two versions -- Versions 2 and Version 3. And, by and large, Version 2 is the most commonly used. It's almost universally available in large practices, laboratories, and hospitals. And the U.S. Federal Government actually requires HL7, Version 2.5 or above, for laboratory reporting. HL7, again, is a widely used international standard. It's used in Germany, Netherlands, France, Japan and many others. So, what is HL7 about? HL7 is a messaging standard. And an HL7 message is composed of segments. And each segment is usually given a three-letter acronym and it is designed to convey a specific type

of information. For example, the MSH segment is the message header. The PID is the Patient Identifying and Demographic information segment. As far as this project is concerned, the OBR and OBX segments are the most important. OBR deals with information about observation requests like laboratory and radiology orders, and OBX is a segment that is used to report the results about this investigations. So, each type of message has a very specific syntax, so that it can be -- so that the content can be transmitted unambiguously. Apart from specifying the syntax of a message, HL7 also has predefined data types. Some examples are: the DT data type, which is a date, which is in this format, CCYYMMDD; PN is for name, which is last name followed by the first name, and then the middle, and then the suffix; and CE is probably the most important data type here, which is -- stands for coded entry. And, I have some examples of the coded entry. So, the coded data type has three parts: The

first part is the code; the second part is the print text, which is a human-readable part of that code, or the concept. Here, for example, for galactosemia in Blood DOT, which is name of a test, it has a code -- 56084-9 in LOINC. So, it is specified as a code element in the following format: the code, followed by the print text, and then followed by the code system. In the design of HL7, in a CE data type, one can send, actually, not just one code, but two codes. So, there can be a second triplet of information if you want to send another set of code that means the same thing as the first set. For example, this is used in case you want to send your local lab codes and lab test names, as well as the LOINC code. So, inside OBX segment that is used to report results, the most important fields are the OBX-3 and OBX-5. OBX-3 is the test -- the name of a test, which is always a coded item. And OBX-5 is the answer. The answer can be a numeric; for example, for a test of serum glucose, it can be a numeric result. It can be a coded result; for example, it can be a code from SNOMED CT, meaning hyperglycemia. Or, it can also be other

data types. So, putting this all together, the coding standard, and also the messaging standard, then we have a full specification of how one can transmit a lab result. So, here's an example of an HL7 message transmitting a hemogram result. The first part, here, is the patient level, which is the PID segment, containing the patient's name, identifiers, and address, and date of birth, and so on. The -- all the report results are -- the segments are the OBR segments and the OBX segments. Here the OBR segment will have a code for the hemogram panel; in this case, it carries the LOINC code for the hemogram panel. And wrote under this is the -- are the OBX segments, which carry the individual test results. For example, you have a segment which carries the result for RBC count, another one for hemoglobin, hematocrit, [inaudible] volume, and so on. So, here are the proposed rules of engagement of sending in newborn screening test results. The newborn screening labs would report both quantitative and categorical results labeled with the appropriate

LOINC codes from the list of codes that we published. They would also report the quantitative measure numbers with the agreed-upon units, as specified. And the categorical results, for example, in hemoglobin [inaudible] studies, if the results suggestive of sickle cell and beta physenia trait, then, this will be coded as a SNOMED code. So, we've also prepared a graph of a mock-up message of how one can report on any one screening result -- on a whole panel on newborn screening test results. And this is actually based on real data, collected from Georgia, but is completely de-identified. And the message structure, as I illustrated earlier -- there are the wrapper segments and also the payload segments. The payload segments, we have the OBX segments, which are grouped together under the OBR segments. For example, HR [inaudible] test, and will also include interpretation in quantitative measures. And this -- each discrete measurement or interpretation is reported in a separate OBX segment. Here's just one part of the payload part of

the HL7 mock-up message. So, we can see here, I am just showing the OBR segment. So, this OBR segment is about the galactosemia newborn screening panel, which is a group of tests testing for galactosemia. And, inside -- and underneath it, you have two OBX segments. The first one is the interpretation of results, which is an interpretation of this suite of tests to see whether this is suggestive of the disease or not. So, in this case, it is a textural statement saying that test -- this test for enzyme defects is inconclusive. Another form in which these tests will be reported will be a numeric result, actually; the quantitative result of the tests. You see in this other segment, you have another test name code, galactose and blood dot, and it's given a LOINC code already. And, the result is 1.6 milligram per deciliter, which is actually the quantitative result of the test. You may say that, "Okay, in the above example, that the test names are not very -- seems like quite long and unnatural, and so on." This is -- these names actually taken from the LOINC long common names,

and these names can be changed, if so advised by, for example, a consensus of the NBS labs. And also, as I mentioned earlier, HL7 has the option of including the original elapsed codes and test names, so this should not be a big problem. So, here's the new site that is just launched, about a week ago, which is right hot off the press. And you can see, this is the first page. And the functions of this Web site are threefold: First of all, you allow the download of this -- the various tables; it can allow a user to look at the table of contents in the customized form -- customized way; and it also has links to related documents and resources. So, to download the tables, you click on the link of the download and then the four tables can be downloaded separately, in the comma-separated value format, which can be opened in either Excel or in the OpenOffice applications. So, for the individual views for tables, there are four different views that we provide. They -- it's either conditionally, can be analytes and measurements only, can be conditions-linked to the

analytes -- that used to diagnose the condition, or it can be analytes first, and then linked to the conditions they are supposed to diagnose. There are also additional filters that can be applied to each of these views. For example, for the conditions view, you can filter them according to the category of the conditions -- for example, where there's hearing-loss screening, or amino acid disorder -- or you can filter it to what is the core or secondary condition. And in analytes views, in filter the tables by the analyte categories or by the -- whether you want to see the derived measures or not. So, here's the step -- here's the page where you can jump off to all the different views. For the conditions view, here is listed all the conditions. And here is also listed the category, where there is a core or secondary test. The enzyme name is shown, and all the accompanying codes, like the SNOMED codes, ICD-9-CM, 10-CM codes, enzyme codes, and OMIM codes, and so on. For the analytes or measurements view, the -- you can see a list of all the measurements is

analyzed. For example, all the hearing -- all the screening tests for hearing, and also the individual analytes that have been tested. Here, we also show their LOINC numbers. So, the third view is the "conditions linked to analytes" view. Here, you can see here this is listed -- the condition name is listed first, followed by the list of analytes that are used to -- either as primary markers or secondary markers for the condition. And, if you want to look at the analytes first, here are the views that show the analytes first, and then followed by the names of the conditions that they are meant to be screening for. So, here's a screenshot showing the filters that you can apply for conditions. For example, we can filter them by the category of interest or either by the fact that they are core or secondary conditions. Here's the filter for analytes measurements. We again -- we filter them by the nature of the analytes, or, you can filter the views by whether you include the derived measures or not. So, here are some additional useful links on

the Web site. There's a link to another NLM site, called the Genetics Home Reference, which contains about 5- or 600 common genetic conditions. And of those, 29 have conditions actually recommended for newborn screening in the HRSA report. There's also a link to the NNSGRC site and other than the Medline Plus topics on newborn screening, and so on. There's also some brief explanation of all the coding standards that we're using: LOINC, SNOMED CT, ICD-9-CM, et cetera. So, this is still very much work in progress. And right now we are still dealing with some additional issues and one of them is the card variables. Card variables are additional information that's being collected about the baby at the time of the screening. This might include things like birth weight, transfusion history, and -- which might affect the interpretation of the test results. Some of this information may already covered in other HL7 segments -- for example, the PID segment -- so, they will be transmitted separately, in another segment. However, some of them may not be covered in any existing HL7

segments, so they would be sent separately in OBX segments. And for this to occur, we also need some standard LOINC codes, either panel codes or observation codes, to code them, so that they can be -- this -- the information can be properly labeled. But, before this -- before LOINC codes can be assigned to them, we need a clear indication as to the core set of data elements that this should contain. Another area we are working on is, we're exploring the use of other special HL7 functionalities that can be used in the special-use case. For example, the hide -- there's a hide function in HL7; meaning that, in this segment, OBX-13, there can be a flag that can be set on and off to hide some of the results from, for example, routine clinical display. As Dr. Zuckerman mentioned earlier, some of the very detailed quantitative results may not be very useful in the day-in/day-out clinical environment. So, it can be decided that those results can be hidden from the clinical display view. However, the results will still be available for management and research purposes. Another functionality of HL7 that we are

looking at now, is that there's a delivery of a full formatted report in addition to the individual data elements. So, HL7 can actually deliver a full formatted report within this OBX segment. And, of course, the special LOINC codes have to be assigned to each kind of report so that they can be received properly. Some of the work that we are now working on includes to build a more complete example and guide of HL7 messaging. And also, we need to flesh out the agreement on the additional interpretation variables that we may need to assign LOINC codes to. So, this is the end of my presentation, and thank you very much for listening. [Applause.]

DR. HOWELL: Thank you very much, Dr. Fung. Are there questions or comments of Dr. Fung? Dr. Getchell?

DR. GETCHELL: I'm just wondering what the process will be for rolling this out to States, for use by newborn screening programs. Have you thought of that at all? And -- that may be a question more for Dr. Zuckerman, but --

DR. FUNG: I think what we are trying to do here, is to establish the standard codes and the messaging format, and make them easily available for people who would use them. But, I think it's for a more general organizational committee, like maybe this committee, to decide how this should be rolled out and what procedures will facilitate the adoption.

DR. WATSON: Are they not currently being -- I mean, don't the labs currently use LOINC codes, at least, or any of those -- or is it just variable from State to State?

DR. HOWELL: He can't -- he can't hear you, Mike.

DR. WATSON: They're only just now being integrated into the equipment that gives back the automated information to the laboratory that has to roll it up into a report and then roll it out as a report from the laboratory. So, it's got a ways to go, I think.

DR. HOWELL: Thank you very much. I think that Coleen's earlier comment is underlined as we hear your presentation about --[Laughter.]

DR. HOWELL: --the fact that there is an enormous amount of "stuff" happening, for want of a better word. And I think that having a group from this committee working with experts in the field to try to stay abreast of it and report back to us is going to be critical. And we've been having a little side discussion over here, of trying to identify a group of people who will be helpful to work with the members of our committee. Piero?

DR. RINALDO: As Jane broke the rule and said something, I propose that she's -- [Laughter.]

DR. RINALDO: -- added to the committee.

DR. HOWELL: I think it's important to have a State lab leader, and she has -- and she has spoken, and she's also nearby, and so forth. [Laughter.]

DR. HOWELL: Actually, there are a number of people that can provide expertise from the CDC side of

the street -- NIH, HRSA, and so forth -- and I think we can get a group together and that we'll try to meaningfully keep this committee up to date on all these things. Thank you very much. Very nice presentation. We're now going to hear about the newborn screening Web portal concept. Greg Downing was appointed, in March, as program -- 2006 -- as program director for HHS on the Initiative of Health in -- on Personalized Health Care. He's joined by Dr. Constanze Coon, who's here today. And they've been working at Deloitte Consulting since 2008, supporting the Initiative on Personalize Health Care within the Office of the Secretary. And so, we're delighted to have Greg and Constanze here today to tell us what they're up to.

DR. DOWNING: Great. Thanks, Rod. First of all, I think we all owe a debt of thanks to a good number of people around the table, and in the room for their hard work on many of the activities that you've heard about thus far. I think, to sort of set the stage for what this last part about

-- is -- and the connections of all of these -- is that, we have, I think, with the gracious help of a number of people here -- Rod and Peter and Duane -- have given us the luxury of working with this committee. We've been here now, I think, three or four times over the last 2 years, and an immense amount of progress has been made to set the stage of the foundation, if you will, for knowledge exchange, to support not only the clinical utility of newborn screening information, but also the research applications, and consumer and patient information overall. I thought -- and I'm -- continue to be impressed with the stories that come from the communities that are involved in this group. And it's -- was one of the initial appealing aspects for which an activity from the Secretary's level and from the Office of National Coordinator has been focused on this unique way in which public health and primary care interface overall. But, listening to the stories last night that, again, come -- are often telling the story about

individuals and patients, about how these affect not only infants, but the lives of those who care for them, and to the notion that the Blood Spot itself has a great deal of redeeming value for learning more about these disorders and how the technologies come about and are developed as a framework for them, I think what you'll begin to see soon are some of the benefits of what the capabilities that standards and coding and terminologies, use cases, and all the lexicon of informatics talks that you've heard here from over the last 2 years, now sets the stage for what connectivity communications can now generate in the terms of clinical knowledge. So, the framework at which we've been working under has been somewhat constrained from the context of being removed from day-to-day decisions, but the framework for which now you have the opportunity to be thinking about begins to look at things from the patient level and a program level. And I think what we would like to do today is to set the framework for looking at new frontiers of where this information can go. And what needs to happen next is that this

Nationwide Health Information Network component begins to unfold, many private-sector standards for health information technology applications are now coming forward so that the information is more mobile and protected and communicates and connects in new ways. And we're beginning to see some of the ideas and notions for that. And I suspect, when you come back here a year from now, you'll be able to see some examples of the ways in which information moves. We came across, in our work over the last couple years, in looking at unique models and ways in which capabilities and new platforms for moving information from different disparate systems might be of benefit to this particular community -- and so, this is a concept that we're going to talk a little bit about today. But, we hope to provide some of the aspirations, inspirations, and perspirations that would now make what has been conceptually connecting the dots components reality, in terms of moving clinical information. To a meaningful way, none of the States, or none of the communities are able to move information

from lab orders or results back from the delivering hospital, to the lab, to the physician or other healthcare provider who needs that information at the time that they need it. And this community, I think, is well poised to benefit from the potential ways in which all of the work that's been done thus far can enable that. So, we are setting the stage today, not with any new program or new tool, but the capabilities around a concept that we refer to here as a "service-oriented architecture" that pulls knowledge and information from different places to support a plethora of needs. And so, this is very much an idea and a notion that we've had some experience with in developing family health history portals and other components around genomic testing overall. So, there's nothing the Committee has to do about this today. You can shoot it down, if you wish, but this is, I think, a culmination of where you are in the perspective of newborn screening nationally; but, at a local level, what can we do to accommodate differences where one State has highly integrated

health integrated networks and lots of EHR penetration for their doctors, and other cases where there -- those things are nonexistent. So, we're going to talk just briefly today about where we are in the big picture about the electronic information exchange. You've heard a lot about the architecture that's evolving. Where are we today? And I would encourage the committee to start looking at benchmarking some of these capabilities overall. I know Brad has got a handle on this, but some of the new infrastructure capacities coming out of the agencies override those capabilities to look at some of the value propositions of what you can do with data. That's something that, I know, in terms of long-term follow-up and program performance, this is within scope. And then, also, this notion of what -- a screening portal that supports service-oriented servicing of information needs to a broad spectrum of needs. And so, I'll ask Connie to represent the work that we've been doing in terms of thinking about some of the business models that might support broad needs

at a State level and health systems needs overall, to accommodate the information needs that they have.

DR. COON: Thank you very much, Greg. So, I'll start by going through the slides and, sort of, setting the scene for the Web portal and giving you some background on what the thoughts were behind it. So, first of all, the purpose: The purpose is, obviously, to improve the quality of care for newborns. To enable and support the early detection and intervention for heritable disorders. As, you know, most of, or all of, you should know, it's special considerations and challenges within the field of newborn screening, that it is at the juncture of public health and primary care delivery, and that it presents a case for continuity of care from the birth center to primary care and follow-up care, which is an important temporal component when looking at electronic information exchange. It also provides an opportunity to integrate prenatal, postnatal, and infant healthcare information. So, at the Personalized Healthcare

Initiative, we've been very busy compiling resources that help -- or can help to initiate electronic information exchange, or develop concepts to exchange newborn screening data. One of them, Dr. Alan Zuckerman has already mentioned, is the use case that is now with HITSP, the coding and terminology guide that has just been presented, as well as an information package that presents an overview of all the materials that have been developed, and a simple guide to what next steps could be taken in implementing the standards and adopting the standards. I want to mention also privacy and security policy guidance that is part of the package, and all these materials are available on the healthit.gov Web site, as well as the coding and terminology guide is available on the NLM Web site. So, the current limitations for electronic information exchange are that public health information exchange systems, such as [inaudible] are still under development, not quite tried and tested, and that the overall, sort of, the efforts for newborn screening information exchange within the States are limited,

although progress has been seen in some States, such as Iowa, Texas, Delaware, and New York, just to mention a few. Why introduce a portal now? Well, the portal would provide an opportunity to connect newborn screening data with data from, for example, immunization, and therefore, build a comprehensive electronic health record, such as is intended by the efforts, I think, within CMS, to build a pediatric EHR. It also would present a case of transfer of care from the birth center to primary care providers, and therefore, could serve as a template for other scenarios within the healthcare field. Electronic information exchange of newborn screening data also supports population health activities and provides a link to research programs and clinical research, as well as program evaluation. And, as Ginger Price mentioned, it is currently supported, or will be supported, by Federal investments through the HITECH Act for Infrastructure and Adoption. So, coming to the rationale on the proposal for developing a newborn screening Web portal. The Web

portal-based information exchange addresses both the importance of newborn screening, as well as electronic information exchange opportunities. Newborn screening is an area of public health importance. It is mandated by all States, and therefore, is also at the leading edge of clinical application of genetic knowledge. An effective electronic communication strategy would prove -- would both improve newborn screening base case and potentially serve as a model for health information storage and exchange to support pediatric and lifelong care, and it bridges the communication among various elements within the healthcare system. And then, finally, electronic storage and distribution of newborn screening data would, as mentioned, provide new resources for research and lay a foundation for use of genetic information in clinical care, as well as expand consumer access to information and medical decision making. So, this is our newborn screaming -- eh, "screaming" -- screening Web portal concept. I have a 15-month-old, so, I know about that.

If anyone has a pointer, it might be easier for me to go through this. All right. So -- and this is a concept, as Greg mentioned -- so, we're not -- we would like your input, your questions, discussion, everything you can give us. In an ideal scenario, the hospital would have an EHR system that would send a lab order -- electronic lab order to the public health lab, followed by the filter paper with the actual lab blood spots on it. The lab subsequently performs the laboratory tests and compiles the lab order with the test results, and then makes it available through the Web portal to the ordering physician within the hospital, as well as the primary care provider, the patient care provider -- which are the parents, the guardians of the infant -- and the research community. These are depicted as green arrows, making -- basically meaning that these would be through queries rather than automatic push of data to these entities. It has been pointed out that sometimes within the public health laboratory, the actual lab site --

the lab system, as well as the public health database, are not connected. So, there would be an information exchange that has to occur there. There would also be an automatic push-out of data to the Federal and State registries who do the monitoring and evaluation of health outcomes and quality measures. And then, the identified test results would be made available to the research community, which could be the Translational Research Network, which could also be researchers looking at quality measures, and so on. I think an important component is also that the patient care provider -- the parent -- who has, through the Web portal, a means of actually controlling and making sure that the lab test has been performed, and put their mind to -- at ease that the proposed care and follow-up has been completed. And obviously, a primary care provider receives the information, receives the lab order information, as well as the lab test results, and then can refer this information on to specialists and other healthcare providers, in due course. So, this is our portal. I want to point out

that, at the moment, this would be the ideal site where the EHRs -- you know, the data flow going through EHR system; but, the Web portal is actually accessible also through, you know, laptops, PDAs, anything that can access an -- the Internet. Any questions? I think this is --

DR. DOWNING: The concept speaks to the diversity of needs and capabilities to access information today. And if one thinks about the types of ways in which health information can move now, whether it's Health Vault or Google Health, the uses of remote devices, that one shouldn't think necessarily about linear transmissions of information any longer. So, the real need here is some file-supporting service -- electronic information-supporting service, through a portal. And what we would propose, in some ways, that these are open-source resources developed and made available at the State level, to healthcare delivery systems, to public health laboratories themselves. And in the world of supporting technologies overall, getting the

base-level operations to move information is really the key. So, the highways are being built now, and what we're looking for, I believe, are the entry points in which the standards are going to be able to connect with that, and that the on-ramps and off-ramps to the highway systems of health information are established for newborn screening information. So, this is pretty high-level, but I think is what is on the horizon for an opportunity. And, as a number of you have mentioned, Where are the communication points that are necessary to happen? Particularly, at this point in time, where massive Federal investments are being made at the State levels, that this is an appropriate time -- Ginger spoke about the 3013 provisions of HITECH -- that this is the exact time to be having those conversations with State leaders, to emphasize that the newborn component built into those requirements that the state plans have accommodate the kinds of needs that you have within the States, overall, for supporting these kinds of services.

So, we'll stop there, and hope that this has given you a vision into what we think might be an opportunity for a newborn screening information handling in the future.

DR. SKEELS: A quick question?

VOICE: I'm, sort of, trying to get my mind around this, so bear with me, but a lot of us have Web portals to our newborn screening systems. We already report results through that route, and we have levels of security and access, and so forth. And I know at least one of the software vendors is about to come out with a Citrix gateway that allows our users to go directly in and use different levels of data. So, my question is, How is this different from that? How does this go beyond? Does this offer something in the way of connectivity and portability that that does not?

DR. DOWNING: That's an advantage, to start with. The interoperability of the codes and terminologies to move unified and common data across different systems will be a challenge, so I won't mention any particular vendor products, but if your

hospital systems have different EHR systems, for example, or ambulatory systems have EHR systems, that are not able to accommodate the support of a message coming from a State public health laboratory now, this may be an application for that. Obviously, in the -- when looking hard at vendor systems that you're going to acquire for your particular applications, recognizing whether it'll support the standards that are created necessarily to support these kinds of services are going to be important. I think we're particularly interested in these cases, where there's no infrastructure at all, in certain parts of the country or regions where health IT has not had firm penetration, the emergence of non-NHIN kind of capabilities, that a portal system may be ideal for supporting places that don't have those kind of infrastructure in place already.

DR. CHEN: The question for you about this -- the "research community" box has two arrows coming to it. One is the de-identified one from the State lab. The other is actually a green arrow from the Web

portal. And I wonder, sort of, what the implications are there of mixing the research use with the clinical use consent, and whether or not that -- how have you thought about that.

DR. COON: As I said -- I have to repeat -- this is just a concept, so I think there are certainly lots of points that need to be refined and sorted out. I think the two arrows, basically -- as far as we understand, there needs to -- or, there is currently -- it maybe needs to be an automatic push of data out of the State lab systems into the wider research community, or like -- I'm thinking Translational Research Network, mainly. The other area is more -- if someone would be interested in not necessarily getting the nitty-gritty data, but getting some kind of aggregate data from the State and using that, or getting an overview, like number of cases of a certain disorder. So -- and also, just a -- sort of a sample. What does the sample message look like -- sample report look like? So, it's not terribly defined yet, but I think you need to keep those two distinct, to make sure

that they're not mixed up.

DR. DOWNING: I think the one example that I think may speak to the applications of this is that, if you imagine the first visit to a primary care doctor for a newborn infant, that the information doesn't have to be prompted, or no one has to call, or no on has to log in to a Web site to retrieve the result status, or if the tests have even been completed. The notion is, is that that information is already presented to you in a way that is useful within an EHR or even, in some cases, a PHR. But, this is foundation for that, enabling information to be delivered without even having to ask for it, if the permissions are in place or the consents are done. And that's a capability we don't have now, but it's certainly within reason to think that one can start to build systems that will accommodate such needs.

DR. BOYLE: Just a quick point. I don't know if you were here earlier, but in our Follow-Up and Treatment Committee we talked yesterday and early this morning about the importance of being able to link the newborn screening results to electronic birth records.

And again, that would just be a -- sort of a -- just a fine tuning of this Web portal, but it really would allow that sort of quality-improvement loop to be addressed.

DR. DOWNING: Right. And, I think that's certainly within the domain of the State systems. I think that some of the other interests that you've been working on, Coleen, in terms of longitudinal data collection, aren't in here. That's an area where some of the standards, not just for the terminologies, but also for the measures, need to be worked on, in terms of accommodating longer-term applications of this concept. But, we -- that's a very good point to make.

DR. RINALDO: I'd like to follow up. I think Dr. Skeels, earlier, mentioned the fact that -- to what extent you have awareness of what is already out there. Because, frankly, you know, you're now starting from a blank canvas, here. But, second -- actually, your last comments worries me a little, because if you really live a little in the real world of newborn screening, you will know that a comment you made is perhaps one of the most

unachievable things, because 99 percent -- well, I would say, most time the physician mentioned on a card is not the physician that will take care of the baby. And I'm look at people who have experience with screening tell you that, "Boy, to reach that point" -- because in -- the reality is, when the child -- when the card is collected and the child is discharged, nobody knows who is going to be the primary care provider. So, my question really goes back to a point -- to what extent have you studied the baseline? Because, you know, I know you haven't shown it yet, so it might not be fair to comment, but when I look at your next slide that was provided to us, I see a lot of things about improving this or reducing using that. So, to me those are, you know, tentatives to have metrics. And so, how you define these metrics and how do you define the targets? So, if you tell me you're going to improve coordination of care, how you measure it?

DR. DOWNING: Well, I think that, to the long-term aspects that we don't have the measures in

place yet to be able to accommodate that. But, the aspects of being able to measure who has gotten electronic results back, and closing the loop, and has the data been collected and delivered to the places that need to have it to be able to perform their clinical positions in response to the test results, you know, that is a feasibility that one should be able to start thinking about in this. I actually do live in this world and recognize the deficiencies that we have today. I think one of the big things that we didn't know, 2 years ago when we started having these discussions, is that it is highly likely that significant impact on penetration of putting EHR systems into the primary care setting will be affected by this investment. So, one can't know today what we're going to have in terms of penetration in 2 years, but it will be significantly different than it is today, overall. So, the technology will be there to support the kinds of information that's in place. I don't know how to convince you that these things are feasible. I think this is the aspirations part of what we've been trying to do through this

group. The standards work is incredibly important to enable some of these aspects. I think we need, clearly, pilot studies to be able to demonstrate feasibility of large practice groups in certain communities, being able to receive messages from delivery hospitals and getting information from different sites. I think that, in the private IT world, that the ability to assimilate information and develop knowledge from it is clearly escalating. And we are hampered, in many ways, in healthcare by the lack of having that connectivity and the ability exchange information. That is going to change. And I don't think we can paint ourselves in any particular box by saying that the limitations of what we have today should prohibit us from thinking about future applications. So, I agree with you that it doesn't seem achievable, but I think, within the timeframes in which the health IT adoption begins to work, that many other aspects of moving information -- that those kinds of concepts of achieving measurable improvements, in terms of effectiveness of information at the decision points

in care, will be a reality in the timeframe that we're talking about.

DR. RINALDO: I really had no intention whatsoever to even hint it was not achievable. I want this to be achievable and I want you to succeed. I'm just saying is -- my question was really more practical is -- as you embark in this really tall order of process, to what extent have you studied --

DR. DOWNING: Yeah.

DR. RINALDO: -- the baseline, or what is already in existence?

DR. DOWNING: Sure.

DR. RINALDO: And to what extent you think -- are you telling us you want to start from scratch or that there is going to be a mechanism to incorporate things that are already exist and work?

DR. DOWNING: Well, I -- that's a good point. And so, in terms of data collection, data is hard to come by in this space, as you know. And we've talked a lot with many of the vendors in this space, and certainly with Brad's help, to what limited capabilities we have to reach into State experiences. We've been off to 10, 15 different public health laboratories over the last several years to get a pretty good composite of, you know, what people have for hardware, how painstaking it is to move information from one lab testing site in a lab to another. So, I think we have a fairly good sense of what the world is like today. There's a huge amount of disparity, as you know, about the ability to move information in various communities -- geographic, as well as within certain States themselves, in terms of policies. So, you know, I think we have, particularly for the information domains -- as you know, have been working hard with us -- we've analyzed and accumulated all of the laboratory inputs from all of the State records. We want to validate that. What we don't know is what the State receives on their card, and what they log into their computer is still an unknown. So, there's probably a lot more information on the card than often gets integrated into the records that the public health labs generate. You know, one particular aspiration, as a

side note, is that we think, you know, perhaps the information generated from the birthing hospital may have a lot more validity in terms of avoidance of errors and the complications of not being able to read files, and so forth, off -- information off of the cards. A system like this can obviate that the -- you know, parts of the errors that are received, in terms of identification, and other kinds of missing information that the cards represent. So, I think -- you know, as you know, we've also been doing a lot of analysis on the outputs that are generated from the testing laboratories, and I want to -- think we've met with all of the vendors in this particular space, and certainly been communicating with them about the development of the standards that are coming into place overall. So, yeah, I think we would benefit much more from having more specific data within States and regions and -- but that these are not easy things to come by at this point. I don't think that anyone here is suggesting that this concept would be massively deployed, but I think that pilot implementation of

open-source system of this nature would accommodate lots of the variations that we see in systems across the country, and provides a great deal of opportunity for innovation, if we can go that far, to think about new ways of moving information to the points where people really need it. The problem I want to solve is that primary clinical care doctor who, on a Friday afternoon at 4 o'clock, sees a patient for the first time, and has nothing to work with. And we should be able to solve that problem. And that's what this kind of -- you know, going out on a limb, in terms of presenting this to this body, but I think that what we need are community-based efforts to work together to solve that particular problem.

DR. HOWELL: Greg and Connie, let me thank you very much for the very interesting presentation. It's time for a break. So, we can continue at the break. We'll stay out for about 15 minutes, and return. Thanks. [Applause.]

[Recess.]

DR. HOWELL: Ladies and gentlemen, let's do have a seat. This is such a social group here, I declare. Thank you very much. We're -- we broke a little longer than we should, there. I guess that's the past of a long break, and so forth, and we're now going to start with a presentation on measures for quality, and we're pleased to have Dr. Sarah Scholle here, who's the assistant vice president for research with the National Committee of Quality Assurance. Today, she's going to present the National Committee of Quality Assurance efforts to improve quality measurements in child healthcare. Dr. Scholle?

DR. SCHOLLE: Good afternoon. I'm really pleased to be here today and to tell you a little bit about the measurement work that we have underway. I'd like to start by just describing NCQA, if you're not familiar with our organization, the work that we've done to try to improve measures for child health quality, including some measures for newborn

screening and follow-up that we're testing right now, and then other work that we're just getting started with in care coordination and women's health. So, NCQA is a not-for-profit healthcare organization. We work to improve the quality of healthcare. You're probably familiar with us from our HEDIS Measurement Set, but our real focus is trying to measure quality, make that information available, and then allow it to be used by consumers and purchasers and others for quality improvement and accountability, and we work with diverse stakeholders to achieve that goal. So, for us, quality measurement means that you use objective measures that are based on evidence that allows you to make fair comparisons across organizations, and that usually means that you need to have sort of audit process in place, and with -- or documentation. And we believe that public reporting is in important and helpful for quality improvement and really making sure that we're getting the most out of our healthcare system. We're probably best known for the HEDIS

Quality of Care Measurement Set and our accreditation programs for health plans. But, over the past few years we've done a lot of work in thinking about how to move this further down into the healthcare system and work with measurement of healthcare providers. And we have recognition programs for physicians. So, what is HEDIS? That's the Healthcare Effectiveness Data and Information Set. It includes process and outcome measures, it includes a HEDIS version of the CAP survey, and also it's being used by health plans in a number of sectors. Our recognition programs are growing. We have more than 14,000 physicians, who are recognized, both in clinical programs for diabetes care, and heart, stroke, and back-pain care, but also our program, Physician Practice Connections, has -- is really burgeoned in the past few years. The Patient-Centered Medical Home version of that program has been endorsed by a number of the primary care specialty societies and others for use in medical home demonstrations. It's also endorsed by the National Quality Forum. And we're continually working to improve that measure. We'll be

updating it next year. And one of the things that we're really thinking about with the update is how you take those measures that look at how a practice is organized to provide care and -- What are the outcomes of care? And one of the concerns that we have is that in child health we haven't had enough measures to be able to pair those measures of the structure and the processes that are in place with the outcome measures. And last -- a couple of years ago, with some support from the Commonwealth Fund, we pulled together a group to try to help us think about, What the issues are and what should be the strategy for improving the quality measurement for children's health? And so, these are some of the key issues, the key points that our strategy group said we needed to think about, tying it to children's health outcomes, and trying to look for ways that we could use technology and that we could build strategic partnerships with groups. So, we're underway in thinking about that. The first step that we took, in terms of test --

developing and testing child health measures, is to focus on "well" care in a comprehensive fashion. And so, in HEDIS, we already have measures that look at whether children have a well-child visit. But, we don't really know what happens in that visit, and so, really, the purpose of this work was to say what -- let's look to see whether children at key ages have received the recommended well-care. And we're working on a field test of the measures at the health plan and physician level and we're doing some work. So, this is the eye-chart part of this presentation, but, I wanted to see it because -- you to see how we're thinking about this. We're saying, by age 2, do children have all the immunizations that they're scheduled to have by age 2? But, at the same time, do they have screening for developmental delay, for autism, have they had counseling for environmental tobacco -- an assessment -- and an individualized care plan, if that's warranted by the kinds of problems? And so, our panel suggested that we look at these ages: age 6 months, 2 years, 6 years, 13 years, and 18 years. And it covers a whole variety of topics at each of

those ages. And it was a tremendous amount of work to review the evidence and to bring our panel together to actually help us create specs. But, one of the things that we're excited about is the focus on children in infancy and looking at newborn screening. So -- and these are two of the measures. And I believe that, in the packet, you have the detailed specifications that we're testing. The point here is that we're looking at measures from the ambulatory care perspective. So, we're looking at a health plan and we're saying, "Take a sample of children who turned 6 months in the year, and find out whether these important pieces have been documented." So, for that sample of patients who turned 6 months, what we want to see in the chart is that -- in the outpatient chart, that there is documentation of the results of the hearing test, as well as evidence that there was confirmatory testing referral or treatment, if it was warranted. So, all of our measures of screening in this Comprehensive Well-Care Set have that piece of follow-up. It's screening plus follow-up. And our panel thought it was critical that

we include measures for hearing screening and metabolic or other screening for the age 6 months, to really make sure that the information about the screenings that are happening in the hospital, that that information gets into the outpatient chart, and that there's evidence of follow-up of any abnormal or indeterminate results. We're testing these measures right now, so probably by the end of the year we'll have some data on how this is -- on what's happening. We're a little bit concerned that this is not going to be documented in a way that we're going to be able to find it in the chart, but that's why we're field testing the measures. And I was really excited to hear about these -- the ideas that were shown earlier today about the way the electronic health records and health information technology could make it easier to -- for this kind of coordination loop to take place. Now, the other piece that I think is relevant to this audience is the measure of the individualized care plan. And so, this applies to children in every one of our age groups, and it's for children who have a documented chronic health problem. And for health plans, we're going to base that on the diagnoses that are billed in their claims data, and for physicians it will be based on the -- on diagnoses that are represented in the chart. But, the concept is that for a child who has a chronic health problem, that there should be a separate document outlining important health information for those children, that it should include information about their conditions, their treatment plan, goals for self-management, other clinicians or agencies involved in the children's -- in the child's healthcare, instructions for the family on when to seek urgent care, the next scheduled appointment and evidence that the plan was discussed with the family or caregivers, and a copy given to the family or caregivers. This is a lot to expect. I've had a lot of people say, "No, you're not going to find any of that." I mean, if -- but, this is what -- there's strong evidence for some pieces of this, some of it just make sense. And so, we'll be looking to see if we can find documentation of this in the chart. This also represents a roadmap for what me

might want to see in an electronic health record, and what should be printed out as a patient summary for children and families at the end of a visit or at a, you know, specific time. So, as I mentioned, these measures are in field testing. Our field test is happening in six different States and we're working with 20 -- up to 20 physicians to participate -- or clinicians -- to participate in the field test, and we expect to have the results ready so that we can present the measures to our Committee on Performance Measurement. And that's the committee -- it's an outside committee that advices NCQA on the HEDIS measures, and we're hoping that they'll approve it for public comment, and then public comment would be next spring. And if all goes well, we would incorporate it into HEDIS for 2011. So, that's really our process and measurement. We're -- we'd -- I'd certainly be interested in hearing if you have comments on the specific -- on the specifications or what we've included there. I wanted to mention that we're -- this is

really the beginning. Bike I said, we have this strategy and this vision for what we needed to do in -- to improve quality measurement for children. And another piece of this is to think care coordination. This is -- again, we have support from the Commonwealth Fund to help -- to have us think about what would be a framework or an approach for measurement for care coordination. We're focusing on children where they're at risk of developmental delay, but, I have to tell you, I think that the processes of care coordination -- when I heard about newborn screening and the actors involved and the -- how the information gets shared, I think they're very transferable, and we'd love to think about how it would fit there. But, what we're thinking about -- what we're going to be doing over the next year is to think about responsibilities at different levels of care or different actors in the healthcare system. So, with children at risk of developmental delay, we're thinking about primary care practice, medical specialty practices, other providers, the community, the State. I think, with newborn screening, you'd want to have

hospitals in the screening programs. There'd be others. But, the thought is to say, What is the structural measures, what should be in place in each of those organizations or those different levels? For a primary care practice, this is very much the kinds of structural and process measures that we have embodied in our standards for the Patient-Centered Medical Home: Is there a process for tracking referrals? Do you have designated staff to coordinate? Do you have ways to support families in self-management? But, you could think about structural things that should be in place in communities, or at the State level, and then also -- for care coordination, when we're thinking about care coordination, I think, it's easy to think about the structures, and then it's also somewhat -- you can talk about outcomes and what are the problematic outcomes. We could survey families to hear about their -- experiences of care. We could look at problems, like readmissions or, you know, number of hospital days or ER visits and say, "That's a problem and an outcome." But, the hard part is really to operationalize what's the measure of whether the information is being shared,

whether there's a shared care plan, whether there is -- the family's being involved in developing that plan, and -- you know, it's really information exchange and making decisions based on information, with families and children participating in those decisions. And that's really going to be the heart of the work that we're doing. We're actually testing some measures of care coordination right now, and we've specified them for use in practices that have electronic health records. And I have to say, this is some of the hardest measurement specification I've ever done, because all -- because you're trying to do -- you're trying to build specifications that are going to make sense in a whole variety of practices that have lots of different kinds of staff and lots of different kinds of incentives. And, so -- But, that's the piece we're really involved in now, and I could see that, you know, some of the things that we've learned about care coordination, generally, in terms of how primary care and specialty physicians communicate, I think would be applicable and useful to apply to the newborn screening thing. And

we'd be happy to be thinking about that. And so, over -- just in terms of this project, what we'll be doing is working with key informants to try to build out the ideas for measurement that are on this chart, and then to conduct site visits with States to try to understand what they think about it. And one of the things we'll be doing is asking States, "Well, how well did -- would this work for other groups of children?" -- not just the ones at risk for developmental delay. The reason we're using that group of kids is because we're building on the ABCD Projects, where the States have committed to trying to improve care coordination; and so, we've got an opportunity to measure where people are committed for improvement, and we think that's critical. And then the last thing I wanted to mention is that we're planning to extend our approach for quality measurement, this approach about comprehensive well-child care, to think about pregnancy care, even preconception care. Our panel -- it's always hard when you pull together a panel to help you think about measures; they always want to go out of your scope, and

we had to say, "Okay, stop." You know, pregnancy is out of scope and preconception is out of scope. But, that's why we -- we've -- we're building here. We've got so much enthusiasm for this idea of taking a population and seeing whether their health needs are being met, that we're excited about applying it to this other population; we think it's particularly relevant here, as well. And we're grateful to support from the CDC and HRSA for getting that effort off the ground with a panel meeting that we're going to be having this fall. And our plan would be to continue to go through the steps that I mentioned for the child health measures --evidence review, specifications, field testing, public comment -- so that we could have measures ready for endorsement and implementation.
So, thanks very much.

DR. HOWELL: Thank you very much, Dr. Scholle. It certainly is, I think, going to be helpful to have some NCQA measurement approaches applied to children, and certainly newborn screening, and et cetera.

Are there comments or questions of Dr. Scholle? Tim?

DR. GELESKE:In one of your early slides, you mention -- or it showed 178 practices that were certified as Patient-Centered Medical Homes. I was wondering how many of those are pediatric practices.

DR. SCHOLLE: I know that we have a good number of pediatricians; I don't know the exact number. I think it's about -- I think about 20 percent of our practices are pediatric practices, and these numbers are the -- as of July, and we just -- I mean, it's growing and growing. But, we do have a number of pediatricians.

DR. GELESKE: And, as I recall, that doing some quality measurements are part of that certification process. And you're testing some measures. I was wondering what kind of measures those practices are using?

DR. SCHOLLE: So, the program asks practices to demonstrate that they're involved in quality measurement and quality improvement. And at this

point, we don't make requirements for what measures that they use. So, it's -- the Physician Practice Connections Program is looking to see, "Do you have a quality measurement program in place? Are you measuring? Are you identifying places where you could improve? And are you developing a quality -- you know, are you actually doing something about it?" So, it's all process-oriented. Now, one of the things and one of the options for taking our Comprehensive Well Care Measures is to attach it to the medical home, so that a practice could say, "Here I've got the structures in place, and here I've measured on these specific quality measurements for kids. And if I do well enough, I could be, you know, kind of double recognized." One of the reasons why we developed -- we began this work on child health is that we saw that we needed measures, we knew there was interest from -- in the public sector, but we also heard, from the private sector, that programs that are rewarding practices for getting the Medical Home or the Physician Practice Connections certification, along with a clinical

program, that pediatricians, or those caring largely for children, were left out of the loop, because there's not a clinical program that really applies to them. So, it's our hope that -- one of the things that's on the table for the reevaluation of the PPC-PCMH would be to allow an option for putting those two together, the out -- the quality measures and achievement on those, along with structures and processes.

DR. GELESKE: And one last comment. You mentioned on your Individual Care Plan -- Individualized Care Plan, you didn't think you'd be able to document whether those were happening or not. I think if care coordination is happening through a Medical Home, you'll be able to document whether a care plan has been instituted. I mean, those things will be part of the medical record on -- what the outcomes will be will be -- that's the tricky part, I guess. But, you'll be able to get half of your list here, I think, documented fairly well.

DR. SCHOLLE: Thank you.

DR. HOWELL: Further questions or comments?

DR. SCHOLLE: Chris.

DR. HOWELL: Oh, Chris?

DR. KUS: Moving into the improving the chronic care measures for kids, 'cause the belief that a good plan really is how the -- how well they care for kids that have chronic problems, have you had any discussion about -- there's research in the past about kids with chronic disease not getting their preventive measures. So, looking at that population and looking at how well they do in terms of the preventive measures might be another way of -- getting a sense of comprehensive care?

DR. SCHOLLE: Actually, that's something that came up -- I hadn't thought of about it, because our sampling approach is to just sample children, but it -- one option would be to sample children -- well -- I mean, without a diagnosis, and then to have another sample of children that do have a diagnosis, because then you could look at how well -- at both of those things. That's a great idea; I'll take that back. There's been a huge amount of concern about the burden of these measures, and how we'll be able to

implement them, because it is a lot -- the -- at this point, these are chart review measures, and so, that's an expensive proposition for health plans. And so, we're thinking about how to do that, and that -- and actually it -- that could be an efficient approach that might make -- resonate with people. Thanks.

DR. KUS: One more comment is that you're project related to kids at risk for developmental problems, the concern I have about that is, how do you identify kids with have -- at risk of developmental problems? -- which I'm not convinced there's good things out there, plus it would mean screening for that -- to do that. So, just to put that on the table.

DR. SCHOLLE: And that project is embedded in an effort already to do screening. So, it's when you've done the screening, what do you do next? And so, your point is very well taken. Thank you.

DR. HOWELL: Thank you very much for that informative presentation. We will now move to a presentation from one

of our committee members, Dr. Ohene-Frempong, about the internal review group that has reviewed the nomination of alpha thalassemia-Hemoglobin H disease, that has been recommended to the committee to be added to the Uniform Screening Panel. Kwaku?

DR. OHENE-FREMPONG: Well, it's late in the afternoon, and there's nothing better to keep you awake than a discussion of thalassemia, so -- [Laughter.]

DR. OHENE-FREMPONG: -- so, feel free. The committee received a nomination to include alpha thalassemia -- specifically, Hemoglobin H disease -- in the panel of disorders for which screening is recommended. The proponent for the nomination was Elliot Vichinsky, who's a pediatric hematologist at Children's Hospital Oakland. This came in April. And, as I said, the condition is specifically Hemoglobin H disease, which is part of the larger alpha thalassemia syndromes, hemoglobinopathy, and this screening method will be using the same dried blood spot that we use. And the treatment strategy

here is for early referral for comprehensive care before the onset of illness. Just some brief discussion of alpha thalassemia. It's important, in this case, for us to think about the molecular genetics of this disease, because that is -- the diagnosis is actually based -- it's easier to make now because of the availability of molecular genetic techniques. Human hemoglobins, as most of you, I'm sure, are aware of, go through developmental changes. And represented in this slide, and those black bars, are -- these bars -- on this one, it's the short arm of chromosome 16, where there's a group of genes that we refer to as the "alphalike genes." They start with an embryonic alphalike globin gene, and then the two duplicated alpha genes, which are part of the mature or postnatal hemoglobins that we see. Then, on another chromosome, on the short arm of chromosome 11, the so-called betalike genes, which also include an embryonic epsilon chain and two gamma chains, which are part of fetal hemoglobin, and then a delta gene, which is part of a minor hemoglobin, A2, that we all make in

a small amount, up to about 3 percent, in general. And then, the more recent form of this complex is the beta gene, which is a component of the main hemoglobin A that most people carry as their normal hemoglobin. So, these globin chains with their genes get expressed at different times during development. The embryonic globins are expressed very early, usually within the first 6 weeks or so of gestation. Alpha globin chain production, though, starts early and remains very high all the way through, because, as we saw, alpha globins are needed for all the adult hemoglobins that we make, or the more mature hemoglobins. Gamma globin chains, which are part of fetal hemoglobin, reach a peak in the early part of pregnancy, about 12, 16 weeks, then they begin to slowly decline. And in the third trimester of pregnancy, gamma globin production actually begins to go down before the baby's born. This line here marks birth. And then beta globin expression or production picks up in the third trimester, and soon after birth it becomes the predominant of the betalike globin chains that is produced together with alpha globin to

make hemoglobin A. So, part of our discussion will involve this gamma chain production and alpha chain production. I'll just move through. Fetal hemoglobin is the predominant hemoglobin during pregnancy for the fetus. And again, it's made up of a product that comes from the alpha globin and the gamma globin; both of those genes are duplicated. We have two gamma globins genes each, and then normally we also have two alpha globin genes each, and they produce fetal hemoglobin. Then, as the baby's getting older, again the same alpha globin, now together with beta globins, produce the hemoglobin A. At birth, about 60 to 90 percent of our hemoglobins is fetal hemoglobin, and we make 10 to about 40 percent hemoglobin A, and there's the minor hemoglobin A2. By 1 year of age, we have switched the production of gamma chains, and therefore fetal hemoglobin, to mostly production of beta -- beta chains with the same alpha globin, to make mostly hemoglobin

A; about 96 percent of our hemoglobins by 1 year of age is normal hemoglobin A, and the fetal hemoglobin is now a minor hemoglobin. Now, thalassemia is interesting, because, unlike the structural hemoglobins, like -- abnormal hemoglobins like sickle hemoglobin, they're really just a production defects, that you don't make enough of a particular globin chain. So, alpha thalassemia results from a deficiency in alpha globin production. Hemoglobin F, as we said, is made up of alpha and gamma, and when there is alpha thalassemia, it affects the alpha globin production, but does not affect the gamma globin production, which, as you saw, is made by genes on a different chromosome. So, in the red cell, when you have alpha thalassemia -- say, in a newborn with a predominant fetal hemoglobin -- there is a lot of excess gamma chains that can not pair up with any alpha globin. And we can see that it is the excess alpha chains that we actually identify as Hemoglobin Barts in a newborn. Globin chains are most stable as tetramers, so if they don't find their partner globin to pair up with, they tend to pair up themselves and

then form -- the two dimers will come together to form tetramers. So, four gamma chains come together as Hemoglobin Barts. There's a lot -- apostrophe here just to remind people, this was named after a hospital in London, Bartholomew's, so it's always been called Barts. Normal Hemoglobin A, alpha 2, beta 2, if there is alpha thalassemia, the alpha chain is deficient and there is excess beta globin, and you end up with tetramers of the beta globin, and that's what we call Hemoglobin H. So, both Hemoglobin Barts and Hemoglobin H actually both signify a deficiency of alpha globin to bind with these. So, depending upon what age you are testing, looking for severe alpha thalassemia, you may see a large about of Hemoglobin Barts in a newborn, but because fetal hemoglobin production dwindles after the newborn period, in an older child or an adult what you expect to see will be Hemoglobin H. As I mentioned before when I showed the diagram of the globin genes, in the normal situation we inherit from each parent a twin of alpha genes per

chromosome. Most of the alpha thalassemia that we see in the world are from deletions of actual genes, so we tend to determine alpha thalassemia by counting the number of genes. The most common form of alpha thalassemia is designated "alpha plus," and in this case, only to mean that there is at least some alpha gene production. And in alpha plus thalassemia, instead of two alpha globin chains, one of them is deleted, and so, you end up with only one. Then, there's a second group of deletion, or alpha thalassemia, is alpha zero thalassemia, in which both of the globin -- alpha globin genes have been deleted. Then, about 10 percent of the cases of alpha thalassemia are nondeletional syndromes in which there're mutations that either produce a reduced amount of alpha globin, or sometimes an abnormal alpha globin, or sometimes no alpha globin at all. The most common of these types of mutations, or nondeletional forms of alpha thalassemia, is the production of a hemoglobin called Constant Springs, and hemoglobin Constant Spring -- there are about another five or six varieties of

this -- there're interesting in the sense that the mutation that produces Constant Spring is the termination codon. The alpha globin produces 141 amino acid globins, and when the terminal codon -- the termination codon is mutated, then the transcription does not stop at the termination codon, but it goes on to the next stop codon, which is about 31 codons down the line. So, hemoglobin alpha Constant Spring is actually a longer alpha globin chain than the normal alpha globin. It is not normal, and so, it effectively is a defective gene, and the product that comes out of it is defective, so you end up phenotypically having a decrease in normal alpha globin, and therefore, alpha thalassemia, although it is not a deletional problem. There are different types of these elongated alphas globins, all of them mutations of the terminal codon. So, again, in a normal person, then you inherit these two pairs of alpha globin genes, and you have four. There are people who have inherited the alpha plus thalassemia from one parent and the normal pair from the other parent, so they end up with one

gene deleted, and they have three alpha globin genes. It is clinically referred to as "silent carrier of alpha thalassemia," because it's not hematologically apparent. They tend to have a normal hemoglobin, a normal MCV, so they don't have a thalassemic phenotype. But, populations in which this type of alpha thalassemia is common tend to have a slightly lower hemoglobin level in their normal ranges compared to other populations. So, for instance, people have known for a long time that if you were to test thousands of people from Africa for what their normal hemoglobin range is, it's a little lower than it is in, say, Northern Europeans, and the reason for that is the high prevalence of alpha thalassemia, mostly a silent carrier. Then, there is a syndrome -- two syndromes that are referred to clinically as "alpha thalassemia trait." And here, phenotypically you can see them with a mild anemia and a lower MCV, sort of typical beta thalassemia trait-type picture, except that, in fact, in most cases in this country, when you see that picture, it is more due to alpha thalassemia than beta

thalassemia. In this case, there are two genes that are deleted. And this can come about when you are homozygous for the alpha thalassemia genotype, in which case you are inheriting one from each parent, or you are heterozygous for the alpha zero thalassemia type of alpha thalassemia, so you inherit that from one parent, and the normal allele from the other parent. Now, these two are important to distinguish, because this is a homozygous condition, and, at worse, you are inheriting two normal alpha genes, and therefore, you have a mild anemia and a lower MCV, but you're otherwise clinically stable. This is a heterozygous condition; but, as we can see, if you inherit the homozygous condition -- I mean, the condition where alpha zero condition from one parent and the alpha plus from the other parent, you end up with only one functioning alpha gene. So, three genes have been deleted. And if you remember, now as such a huge deficiency of alpha chains, the other chain, either gamma or beta, is now in excess, and so, you are going to form tetramers -- abnormal tetramers formed by the excess chain.

So, this is Hemoglobin H disease, but in newborn screening we don't really see the Hemoglobin H. What we see is the excess gamma chain, or Hemoglobin Barts. But, when you start making hemoglobin -- supposed to be making Hemoglobin A, where there will be excess of the beta globin chains, then we see the Hemoglobin H. So, in the newborn period, Hemoglobin H disease is actually seen as an increase in Hemoglobin Barts production. The most severe form of alpha thalassemia is where you inherit the alpha zero thalassemia from both parents and end up with no normal -- no alpha globin gene, and therefore, no alpha globin chain production. Since fetal hemoglobin and Hemoglobin A both rely on alpha globin binding with a betalike globin, this is generally considered a condition that is not compatible with life, but actually a few children have been diagnosed prenatally and have been -- pregnancies have been sustained with in utero transfusions; and, of course, they have to be continued on transfusions if they're lucky to be born, because they don't make any of the normal hemoglobins. The -- just a little genetics -- the

mechanism of forming these deletions is somewhat interesting. When you have a duplicated gene, where most of the structural sequences are the same, sometime during meiosis there is a misalignment of the alleles, and, in this case, instead of -- this is suppose to be yellow -- instead of the yellow allele lining up with the yellow and the green with the allele and then going through a little bit of recombination, when there is this misalignment, you can have a crossover event where, if you start with this pink allele -- sort of depicting them as pink, maybe for mom and the blue from dad -- and there is a crossover event here, what will happen then is that when they separate -- let's start with the blue one, you're starting with one yellow gene, and now crossing over here, and continue over here, you end up with an allele that now ends up with three alpha genes, and then the other side will start at the pink end, cross over here, and you end up with one alpha gene. This is the most common way in which the single gene alpha thalassemias are formed. And depending upon where the crossover occurs, we characterize them by how much of the genetic

material is deleted. So, for instance, in people of African descent, the most common type of deletion, or alpha thalassemia, has a 3.7 kilobase deletion, and the less common type is the -4.2 kilobyte deletion, which is more common in Asians and people from Mediterranean areas. Then, the alpha zero thalassemias are caused by larger deletions of this genetic material, so that both of the alpha globins are deleted. And they are also named after either the length of the deletions or different parts of the world where they were discovered. So, for instance, this long deletion is called the "Southeast Asian deletion," and another one, "Mediterranean deletion;" they all have different deletion points. So, Hemoglobin H disease, as we mentioned, is a situation where you end up with one gene; or, if you inherit this Constant Spring from one parent, it is typically linked to one normal alpha globin gene, and you inherit the alpha zero thalassemia from the other parent. You end up similar to the hemoglobin H here, which is combining the alpha zero and alpha plus,

because you have -- you're missing two functional genes, and this is also dysfunctional, so you end up with only one functional globin gene. So, these two conditions become clinically similar, in that there is excess beta chain or excess gamma chain, depending upon which age you're testing. This busy slide really just describes whether the -- the geographic distribution of these different forms of alpha thalassemia. And as you look at, say, sub-Saharan Africa, there's almost no alpha zero thalassemia in Africa -- sub-Saharan Africa; and the alpha thalassemia that we see there is mostly the alpha plus variety, almost 100 percent of them being the alpha 3.7 deletion. The gene frequency can be quite high, as high as -0.3 in some populations in Africa. Then, the Mediterranean basin has a combination of both the alpha zero thalassemia, with both genes deleted, and the alpha plus, all the way through. But, you can see that the distribution around the world for these alphas thalassemia syndromes sort of falls in the tropical/subtropical belt of the world, the same sort

of distribution that has been historically associated with endemic malaria. So, it is suspected that alpha thalassemia also provides some protection to children from -- dying from malaria. But, exactly how this effect actually occurs is not well understood; but it must be powerful, because alpha thalassemia is supposed to be the most common human genetic disorder. So, there are millions and millions of people in the world with these conditions. Luckily, most of them inherit the alpha plus variety, they're only slightly anemic, if anything at all, or they are silent carriers. But, even a silent carrier must provide some protection, because there are so many of them surviving. So, I want to just move on quickly. These are examples of the alpha zero thalassemia in different populations. Some studies done in California, the California pilot data, and then some studies from Canada and also Hong Kong, listing the types of deletion, or alpha thalassemia syndromes, that have been seen. So, the pathophysiology of hemoglobin H disease, is a condition in which you have a deficiency

of the alpha globin messenger RNA, because the genes are not there, and therefore, the resulting chains are also deficient; and the alpha-to-beta ratio, which is generally close to 1, meaning that the products from the chromosome 11 beta genes and the chromosome 16 alpha genes tend to balance quite well. But, in this case, there is an imbalance because there's an excess of the beta. In fetal development, there's the excess gamma globin chains, and it forms the Hemoglobin Barts, and, as we switch, we form the Hemoglobin H. Hemoglobin H itself is, unfortunately, not benign. It has a high affinity for oxygen, meaning that it does not oxygenate tissues well, and it really has almost no oxygen delivery to the tissues. It is unstable. When it's oxidized, it forms precipitates inside the red cells, and this we can also test by subjecting red cells to supravital stains, and you can actually see inclusion bodies in the red cells. Those precipitates also cause early death of developing red cells, and so, there is ineffective erythropoesis in the bone marrow, and they also cause

membrane damage. So, clinically, what we see in Hemoglobin H disease is a hemolytic anemia, not caused so much by the thalassemia, meaning the production defect, but caused by the excess chain that is left hanging around in the cell; the Hemoglobin H is what is causing the disease. It's not the alpha thalassemia, which is just reduced production of the alpha chain. So, this disease translates into a chronic hemolytic disease. The largest series of people with Hemoglobin H that has been published was published by Prawase Wasi in the '70s; he described a clinical picture in about 1,000 patients, about 500 of whom were adults, and almost the same number as children. What is interesting is that the age of presentation for these patients, some presented at birth, and some did not present until their 70s. Now, presentation at birth would be somewhat expected, because fetal hemoglobin is the predominant hemoglobin at birth. So, if you're not making enough normal fetal hemoglobin, you would think that children will all be born quite anemic. But, that's not the case. The degree of anemia at birth

varies greatly. Some of this is still not understood. We know that those with the deletional forms tend to have a little milder clinical picture, and those with the nondeletional forms tend to have a more severe picture. Only 24 percent of the cohort in Hong Kong, 114 patients, presented with symptoms. The other 76 percent were discovered incidentally, meaning that, for some reason, they had a CBC, a complete blood count, done, and they were discovered to be anemic, or that they were going through routine testing; but they were not symptomatic. When the growth of the young children in this group were looked at, only 13 percent of them seemed to show severe growth failure, being less than third percentile. So, it is known that this is a disease with very, very variable cause, and that most patients are only discovered routinely, and not because they are ill. Here is a hematologic picture for -- I think this is the group that were put together between California group, the group in Canada, and also the

Hong Kong group. So, in the males, hemoglobins are running -- and this is grams per liter, most of us are used to grams per deciliter, so, this would be like 11.1, or, in this case, 111 -- so, hemoglobins in the 10 to 11 range for the males, in the -- about 9-point-something in the females. This is the deletional forms, maybe slightly severe in those with the nondeletional forms. So, the anemia would be described as either mild or moderate. The hallmark is that it is microcytic hypochromic anemia, so the MCV's are low, in the 60s in the deletion forms here, and the MCH is very low. The low amount of hemoglobin in the red cell may actually be what is giving them some protection against malaria. This is a typical smear, on the left side, very hypochromic microcytic cells, showing a lot of poikilocytosis, just many different forms, looking sometimes like very severe iron deficiency, except in this case, because it is a hemolytic disease and the born marrow is working hard, you will see nucleated red cells sometime from the smear. And this is a stain that shows some of the exclusion bodies in this

disease. So, typically, the clinical course shows a wide spectrum. Acute anemia sometimes can occur with febrile illness, and -- or sometimes when they're exposed to some oxidizing agent. So, just like [inaudible]-deficient patients, Hemoglobin H disease patients are sometimes advised against certain types of medications. Their anemia -- their acute anemia in febrile illness is mostly hemolytic, they tend to hemolyze more and have a high bilirubin at that time. But, sometimes, it may be caused by erythroid aplasia, typically an infection from parvovirus B19, which can drop your reticulocyte count to very low levels, and a transient anemia that almost always resolves. A large number of the patients will show splenomegaly, but enlarged spleens -- I mean, livers -- are not common. Iron overload, as in all chronic hemolytic anemias, is also common. And this is not iron overload, typically, from chronic transfusion therapy. Patients who are severely anemic with ineffective erythropoesis tend to absorb more iron in their diet than normal, and even without transfusions, over time

would develop iron overload. Also, formation of gallstones because of chronic hemolysis is common in this condition. And in pregnancy, it is known that the anemia may get worse; also there's a higher incidence of -- prevalence of preeclampsia in this group, and sometimes patients severely anemic have developed congenital -- I mean, congestive heart failure during their pregnancy. So, treatment for this disease, and as the nomination said, is really primarily preventive and supportive. Most patients are placed on folic acid supplementation just to be sure that their ability to produce red cells is not compromised by folate deficiency. Families are educated about signs of acute anemia, particularly for young children when they have a febrile illness; and when their spleen becomes palpable -- families will be taught how to palpate the spleen so they can report it if it becomes acutely enlarged, as avoidance of oxidative medications. Because their picture sometimes looks like iron deficiency, and particularly for those with only a mild anemia, there's a tendency to treat them

repeatedly with iron, and often parents are accused for -- about not giving the iron, because the child's hematology picture does not change. They should not be given iron unless iron deficiency is documented. And they should be monitored, particularly as they get a little older, into their teens, for iron overload, and if their iron overload reaches a certain level, then chelation therapy may be necessary. Almost all of them will require episodic red cell transfusions sometimes. If they're closely followed, and if they develop acute -- episodes of acute anemia, they may require transfusions. A few patients, not the majority, actually are chronic transfusion-dependent, meaning that they maintain such a low hemoglobin level that they need to be supported if they're going to grow well at all. During pregnancy, the women need to be monitored. Occasionally, patients develop such a large spleen that they develop what we call "hypersplenism." The hemoglobin's platelet counts and white counts tend to be low because they're all being captured in the spleen. And if that becomes a condition to require

transfusion, then they may be splenectomized. These are indications for chronic transfusion. They're very typical. That's the same thing we would do, say, considering somebody with severe beta thalassemia -- the severe anemia, poor growth, boney changes; to prevent these, chronic transfusion therapy may become necessary. The screening test in the neonates, the same test that had been done for sickle cell disease and other hemoglobinopathies pick up Hemoglobin H disease. So, HPLC and isoelectric focusing, both of them can pick up the presence of Hemoglobin Barts. And the question that is really -- must be decided is, Just what level of Barts depicts Hemoglobin H? And the amount of Barts varies between the different tests. But, each test can be set up so that it has a range of Barts that actually would make the suspicion of Hemoglobin H very, very high. There are other less common tests. Typically, when isoelectric focusing is done for the diagnosis for sickle cell disease and other hemoglobinopathies, it is not a quantitative test, it

is qualitative; it tells you what types of hemoglobins there are. HPLC, of course, is quantitative. So, to use IEF as your screening method, if you want to pick up Hemoglobin H disease, you need to determine how much Barts you've seen. And you can then have to -- you may then have to scan your IEF gels -- or, films -- to determine how much Hemoglobin Barts is being made. So, for IEF, it would be a two-step method -- the usual, plus scanning -- and for HPLC, you would get the quantity. Different levels of Barts had been determined. And I might say that these were done -- some of them are quite old, from old electrophoresis, and the quantitation of the Barts here is also quite different. So, for instance, the children with silent -- who are silent carriers, who have three alpha genes, have Barts in the range of 1 to 2 percent; those who are missing two genes, have Barts in the 3- to 10-percent range; and those with Hemoglobin H will fall more into this range. The California pilot study determined that their cutoff range for the HPLC method for Hemoglobin H

was 25 percent. And, as I said, these need to be validated based on the methods that you have. But, it's something that is doable. Nowadays, to confirm Hemoglobin H disease, we don't do globin synthesis studies, but we actually count the genes, and there are several molecular techniques that have been used to confirm these gene deletions. And where there are nondeletional, then one has to look for specific mutations, and there are PCR methods for doing that also. So, the largest pilot study that we have is the California study, and this is a report that came out early this year from the California group. And I think the next slide summarized what they have found. They have a -- California has a reference lab for hemoglobinopathies that confirms findings and look for unusual findings in their screening program. So, for the hemoglobin genotype that they have diagnosed between '98 and 2006, they had picked up about 700 with sickle cell disease, for an incidence of about 15.2 per 100,000. And the second most common hemoglobinopathy they had picked up is Hemoglobin H disease; 11 per

100,000. And then the beta thalassemia syndromes and a variety of mutations. So, clearly, this is not an uncommon finding in the California screening program. Will it be the same in other States? It all depends upon the population mix. I think the States that have a more global mix of population will have a lot of alpha thalassemia and Hemoglobin H disease will be common. So, to go back to the origin, how does this nomination sort of meet the questions that we tend to ask about disorders? It's a condition that is medically serious. Yes, for some of them, it is serious, a fair percentage, even though there is a -- clinically, a variable cause, and some are actually mild. Are pilot dates available? Yes, the California experience has a very strong set of pilot data. Is the clinical spectrum known? I think it is known, but it's not easily predictable; meaning that if you diagnose a baby at birth with a large amount of Hemoglobin Barts that fits Hemoglobin H, there is no easy was at that time to determine whether this baby is going to be severe or not. If the baby has a

nondeletional form, like say hemoglobin H Constant Springs, you can sort of say that that tends to be a more severe condition, but only 10 percent of the patients have the nondeletional form. So, that ability to predict how the baby is going to do is not that strong. As the screening test specificity -- again, the cutoff of 25 percent is not an exact science; there may be some children with a lower level of Hemoglobin Barts who may be missed if that cutoff is used. California initially used 14 percent, if I'm -- if I remember correctly, as their cutoff, that about 14 percent is suspected Hemoglobin H disease. After a number of years of experience, they were including too many babies who did not have Hemoglobin H disease, but had the two-gene deletion, so they raised the bar to 25 percent. So, again, depending upon what method is used, one will have to validate what the cutoff point would be to try to avoid a lot of the false-negatives. Severe cases are easily identifiable over time. The way to call somebody "severe Hemoglobin H disease" is really just the -- their baseline

hemoglobin. If a child, as he's growing up, maintains a hemoglobin that is less than eight or particularly less than seven, you know that they have a severe form of this condition, and there will be talk about chronic transfusion or not. Those who have a higher level of hemoglobin tend to have a milder course. Treatment, asymptomatic. Most patients do not require -- other than the folic acid supplementation, do not require any ongoing care beyond that. They need frequent evaluations and reinforcement of education on what to do when the child's condition changes. So, as a summary, the current newborn screening labs are truly capable of diagnosing the presence of Hemoglobin Barts, and they can determine the quantity of it with little or no additional equipment, based -- depending upon what they're doing now. I think State programs can include specific training for quantification of Hemoglobin Barts and reporting it. Some States now report the presence of Hemoglobin Barts, although typically they don't report the quantity of it. But, if they knew how to determine

the quantity, they could report it, or we could educate all programs to just report what they see. And then those with -- who meet whatever the cutoff is, could be referred to reference labs to determine what type of alpha thalassemia they have. And the physicians and families need education and counseling about alpha thalassemia. So, I think one of the real questions is whether this is a disease for which we are actually testing now, except that most programs have not recognized it, and therefore, what we need to do is really just elevate its profile so that they look for it and train their labs and educate the physicians to refer it along whatever channels they have so that these patients can get care, or whether to consider this a new and separate disease for which they need to tool up. That's the end of my presentation, I think. Thank you very much.

DR. HOWELL: Kwaku, thank you very much. I think we're all ready now to take the boards on hemoglobinopathies, and so forth --

[Laughter.]

DR. HOWELL: -- and then -- now that we're all refreshed on what comes up and what goes down, and so forth. [Laughter.]

DR. HOWELL: The -- your committee that you chaired has looked at this, and what recommendation would you have about this nomination to the committee?

DR. OHENE-FREMPONG: Well, if there are other members here, they could chime in on it. I think that the fact that the capability to diagnose this condition exists, I think generally, if I remember correctly, was that this is a condition for which we can just adapt the current programs to report, and that there is some education -- educational efforts will be needed. I think some programs will need to just add their ability to quantitate Hemoglobin Barts to whatever methods they have now. But, I think that, with just education and a little more training, that this is a condition that most programs are capable of determining and reporting. And the same care teams that follow other children with hemoglobinopathies are

the ones that would manage this disease also.

DR. HOWELL: Yeah, can it wait just one second and then I -- Michelle, the recommendation that came from your committee is actually in the minutes, and so, Michelle might want --

DR. PURYEAR: So, I was going to read the recommendation for the --

DR. OHENE-FREMPONG: Oh, okay.

DR. PURYEAR: -- internal group -- work group. It says, "The work group recommends that this nomination should receive a complete evidence review based -- focusing on moving the condition Hemoglobin H to the core panel from the secondary panel. The combination of incidence, potential severity, and available effective treatments for the most severe forms of Hemoglobin H disease make it worth considering for newborn screening."

DR. SKEELS: I just want to say that, like most State screening labs, we use isoelectric focusing for the primary screen, and then HPLC to follow up. And the last thing you said in your

presentation is really, really important. We're looking at these babies, we see all of these Barts, they're everywhere, and then we take no action on them. And we've always felt uneasy about that. And, as you also said, for some of us it would be simply a matter of increasing our HPLC throughput and following up on those infants. For others, it might involve using HPLC as a primary screening method, which we would also welcome, if there were a way to do this in a high-throughput manner, which I think is what California did, if I'm not mistaken.

DR. OHENE-FREMPONG: California uses HPLC as their primary screening method. One thing, though, is that it is not a -- you cannot diagnose this condition depending on a second sample that comes a few weeks later, because the Barts will be going down right after birth. So, it's not one for which we ask for a repeat sample. So, your initial sample and your quantitation should be based on the sample at birth, because that will have the highest level of Barts. The Hemoglobin H is not going to be picked up until the child is much older, when the beta globin production is high and the

gamma chain production is very, very low. So, the initial reason to refer a baby for molecular testing would be based on the sample at birth.

DR. HOWELL: So, Michael --

DR. OHENE-FREMPONG: I don't want to say that it cannot be done by IEF, because there are methods for quantitating the IEF results also. DR. HOWELL: So, Michael, I gather your comment would support Kwaku's committee's recommendation that this go forth for a formal evidence review, and, based on that, then move this basically from a secondary to a primary condition. Is there further discussion about that recommendation? The recommendation would be to send it forth for a formal evidence review, and, obviously, that review would come back to the committee, we would hope, with considerable alacrity, and we could look at it again. Are there further comments or disagreements? Piero?

DR. RINALDO: I went back to the -- to the report of the expert panel, and the final comment of

assessment was, when it was recommended that all variants are considered as secondary targets, that the expert group reaffirmed prior recommendation and all clinical significant results from a newborn screening be reported. So, it goes back to a point, that apparently this is a finding that apparently most programs just look at it and do nothing about it. So, I really think it seems to be a fairly modest incremental effort to achieve a better status and provide better care.

DR. HOWELL: Any further comments? I think the question of equipment and what people are actually doing in the technology there're using and how they would have to modify it to quantitate, in other words -- I know many States do report -- Florida reports Barts, for example, but not quantitatively. And, so, I gather that's some of the thing -- Any further comments?

DR. RINALDO: Actually, I do have one, and it goes back to the discussion this morning at the [inaudible] Committee. I would like to know more about

the capability for molecular confirmation. This morning we talked about the regionalization of certain services. It seems to me this could very well be an excellent example of something that could be set, instead at lab by lab, but could be set on a regional basis.

DR. OHENE-FREMPONG:I agree with you. I think that, you know, it would be too much for each lab -- each State to develop these molecular techniques. And I think, for quality control and everything else, just a few labs in the country should be able to handle the volume.

DR. HOWELL: And that, conceivably, could be a recommendation that could come forth out of the evidence review.

DR. PURYEAR: [Inaudible] we need to know if Ned and Denise are on the phone.

DR. HOWELL: Ned, are you and Denise still with us?

DR. PURYEAR: We can't hear you.

DR. CALONGE: You can't? Hold on.

DR. PURYEAR: Oh, now we can.

DR. HOWELL: Now we can. Excellent.

DR. CALONGE: I'm sorry --

DR. DOUGHTERY: This is Denise --

DR. CALONGE: -- you can't?

DR. DOUGHTERY: -- I'm still here.

DR. HOWELL: Oh, outstanding. Would you -- would either of you like to comment about the recommendation of Kwaku's committee?

DR. DOUGHTERY: I'm in support of moving forward for an evidence review.

DR. CALONGE: I agree, as well.

DR. VOCKLEY: [Inaudible.]

DR. HOWELL: Yeah, Gerry?

DR. VOCKLEY: Just a couple of comments. First of all, I'm also in favor of moving it forward. I would like the Evidence Review Committee to give us a more complete picture of that first year of life, and what it is we're preventing by identifying it, say, in the newborn period versus 1 year of age. That would really help, I think, cement the final recommendation. The other piece of it, though, is relative to the molecular testing. I think you're looking at

the molecular testing -- and this point almost as -- I mean, that really becomes the confirmatory diagnosis. And so, that's at the discretion of the clinician now seeing the patient. In follow-up, though, State labs could, in fact, make the decision that they want to -- because they can, they want to go ahead and do the final diagnostic testing. But, we have really either a private -- a primary test of isoelectric focusing, which we've heard can be followed up by HPLC, or can go to the molecular testing. So, I'm not sure that the ability -- the reason I'm saying this is, I'm not sure that the ability of -- to, sort of, influence who's doing the molecular testing needs to be a major part of what the committee's decision is. I think it's going to be -- it's going to handle itself in this setting.

DR. HOWELL: This is jumping ahead a little bit, but one of the issues that this committee is going to have to eventually look at is the availability of confirmatory testing that is surfacing in many private physicians' labs, when they get a patient and they're having trouble getting confirmatory testing. Mike?

DR. WATSON: It's actually interesting that the Oakland Children's Hospital lab was a national referral lab that was federally supported up until about 2 or 3 years ago. And there may be a lot of information about really what it take to have a reference lab of that type. I don't think they got enough referrals, was their problem. People didn't know they were there, so they sort of faded away. But, they were certainly there for quite a long time.

DR. HOWELL: We can request the review committee to look at that, and so forth, and include Gerry's comment. Any other questions or comments from the committee?

DR. CALONGE: Ron, this is Ned. Can I just follow up on another -- on the first-year-of-life comment?

DR. HOWELL: Please do.

DR. CALONGE: So, I think that's an important issue, to make sure that we're considering the benefit of early detection; that is, the detection of asymptomatic kids. I just remember there was one of

the slide that said that treatment was mainly symptomatic; and so, that -- I'll just tell you that -- if that was the only thing I saw, I would say, "Well, if you only treat it when it becomes symptomatic, what's the value of early detection?" So, that's one thing I hope that review committee keeps in mind. And the other is to make sure that, if we do diagnose it early and have confirmatory testing, and treatment is symptomatic and early -- treatment of asymptomatic conditions doesn't change the outcome, I would want to make sure that we're not increasing treatment just because we have the diagnosis and not necessarily improving health. So, you know, kind of the potential downsides of early detection -- early detecting conditions when we wouldn't otherwise do that.

DR. HOWELL: Thank you. Michelle has made notes of that, in addition to the potential early benefit, the potential downside. Any other members of the committee -- Denise, do you have any further comment?

DR. DOUGHTERY: No.

DR. HOWELL: Okay, thank -- having no

comments from the floor, we'll go to the microphone. And Sarah is the first in line.

MS. COPELAND: Yeah, Sarah Copeland from the Iowa State Newborn Screening Program. I just wanted to reiterate what Gerry said about the fact that the mutation really needs to be considered confirmatory testing, because it's not part of the screening test. And at the State level, I think we're really trying to differentiate that. And also, I'm sure -- as I'm sure the review committee will find, but there have been some good articles recently, at least on iron deficiency anemia, I'm not sure about anemia in and of itself, as a determinate for developmental delay.

DR. HOWELL: Fred?

MR. LOREY: Fred Lorey, California. Excellent talk, thanks very much. As Dr. Frempong mentioned, we've been screening since 1997; have probably screened 5 million kids now. And I wanted to accentuate what was said earlier. It's really very easy, if you're doing HPLC, to adapt your system. We really did nothing to our

system. And this came about both -- pressure from the hematologists in California, who saw a lot of patients, and our own chemists, who saw the Barts coming off and didn't feel comfortable not reporting it. So, really the only thing we had to do in the pilot was find that magical cutoff; and once we did, it works really well. We don't know of a false-negative yet; the false-positive rate is extremely small, and they're going to be 2G deletions, if they are. And the second thing, an interesting thing that we didn't even think about, was, we've actually detected now ten cases of alpha thal major. So, some are live bursts; they make it to the newborn screen. And, two of those kids were transplanted and are doing fine. So, that's kind of an unexpected benefit; it's just a small portion of the total, but --

DR. HOWELL: But, it's 10?

DR. PURYEAR: Yeah.

DR. HOWELL: So, when you're multiplying by 5 million babies -- 500,000 babies a year, it gets to be real -- a real thing. Brad?

VOICE: Yeah, I too appreciate the talk, Kwaku. The -- having come from a State that debated this many, many times, and seeing other States that have debated this, I don't think that, in the past, there's been complete concurrence of the hematologists that this is something -- so, it'll be interesting to bring that perspective to the review. Also, for those states doing second screens, confusion about other hemoglobins that might exist with that -- in that same location on first, can be clarified by the second specimen not showing it; it sort of confirms it was Barts on the first.

MS. WISE: Sheila Wise from Washington. We've been doing hemoglobin screening since 1991 and been reporting out, actually, low level of Barts and how to amp up our cutoff. But, my question to you, Dr. Frempong is, Do you think it's important to distinguish between the deletional forms and Constant Spring at the newborn screening level, since they are different clinically?

DR. OHENE-FREMPONG: Probably not. I think

that the first -- the question about the first year -- you know, during my fellowship, which is longer ago than I want to remember, my mentor, Eli Schwartz, when he was at Jefferson about 14 years before, had -- they had done some newborn screening at Jefferson, and now molecular methods for determining alpha thalassemia came about. So, he wanted me to go and find some of the children that they suspected had alpha thalassemia, but had no way of confirming, other than the fact that they had [inaudible] at birth. And I found nine of them. Everyone of them had received more than 10 iron-deficiency treatments through their life. They had repeatedly been treated with iron by their physicians and the parents were just ecstatic to find out that it wasn't the iron problem, because the doctors never believed that they gave, you know, iron. So, in this case, making the diagnosis early actually stops unnecessary treatment. It's not that we'll overtreat them; we will actually manage them properly, because they tend to be overtreated for iron deficiency that they don't have. But, I don't think that we need to

distinguish between the nondeletional and deletional. I think that, again, from a clinical point of view, you know who will be severe, just based on the degree of hemolytic anemia. I think it's of interest, and genetic counseling and everything else, to know specifically what the gene defect is; but, from a clinical point of view, and certainly not in the newborn period, it's not necessary.

DR. HOWELL: We've had an excellent discussion, and the -- I would like to call for a vote on that recommendation. Let me point out, a question was asked, just before break, about voting members; and that is, is that the ex officio members of this committee that represent the Federal agencies are voting members, and the liaison persons are not. So, can we see those favoring recommendation that this be sent forward for formal evidence review? And Michelle has made comments about the questions you've raised that you would like focused on in that review. Can we see those favoring such a recommendation?

DR. CALONGE: I would say aye, or my hand's up.

DR. HOWELL: And --

DR. PURYEAR: And Denise?

DR. HOWELL: -- and Denise is your hand up?

DR. DOUGHTERY: My hand is up.

DR. HOWELL: Good. [Laughter.]

DR. HOWELL: So, okay, any opposition? It's a unanimous recommendation, and we will send that forward, and so forth.

DR. CALONGE: Are you still there?

DR. HOWELL: And we'll see you at 7:30, for those who want to eat. And we'll see you at 8:30, for those who have eaten.

[Whereupon, at 5:06 p.m., the meeting was adjourned.]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
HEALTH RESOURCES AND SERVICES ADMINISTRATION
Meeting of the Advisory Committee on Heritable Disorders in Newborns and Children

Friday, September 25, 2009, 8:30 a.m.

Bethesda Marriott
5151 Pooks Hill Road
Bethesda, Maryland

PROCEEDINGS

DR. HOWELL: Good morning, ladies and gentlemen. Welcome to the second day of this meeting. We had an extremely productive day yesterday. Let me make a few comments before we hear about the important effort on residual dried blood spots. It was recommended by the committee yesterday that we draft a response to the President's Council on Bioethics that would be prepared and reviewed by this committee and submitted for publication so those comments could become indexed when people look. And I've asked Tracy Trotter to chair a small group to draft such a paper, and he will be ably assisted in that area, I'm pleased to say, by Dr. Burton and Dr. Fleischman, who will work with him, and I would like to participate in that. So we can expect to see a draft of that response at our next meeting and so forth. And the second thing is we had discussed the fact that there is so much information and material emerging on datasets and registries and so forth that this committee needs to have a group that looks at that. And again, that group is forming and will be organized with professional help from HRSA, the NIH, CDC, in addition to other members of this committee and so forth. So we'll expect to hear from that. Today, we are going to focus our attention this morning on the use and storage of residual dried blood spots, and we'll hear a report from the workgroup. Now each of you has received a copy of their white paper that this group has been working on for quite a long time, and it's a very thoughtful document. But we'll hear a summary of that. And what the plans are is we'll hear a summary of that. We'll discuss the paper that each of you have, and this committee should have some recommendations about that paper and the recommendations that are contained therein. So, Jana, Brad, Harry?

MS. MONACO: Good morning. As you all know, this issue of the use and retention of dried blood spots is such a prominent topic in this arena. So we are here to give you a little overview of what was worked on and consolidated

what is a 70-, 80-page paper into this 20-page paper into a brief summary for you today to understand and have an idea. I am here with our workgroup chairs -- Dr. Brad Therrell, who is the Director of the National Newborn Screening and Genetics Resource Center, and Dr. Harry Hannon, who is the Emeritus Director of the Newborn Screening Lab at CDC in Atlanta. And the rest of our workgroup members is Don Bailey from Research Triangle and he is a consumer representative as well; Dr. Alan Fleischman of the March of Dimes; Ed Goldman, who is an attorney at the University of Michigan and the CEO of the foundation developing their biobank; myself; and Dr. Bent Pedersen, who is the Director of the newborn screening program in Denmark and the director of their biobank; and Sharon Terry, who is the CEO of the Genetic Alliance. And we can't forget Alaina Harris, our HRSA staff member, who has worked diligently to keep us on task and productive. I just wanted to briefly go over the process of the paper preparation, and the background is the committee had asked for a draft outline for us, for the committee to review. So back in February, that outline was provided. Dr. Hannon came and presented that. The next step, the committee, if you recall, approved the outline and recommended a workgroup be formed, and that's where we all came in. We have worked, and we've reviewed. A lot of work went into reviewing and validating the current State storage systems and times and what entailed with those. We worked to complete the background literature review, a lot of the work on these two wonderful chairs, put a lot of time and effort into gathering that literature review. We, together, had many conference calls. We all worked together to review everything. We went over various sections of the paper. Different workgroup members had to work on sections of it, go back and look at those extracts together, and provide it to the chairs. After that, the chairs gathered it all together. They assimilated the material. They massaged it and brought it into a working draft, along with the executive summary and the recommendations. Again, we met to review it together. We hosted three webinars, were about 1 to 1.5 hours each with over 350 participants, to gain input from outside resources and community members. And one final attempt was with the workgroup. We came together again, and we provided input together and gathered approval of all the final editions of the paper, the summary, and the recommendations. And once we were satisfied with that, after the review, we are here today to present it to you.

DR. THERRELL: So continuing on, just to review for a second the community input that came from the webinars, there were three webinars, and they were designed to give an opportunity for people to comment on what had been done. So the people who participated in the webinars were provided with a draft executive summary and draft of the recommendations that were going to be made so they could comment. The participation included from the Genetic Alliance webinar about 106 participants logged in. We had a webinar with the regional collaborative and the principal investigators there. There were about 38 participants. And the Association of Public Health Laboratories, over 220 participants. So I think you can see where the interest is. The interest is in laboratories and parents. So from those webinars, we had open mike discussions and questions submitted. There were basically three types of questions. There were technical questions, education questions, and policy questions. And I want to give you a few of the questions and I won't talk about the answers. But just for you to get a feel for the types of discussions that the outside community wanted to have. So the technical questions included things like what's the temperature of the biobank? What should be done with unsatisfactory specimens with respect to biobanking? Should they be kept or not? Do you have support from prenatal providers for improving education materials about newborn screening? And all these

we've touched on in the document itself. So I'm not going to go through that too much. Public education, questions about will we discuss the possibility that more parents will opt out due to the fear of research on their child's DNA? And that certainly is discussed in the paper. What's the likelihood that prenatal care providers will follow through with an educational mandate? This question came up a couple of times. People were interested in if there are recommendations made to the programs, can there also be recommendations made to the prenatal providers to help out with this sort of thing? That's something for you to think about. Do you have support from the prenatal providers for improving these materials? In accordance with the recommendation that States need to be more proactive, it would be helpful if ACHDNC would make a similar recommendation to professional organizations. So the States don't want to be the only ones assigned responsibility in this. They think you should assign some responsibilities to other members of the system. In terms of policy, are any of the States that don't keep blood spots very long considering changing their policies to store specimens for longer periods of time? And basically, the answer to this one is it goes both ways. Some are. Some aren't. Some of the ones keeping it long are thinking about shortening it. So there is a lot of discussion, and your guidance is very dramatically needed here. Are you aware of any States that use a scientific advisory committee in addition to an IRB? And the answer to that is yes, and that's mentioned in the paper as well. Would you comment on the added costs that come from requiring the duties of programs to be expanded to include retention and storage? And that is -- there is a whole section on financing in the paper that gives you some anecdotal information that we have from programs. There is not much published on this. So we put out a call to programs that already had biobanks to tell us what it was costing them, and so we've made some comments about that. And there is a recommendation or two that relate to that. There were some general questions. Do these policies address the issues pertaining to deidentification of the stored samples? What type of policy recommendations can you speculate are needed if DNA sequencing becomes incorporated into the screening panel? We didn't really get into that one very much. We had enough on our plate with other things than talking about the distant future. Likewise, we chose not to address the question of what happens to those specimens from the past, but recognized that that is an issue that may need to be addressed. Is there a potential for recommendation regarding what researchers can do with anonymous findings that might be of interest to newborns? And there is a recommendation which you will see pertaining to that. So those were the types of questions. We've provided you, I think, with two papers, which we think you should be aware of. One is a guidance paper that we wrote many years ago for U.S. programs, and it just outlines the basic issues and suggests to States that they should be developing policies. Another one is this paper from our Canadian colleagues that is more legal in the way it's presented, and it gives you some of the legal issues. There are many, many, many more papers about this, but we picked out these two as sort of summations of what's going on. It will give you the idea of the field. For those of you who aren't familiar with biobanks, this is a picture, actually, of the Danish biobank. Basically, it's cardboard boxes with samples in it in a specific order so they can be retrieved. And this is Dr. Pedersen from Denmark. This is a secure facility inside of a secure facility. So you have a lock to get in the building, and then you have a lock to get in the freezer, basically. And this definition and discussion of what is a biobank? This is the definition that's used in Denmark. We chose to use the term "biobank." We talked about a number of ways we could address this, kind of avoiding this issue of biobank, biological repository and all those sorts of things. We decided that if the parents are calling it this and the media is calling it this, then we should call it this and let's get on with it. In terms of background policy, the AAP Task Force in

2000 actually had some comments on this. There were three points made. One, that there should be policies for unlinked and linked residual samples in research and surveillance. There should be collaborative efforts to develop minimum standards for storage of residual samples at the State level. And there should be created a national or multi-State population-based specimen resource for research, or at least there should be consideration of that. There are a couple of policy papers that you may be interested. One comes from the Association of Public Health Laboratories, which points out that there are reasons to save these specimens with respect to QA, and there are other reasons to save the specimens as well, including research. But there needs to be some clear guidelines and clear national consensus recommendations. And you are familiar, I think, with the American College of Medical Genetics position paper, which came out more recently. And the thing about this one is I draw your attention to the last statement, which says, "Parents should have the option to have their child's specimen stored in a national repository for research." This gets to the question of what happens if a State is not storing them. Should the parents be able to pull them out before they get thrown away and given to some other sort of bank for long-term storage? Now, on to the recommendations. Just to show you what the status of State storage is right now, we went and surveyed the States. We validated these data with the States, and then, of course, there is a couple of States now that have come to me and, well, it's wrong. There are a couple more things. But basically, if you look at this diagram, across the bottom are the names of the States, and then the Y-axis is the years of storage that the spots are in the different States. So you'll see that there is one-third of the program -- exactly one-third, 17 programs -- store their specimens for longer than 18 years, or 18 years or longer. That accounts for 54 percent of the babies, okay? Now, some of the States in this group are actually looking at longer term storage, but right now, they've only had them for 18 years. So they called it 18 years. Next year, it will be 19, and it slowly moves up to indefinitely probably. The other groups are those States, two-thirds of the States, but 46 percent of the babies' specimens are saved for less than 3 years. And in fact, this is where the change has been made. There are two States in this group who have now moved to 5 years. But still there is a big gap between 5 years and 18 years where nobody is in that group. You're either short term or you're long term. So, getting to our recommendations, we thought it would be prudent for us to give you some wording that you could chop up and discuss. So we've made six or seven recommendations -- I guess, seven recommendations -- and each one of them has some caveats. So I'm going to just show you the recommendations and the caveats, and then we have another recommendation that we'll discuss. So the first recommendation that we have is that all State newborn screening programs should have a legally reviewed and accepted policy addressing the disposition of dried blood specimens remaining after newborn screening testing is complete and the screening results have been validated. I think the key here is maybe the "legal review and accepted" because a lot of States sort of do things without thinking about it, and then later on, they get into lawsuits. And the lawyers at the States say if we had known this, we would have told you to do something differently. So we think it's prudent for the States to seek some legal advice about this issue. And so, in developing the policies, we think there should be multidisciplinary input, including consumers, and they should be solicited and thoughtfully considered in developing such policies. Specimen disposition policy should include the length of time for which specimens will be stored and the storage conditions, compliance with processes included in the Standard for Blood Spot Collection on Filter Paper, which is CLSI Standard LA4-A5, or its current edition as recommended. Any data linkages should be carefully addressed, and privacy and confidentiality assured. Okay, so that's the first one, and we think you should take it as a whole, not just the first

sentence and forget the rest. Second recommendation is similar, but it has to do with access. And so, it says again, "All State newborn screening programs should have a legally reviewed and accepted policy that specifies who may access and use dried blood specimens once they arrive at the State-designated newborn screening laboratory, including further access after newborn screening tests are completed." This gets to the issue of tracking throughout the process for legal reasons, chain of custody. And again, multidisciplinary input, specimen access policy should include any uses prior to and after the newborn screening laboratory testing and validation process. If the uses of dried blood specimens outside of newborn screening are allowed, then handling and disposition of the specimen should be addressed, and privacy and confidentiality of any associated parent information assured. Our third recommendation has to do with education because we see the bigger issues here as education. As part of the educational process of the newborn screening system -- again, emphasize "system" -- all State newborn screening programs should maintain and distribute educationally and culturally appropriate information that includes basic information about the use or potential use of the dried blood specimens. That relates to the fact that there are some ongoing studies right now that have shown that only about 12 States actually mention what might happen to the blood spots at the present time in their literature. So the caveat here is where long-term storage policies or other options exist relative to storage of residual dried blood spots, such information should be included in prenatal education materials. Fourth recommendation is that all State newborn screening programs should work proactively to ensure that all families receiving prenatal care are educated about newborn screening. And I think the key here is "proactively." There is not a lot of emphasis right now put on prenatal education, and there needs to be more, especially with respect to this issue. So this activity should include appropriate steps to inform and train prenatal care providers regarding their educational responsibilities within the system. Processes should be in place to evaluate the extent, timing, and understanding of prenatal education with an eye toward educational program improvement. That is, if you're going to have a program, you need to evaluate it and improve it. And we'll have another recommendation later that talks to the expense of this and the help from the Federal Government. Recommendation five. If residual blood specimens are to be available for any process outside of the legally required newborn screening process for which they were obtained, an indication of the parents' awareness and willingness to participate should exist in compliance with Federal research requirements. Again, this gets to the issue of consent or dissent for saving specimens. So we say that a consent or opt in or a dissent/opt out process may meet this requirement, depending on the purposes for which the specimens will be used. The use of residual specimens for program evaluation or process improvements are valid components of the newborn screening system and, therefore, should not require additional consent. So we've defined the newborn screening program to include the use of those specimens for QA and validation. Recommendation six. The newborn screening programs should assess the utility of any additional consent/dissent process implemented in order to better address issues of storage and use of residual dried blood spots. So, again, we're talking about assessment of the utility of their processes. And the Federal Government is encouraged to consider this as a priority and to provide funding for utility assessment projects over the next 5 years. So we recognize it's going to be expensive in some cases. Recommendation seven has actually four parts to it. And this, again, is what we're encouraging the Federal Government to do with respect to this issue. So the Federal Government is encouraged to provide administrative support and funding to develop: A, model consent/dissent processes for the use of residual blood spots; 2, model educational programs for the general public on the importance of newborn screening and the potential uses of

residual specimens to generate population-based knowledge about health and disease; third, the national data on the utility of any additional consent/dissent processes implemented relative to potential resource uses of residual specimens; and finally, the Federal Government is encouraged to provide administrative support and funding for educational materials with facts about potential uses of residual blood spots for both consumers and prenatal healthcare providers. So that was the extent of our recommendations on the webinars. Now after the webinars, we got some input that made us think about another recommendation. And so, we've listed this one as an optional recommendation that came from the vetting process that you might want to consider. As a committee, we didn't feel we had had adequate time to maybe debate this amongst ourselves. There were different opinions as to whether this was good or bad. So the way out of this is to give you something that you can talk about. So where State newborn screening programs elect to maintain a long-term newborn screening biobank of residual specimens, a secure third-party key holder system, or the honest broker system, with appropriate consent should be used to allow for emergency linkages in deidentified specimen studies. So this gets to the issue of what happens if there is a research project on anonymous specimens and something is learned that might benefit the patient critically or something else is needed that might help interpret some of the results? Is there a way to get back to that specimen, even though it's anonymous -- deidentified?

DR. FLEISCHMAN: Yes. Be careful on your language.

DR. THERRELL: Yes. Deidentified. Okay, and so the key holder would have the ability to reveal critical health information to a study subject, should such information be discovered during the course of the research and the ability to obtain and reveal personal information from a subject to a researcher if such information were deemed to be of critical importance. In either case, consent from the study participant or appropriate parent or guardian would be required. So that's basically what we've done. As Jana said, it started out about 70 or 80 pages. It's come down to about 20 pages. I know you wanted only 4 or 5 pages. That could be done, but we think you'd miss a lot of the points that we need to discuss.

DR. HANNON: That was the reason we did the executive summary.

DR. THERRELL: Yes. So, Dr. Hannon is here to add his comments as well and answer the questions that you might have.

DR. HANNON: It got so big that was the reason we did the executive summary, to bring a little different spin on the introduction and put all the recommendations over there. Part of the text is redundant in that this information is again included in the text. So it's there twice, which makes the document slightly long. We spent a lot of time researching literature, pulling information from literature. You can see we have close to 100 references. A lot of the stuff we gathered we didn't use, but it was overwhelming in 3 months' time, and it was intense. I think that's about all I worked on for the last 3 months. So the floor is open for any questions, comments.

DR. HOWELL:Thank you very much for that report and so forth. Now the floor is open for comments about -- the committee has had this document, has read this document. So let's have comments about it. I think that the issue of dried blood spots, their use and retention, has become

one of the more widely discussed areas, and it's important that we come up with a recommendation that really is the right way to go. Rebecca? Your microphone?

DR. BUCKLEY: Okay. The issue about consent that you refer to several times I think is something that's very important, and I don't understand why we don't have that from the very beginning. In other words, from the time that the blood spot is obtained. Because if you're going to go back and try to get consent later, the difficulty in finding these people is going to be formidable. And the other question that relates to all this is who owns the dried blood spot? Because I know that in the studies we're doing with SCID right now, we have IRB protocols where we can get the parents who consent to release the blood spot from whatever State lab there is. But do the parents have the right to that blood spot?

DR. THERRELL: So Dr. Hannon can answer this, but I'll go ahead and take a shot at it. In the first case, the newborn screening programs traditionally have been mandated by law, and therefore, a dissent process is in place. With respect to research use of specimens, initially, that wasn't a big deal. Over time, it's become a big deal. And so, that's a question that this committee should probably try to answer is should there be -- is it necessary to have a consent process up front not only for newborn screening itself -- that's one question -- but what about storage of specimens? That's another question. What about use of specimens? What about the data itself? Because one of the lawsuits that is currently in place not only would eliminate newborn screening specimens from being stored, but it would also eliminate the data from being stored after a couple of years. Then what was the other issue?

DR. HANNON: It was about ownership.

DR. THERRELL: Oh, ownership. We had a lawyer on the group for that reason, and he researched this issue of ownership. So, legally, it would appear that ownership probably is the property of the State once a specimen is taken. Because there is a lawsuit that was in California having to do with human tissue that ultimately was resolved by the Supreme Court of California, which held that once you'd given up bodily tissue for medical reasons and there is an opportunity to consent or dissent, which technically might be present in the States, then it becomes the property of the States. Now that's a California Supreme Court decision, and whether or not that's upheld in other States is another question. But even given that legal opinion, there is still the ethical question is if you can legally do it, should you do it ethically? So --

DR. HANNON: A few of the States openly declare that they own the spots, okay? Although that most of the parents would dispute that ownership, and I don't think that's been tested. But I know at least in the -- I believe it's in the Michigan biobank, they declare ownership of the spots and that it is the property of the State. So that's an open dispute also, but there only are a very few openly declare ownership of the spots in their Web site or other literature.

DR. THERRELL: That's all documented in the paper, by the way.

DR. HOWELL: Piero?

DR. RINALDO: Thank you for really summarizing all this. I really would like to revisit your first recommendation because I really am troubled by what I think is a significant discrepancy between that graph that shows some States has extremely short period of time retention, a month or 6 weeks -- and if you go one more, okay -- and the last part of the statement. Because I tell you often what I encounter, being on both sides of the screening activities and the confirmatory, the elephant in the room of newborn screening is false negatives. And many times -- unfortunately, too many times cases are diagnosed at 6 months or a year of age or 4 years of age. So I really have a problem when you say that after 6 months, somebody can say with a straight face the screening results have been validated because I found very convenient that time after time I am told, "Oh, they've been thrown away. We cannot check." So how those States are able to say that they validated their results when they prevent any possibility to go back and revisit if things were done properly?

DR. THERRELL: Yes. So this is an issue, again, that's been debated for years in the newborn screening community, and it has to do with the fact that many of the analytes that are tested for in newborn screening do not survive over time. And therefore, there is a legal opinion -- now here's where we mix health and legal, I guess -- a legal opinion in many cases that if you maintain those specimens for long periods of time and then try to prove or disprove your result, you've got a big problem on your hands.
And so, they were collected for a specific purpose. They were used for that purpose. They were used for validation of that purpose for a certain length of time, and then they should be gotten rid of. I'm saying that's not my opinion. That's the opinion of some of those States.

DR. RINALDO: But that's really not a credible opinion and I tell you why. Because if I retest a year or two later and I don't find an abnormality, it actually would work to the advantage - - I hate to call it "advantage." But if a year or two later, regardless of the decay, I can still find significant -- something that is significantly abnormal, frankly, I don't know how people could argue against that.

DR. THERRELL: Well, the argument is maybe you can, maybe you can't.

DR. RINALDO: And we've done retrospective testing of so many cases, and I tell you, well, show me the data. I can show you the data how many times we have confirmed diagnoses a year, 2, 3, 18 years later.

DR. HANNON: Well, there are two issues on stability. One is the ability to declare something positive and the fact of looking at whether an analyte declined or not. So if your indicator is whether it's abnormal or not, you can tolerate a lot of decline in the analyte. Whereas, if you look at the analyte itself and declare a disability, then you can also document the analyte as declining. So this is a debatable issue in terms of what you declare as your endpoint for stability.

DR. RINALDO:Okay. But then going back -- and again, I'm not shooting the messenger, I hope. But if you go back to the next slide, I really think there should be a clear definition of what validation means because I don't think this has been covered adequately.

DR. HANNON: Also, with DNA, which we all know, and RNA, which is extremely stable in the dried blood spot, if you're going back to a molecular testing, stability might not be an issue at all.

DR. CALONGE: Is my microphone on?

DR. HOWELL: Would you like to comment?

DR. CALONGE: Oh, I have a question. This is Ned.

DR. HOWELL: Yes?

DR. CALONGE: Piero, I was hoping you could help me understand, the farther out the reason for validating the specimen is to -- I mean, are these -- just help me understand. Are there conditions that I couldn't diagnose with a future specimen? Is the issue really about improving the original test that was taken, validating the original test that was taken 10 years ago? Or is there something about the actual diagnosis of the condition in now a 10-year-old child that the original spot is important for?

DR. RINALDO: Well, the question is, you know, it goes back to a fundamental difference between cases that do not present with a detectable phenotype. We know this is possible -- glutaric academia and other conditions. There is nothing there to be picked up.
But I have to say that too many times I've encountered cases where the conclusion of a normal screening was based on a questionable interpretation of the results, again, based on cutoffs defined in ways that perhaps wouldn't stand scrutiny. Those are the cases I'm talking about. And again, I have found several occasions where it would be easy for me to document where it was just not possible. "Oh, sorry. We threw it away." And we're not talking about 10 years. We're talking about 6, 7 months.

DR. CALONGE: Well, I'm just saying from a State standpoint, 18 years and a year I think are different, at least as we've looked at our policy and wrestled with these same issues. So I think having a cutoff longer than the really short ones or even longer than 6 months because there's a clinically important and/or laboratory important reason to keep those, I think that might help us set the standard at a later time.

DR. RINALDO: So my question is, is it possible to recommend there should be "not less than," and I would say, again, I come from a State where after 2 years, everything is destroyed because that's really what the law. But I would say that at least 2 years. I wish you could say 4 or 5, but at least 2 years things should be kept for verification in case an event happens and we had somebody who experienced a false negative or something.

DR. HOWELL: We've got comments on this side from Mike and from Sharon. Mike?

DR. SKEELS: Thanks, Rod. I find myself once again agreeing with Piero almost. Could you just go back to the recommendation? I think that the last part of that sentence that says the screening results have been validated is unnecessary and confusing. I think if you put a period after the word "complete" and then let each State decide what complete means, you've got something.

Because we have different algorithms -- some of us go deeper into confirmatory testing than others, and I'm not sure what "validated" means in this context. So I know we're not -- you don't want to get into wordsmithing here, but this is, I believe, a fundamental problem with this recommendation.

DR. HANNON: Remember, these recommendations are put on your table for you to decide.

DR. SKEELS: That's right, and we're --

DR. HANNON: They're not our recommendations. They're only what came out of our work.

DR. SKEELS: Right. But we're now in the discussion period of the recommendations, and I'm discussing them.

DR. HANNON: I understand. I just wanted to remind you of that.

DR. RINALDO: If I can quickly -- I feel so much better now because we finally disagree. [Laughter.]

DR. RINALDO: I know, but I need to disagree now. I think getting rid of that is the easy way out. I think that they have touched on an extremely important point and I think it shouldn't be eliminated. You should elaborate and explain and perhaps even add a paragraph that says because there is a latency in findings, you know? And I can, again, truly think of case after case where the timeframe can be of months. It can be of years. But I would say that because the primary screening is really not completed and certainly not validated for a period of time, there should be a minimum retention, minimum period of time that retention should be kept for verification. And I have learned from the diagnostic work that even with the most trivial test -- glucose or the electrolyte -- specimens are retained in laboratories for variable period of times because there is always a possibility that something doesn't quite gel and people need to verify. It's the prevention of verification of a primary screening that is my problem. I really think it should be addressed, and it should be addressed by defining a mandatory period of storage -- not for research, not for test development, but simply for verification of the accuracy of the results.

DR. HOWELL: I think what you're suggesting is that this -- let me make a comment, and then we'll go to Sharon. You're suggesting the recommendation stay essentially this, but in the text that follows these recommendations, you would suggest putting a specific time limit. Is that what I hear and so forth?

DR. SKEELS: Well, I just want to respond I fundamentally disagree with that. [Laughter.]

DR. SKEELS: Thank you. We're now back on track. Each State has a person or a group of people who are the stewards of these samples, and we bear the legal responsibility for them, and we bear a personal liability for them, I might add. If we do anything that goes beyond our authority as State employees, if we are acting beyond what's covered by State law, the doctrine of sovereign immunity does not apply, and we are subject to personal malpractice liability. So

anything that puts us in too much of a box in terms of how long we should keep these or what we should do with them is a problem because every State is different.

DR. HOWELL: Let's hear from Sharon, and Jane also has some comments. You have to keep your finger on it.

MS. TERRY: Okay. So I think the nation's patients, parents, and babies might ask here that this might be a good place for us to have a caveat to this recommendation that this is another place that administrative support and funding should be given to reaching some kind of consensus. Clearly, if the States vary a great deal, which I know they do, perhaps professionals vary a great deal as to what is validation. Then this would be a place for professional societies, the States, the laboratorians to come to some kind of consensus. And again, I know we don't want a national standard by any means, but there is some science here that should be addressed, and it isn't. And I would say we leave our recommendation the same, but have a caveat that that's another place where we need to come to consensus.

DR. HOWELL: Jane?

DR. GETCHELL: Okay. I have a few comments. First, on the issue of validation. I know exactly what validation means in my laboratory. It's in my SOP. And it probably isn't the same as what Piero means by validation, and I don't think that's ever going to change.
The other thing I wanted to say about all of these recommendations, with one exception, is that I am pleased to see that they don't say "thou shalt," for example. They are guidelines. They are recommendations. And I can live with that. This really is up to -- and Mike said this -- up to the States, but the States could use some guidance. The only one that does say "thou should," I believe it was, was the one about the honest broker, and I'm a little bit uncomfortable with that. The other thing I want to say is when it comes to the legal review, there, too, our attorneys general will have quite a say in exactly how we handle these spots. And I think this group has to keep that in mind.

DR. HOWELL: Let me add one thing to what Jane has said is that what we need to do today is to discuss this thoroughly among the group and hear from our audience and so forth. Before we sign off on it or vote on it, we will do two important things. Number one, we will contact the NCSL, the National Council of State Legislators, to get input about that. And the second thing, we will work through the Office of the General Counsel of HHS to see how these recommendations should or could be handled as far as the authority and so forth that will -- you know, a comment that can be made that will clearly not get involved in the issue of the State responsibilities.
And both of those have to be done before we vote on it. Otherwise, we will find ourselves on the wrong side of the track. Coleen? And then Kwaku has a comment after Coleen.

DR. BOYLE:I had a little bit of a different, I guess, question, and when I look at the title of the paper is called "Retention and Use." And I guess I'm looking at all the recommendations, and for me, retention and access is sort of more the descriptor for the recommendations. And I guess I have a question in terms of maybe your charge and whether this came up.
Have you considered a recommendation about use, sort of capturing perhaps what was in the first

bullet of your slide under the ACMG position? That was a recommendation that residual dried blood spots are a valuable national resource that can contribute significantly to the health of the children and that we, as a nation, should put in place procedures and a process to use those in a meaningful and scientifically valid way. Something like that. Something that captured use versus just retention.

DR. HANNON: The use is very broad and generic. So we use the word "research." And if you look back at the education recommendation, it talks about educating the population on potential uses. So I mean, they're used in such a variety of ways, and most of the Web sites -- well, some of the Web sites will describe some of the uses, especially the Minnesota one, that they have been used for that benefited the child and family. And so, that was an issue.
Yes, access is an important issue, but we deal with research aspects in the document extensively. So the real title had to do with retention and use, not access.

DR. BOYLE: I know you deal with all of these, but I guess as a committee, I was hoping we would get a recommendation that actually sort of

embodied that concept that we should be using these as a right.

DR. HANNON: As I said earlier to Mike, these are guidelines for you to modify as the committee best sees appropriate and agree upon. Our assignment was to develop the document, do a broad research aspect, and come up with some guidance, recommendations for use by the committee.

DR. THERRELL: And I guess the other point is that two-thirds of the States get rid of them and don't save them for research.

DR. HOWELL: Kwaku?

DR. OHENE-FREMPONG: Thanks. I had a simple question. It sort of relates to the ownership. Are there any States where the sample identification number, whatever it is, is actually made known to the family? Because it sounds like if they're going to consent to owning something, it's like having money in the bank, but you don't know the account number.

DR. THERRELL: So are you asking whether they know their accession number? I mean their serial number?

DR. OHENE-FREMPONG: Yes.

DR. THERRELL: I don't know. I don't know of any right off hand, but I wouldn't say that that's for sure.

DR. HOWELL: Chris has a comment on that, and apparently Jane has another comment.

DR. KUS: Yes, I would just get back to the first one. To me, Jane is saying that there wouldn't be an agreed-upon definition of validation, and if there isn't an agreed upon one, I don't know how I can interpret that recommendation or go further with it.

DR. HOWELL: Alan?

DR. FLEISCHMAN: Yes. I'd like to comment on three different aspects that we're talking about at the same time. I think Coleen's point is a good one that there ought to be a kind of an overarching preamble here and I would hope that it would include that whatever we conclude about the good of additional uses, that the primary purpose, the public health purpose be protected while we consider the potential goods of other uses. But I think it's kind of a nice way to begin this process. The second comment would be it strikes me, Piero, that the controversy is not about time, but about uses. And I may be wrong on that. But the controversy, the reason people want the specimens to be in the hands of the State for a short period of time has to do with the distrust about future uses. So if, instead of talking about length of time, we talked about uses, we might be able to solve the problem of the distinction between Piero's validation procedures and your validation procedures because I don't think anybody minds your validating and I don't think anybody minds Piero validating based on his best assessment as to what that means. And the third comment I'd like to make. Dr. Buckley, I think, threw a gauntlet down on

the table early on that we've not yet talked about, which is absolutely critical, and that has to do with the consent question. I think it would be inappropriate, extremely harmful to consider the process of consent prior to obtaining newborn screening specimens. Consent for this purpose has the potential to jeopardize the public health purpose, and the idea of having mandatory screening is something that was hard fought and won, and I don't think we should step back from that. The children of America really need that.

DR. HOWELL: Sharon?

MS. TERRY: So I think it's also important that we remember that we're in an age that is really changing how consent is even going to be administered, particularly -- I'm sitting on the HIT standards committee for the Secretary. There are a lot of things that are going to change in terms of consent, and there will be ways to consent that are much less onerous than they are today, that are dynamic, that can be used later. So imagine, let's be pretty imaginative and imagine a system whereby the blood spot can be taken because it's mandated, and there's no consent needed for that, but that there is a system whereby that person could be contacted in proxy for the child and then assent when the child is 10 or 12 and then consent when the child is 18 or 20 that would allow, dynamically over time, progressive studies to be done. And that's happening now and will roll out this year. So I think we should be a little more imaginative. It's not just a piece of paper when someone's in labor.

DR. HOWELL: Piero?

DR. RINALDO: The point I was trying to make earlier is that I think we are already discussing the moral, legal, ethical issues of Phase 2, but I don't think a Phase 1 is over yet. So that goes back, Jane, you're saying you know when it's validated. Well, it depends. If you have a perfect record of never having false negative results, then probably you are there. But you will be the exception, not the rule. So I think that consent and all these other issues, the research, are a different issue. I'm saying is the screening results, if I -- and again, you opened the door, in a sense. So, with this group, the last sentence really is opening a can of worms, and I'm glad you did. Because I really ask for the definition of validation, and to me, validation, you know, we give a lot of lip service to really the needs of the public and the patients, but this is really where the rubber hits the road. I think a family of a child with a false negative result by screening has a lot of rights, and I don't see those rights being represented adequately here, and that's why I am speaking out. The validation of the screening results means that it should be possible, go back and verify things were done properly.

DR. THERRELL: I think we tried to give you the evidence for that and the trouble is there are 54 conditions being screened and they all are validated at different times. And the majority of specimens that would be questioned would have to do with thyroid and sickle cell and those sorts of things. And for thyroid at least, the analytes aren't stable enough over time. And so, the question was what do you do if some things are not stable and some things are? And we came to this sort of middle of the road recommendation.

DR. HOWELL: Mike has more comment.

DR. SKEELS: Just very briefly, if we're talking about verification of screening results, I agree with you that we should keep the samples long enough that we could go back and verify whether our screening results were correct or not. But the word "validation" I think is the problem here because that's an endless, long-term issue that we really -- I don't think that we're prepared to deal with. Okay -- darn, I agree again. [Laughter.]

DR. RINALDO: So let's change that word. I think it should be verification. The screening results have been verified.

DR. SKEELS: As long as each State gets to follow its own verification algorithm.

DR. HOWELL: Well, that clearly will happen, regardless of what anybody says. Fred?

DR. CHEN: Thanks very much. I really appreciate the tone and the tenor of all of the recommendations in the report. I also have reservations about the optional recommendation in that I'm not sure there is much precedent for that within the realm of research. I think the charge to this committee is or the challenge is really deciding whether or not this is the right tone to strike, or whether or not we are going to take on the myriad definitional issues around what is validation? What is the right time? Who owns these? What is consent? And provide an answer to those questions, which apparently nobody else has been able to actually provide an answer to. So we certainly have a choice here, an ability to make a strong sort of recommendation. I know a lot of people around the table feel like these should be preserved lifelong or indefinitely for research purposes. But I'm not sure that that's -- that even around the table, we're going to come to an agreement around that. So because of that, I actually appreciate sort of what's reflected in the current recommendation, in the draft recommendations.

DR. HOWELL: So, fundamentally, you're content with the tone of the recommendations as we see

them and so forth. Chris, you had comment?

DR. KUS:Yes. I'm getting more confused because when I'm listening to Piero describe a validation process and talk about no false positives, then, to me, that means that the screening test becomes diagnostic. I guess I don't completely understand, and I'm also concerned that we wouldn't have any agreement about verification. So from State to State, things would be different. I thought part of this group's process was to get States closer.

DR. RINALDO: I was actually talking about false negatives, which is very different.

DR. KUS: Actually, I misspoke. But false negatives. If you are going back and saying that your screening test is not good because it didn't pick that one up, I'm saying that that's really saying it becomes a diagnostic test you're looking for. But it's a screening test. It should have some false negatives.

DR. RINALDO: Well, yes and no. Nothing is perfect. And I certainly not -- although we strive for perfection, I think it's unlikely we'll ever achieve it. Nevertheless, that doesn't mean you shouldn't try. The problem, Chris, is that there is, let's say, anecdotal -- strong, but still anecdotal evidence that egregious mistakes have been made and continue to be made. And I believe that the parents of a child have a right to know that that happened because, as painful it might be for them, I hope that some good can come out of the fact that that could be the force behind a change of behavior or an improvement of performance.

DR. KUS: So you're talking about not a limitation of the screening process, but something wrong in doing the screening. I mean, that's the difference to me.

DR. HOWELL: Further comments of the group about the paper? Any suggestions of what you would like to see done? I've already mentioned the fact that at the conclusion of our discussion today, it will have to go forth with some legal opinions from both State folks and the Federal folks, and so that's a given. But as far as what would you like to see done with it? This is a wonderful document that they've worked on, and I guess what you would recommend we'd do to the document before we send it forth for further review? Mike?

DR. SKEELS: I'm sorry. I just have kind of a procedural question. Can you refresh my memory about what sort of committee action will be expected of us after we've perfected this document? I mean, are we going to adopt this in some way or endorse it, or where are we going with this? Because my answer to your question depends upon how formal an action we're going to be taking.

DR. HOWELL: It would be my intention that once we get -- we review it, and once it's looked at by the legal eagles in the various agencies to be sure that we're going down the right path, that the committee should review it and endorse it.

DR. SKEELS: So we would endorse it, but not adopt it as a position paper of the committee or anything like that?

DR. HOWELL: I would assume that that's the same, basically. In other words, if we adopt the paper and review the paper, it would be a position of this committee.

DR. LLOYD-PURYEAR: I would also like to get comments from various other entities within the department, the Secretary's Advisory Committee on Genetics, Health, and Society, the Office of Human Research Protections, before we come back to the committee to just refine.

DR. HOWELL: Gerry? Ned, is that you?

DR. CALONGE: Yes.

DR. HOWELL: Okay.

DR. CALONGE: Is there a chance to make a comment?

DR. HOWELL: By all means.

DR. CALONGE:So I wonder if -- I mean, again, I want to applaud this document. The information is tremendous, and I recognize there are some key words missing that folks are talking about. I would like to make sure we get a feeling from the committee members about the optional recommendation, and just to put my feeling on the table, I think there are so many issues involved in this last one that I'm just uncertain it needs to be a recommendation that's nationwide. I mean, I understand the reasons behind it. I do have real worries that, one, when you create a system that you say is deidentified and unlinkable, you create a system that is deidentified and unlinkable. And to create a workaround, I think, is something people could do on a State-to-State basis if it's something they really wanted to do. But I think it puts in front of those of us who might want to try to take the recommendations and expand the ability to retain specimens over time, I think it puts in a loophole that might raise more concerns than it's worth on kind of a national basis.

DR. HOWELL: So you're speaking against the committee's adopting the optional recommendation and so forth. Gerry?

DR. VOCKLEY: Yes, actually, Ned beat me to the punch there. I completely agree. I think that last optional recommendation is a completely separate issue from everything else that is dealt with in the document. So I think their initial take on not having that there was correct, and I can see why it was brought up during the vetting process. But I also don't think that -- it's going to be virtually impossible to reconcile the rest of the document with that one in a realistic timeframe.

DR. HANNON: You are aware that this exists in the Michigan biotrust?

DR. CALONGE: Yes.

DR. HANNON: I just want to put that on the table. It's explained in the examples of banks in the back of the document. So if you want to look at that, but I just wanted to let you know it does exist. It's been used by one particular State's biobank.

DR. HOWELL: Dr. Alexander and then Sharon again.

DR. ALEXANDER: As we move on to our consideration of this document, I'd just like to come back for a minute to the point Alan made about the

consent question.

DR. HOWELL: Can you push your --

DR. ALEXANDER: I did, but --

DR. HOWELL: You have to hold it, unfortunately.

DR. ALEXANDER: Oh, sorry. Okay. Missed that part. I want to come back to Alan's point about the consent issue, and one way of thinking about this is that we routinely do not get special consent for routine medical practices and you don't get anything more as routine medical practice than something that's mandated by law in virtually every State. The question that I think we need to look at is where does that routine medical practice end? Does that good medical practice include retention of specimens for a certain period of time for checking for possible false negatives, what went wrong with the process? Is that part of good medical practice? I think you can argue that that is the case, but each State might want to differ in where they define that good medical practice starting and ending. The consent part has to arise when you want to use those specimens for research that's not just related to checking on false positives, false negatives, whatever. And if you want to use that for developing new tests, for standardizations or whatever, for other things, then I think you need to be able to have some kind of consent. That consent can be obtained up front at the time that specimens are maintained -- or obtained. And if a State decides that it wants to have its specimens available for research, then I think that is the time that they need to get something beyond just the routine medical practice and get consent involved into that process. I just put that forward as something that we might want to look at as we consider this document.

DR. HOWELL: And Sharon?

MS. TERRY: So, in fact, following up on that, when we do get to this recommendation, and I do understand that perhaps we want to demote it, I think it still has to be considered because I think once we do move into the research realm, we need to look at what does it mean to give back clinically relevant results to people who participate in research? That's part of the standard of practice in the U.S. today. And again, I know we're looking at deidentified samples with dynamic consent, et cetera. This sort of thing is again not hard to reidentify someone to give information back to them. But I also agree that even our committee -- that's why this says "optional recommendation" -- was in a kind of turmoil over this and can't in a timely manner, I think, resolve it either. But I still think we have to say this is one of the issues that need to be considered going forward.

DR. HOWELL: Mike?

DR. SKEELS:I think if we ever have a paper on how to operate a biobank, this would be one of the great things to include in it. But I think that's a completely different issue than what you should do with dried blood spots when you're through with the screening process. This implies that biobanking is maybe a great idea, and here is a way you can get around a nagging little

problem. I personally agree with what Ned and I think Dr. Chen said about -- and I think Gerry as well -- about nuking this one. Those weren't your exact words, but -- [Laughter.]

DR. HOWELL: Piero?

DR. RINALDO: I realize that my interest on the first recommendation is somewhat isolated from most other people, and I think the seventh or potential last one is obsolete as it really goes to the core why all this has been done. But I still feel strongly about the first one. So my question to you is, is there a possibility to suggest different modified language? Because I would like to do so if that is possible, or I'm not sure it's welcome, but I would like to know if it's possible?

DR. HOWELL: Well, it's possible, of course. Whether anybody will accept it is a different issue, but --

DR. RINALDO: Well, I would like to make a recommendation if you can go back to the first, that one? I would like to say at the end, "Disposition of

dried blood spots remaining after newborn screening testing is completed and a reasonable interval time is provided to verify, if feasible, the accuracy of the results."

DR. HOWELL: Any comments about that wording?

DR. SKEELS: Yes. I'd like to go back to my recommendation that you put a period after the word "complete." [Laughter.]

DR. SKEELS: Because it's until you verify the results, it's not complete. That's part of the completion process is that you verify the analytical accuracy of what you've done and you report it out. If we're talking about waiting a period of time so that false negatives can be discovered, I believe that's a completely different issue than what's being addressed by this recommendation.

DR. RINALDO: Mike, I feel much better when we disagree. So it's perfectly okay.

DR. HANNON: I'd like to comment on Mike's use of the word "nuke." Remember, when you nuke something, there is fallout. So you might use a different word than "nuke."

DR. HOWELL: Any comments about the wording from the group around the table? I mean, you've heard considerable discussion. Michele has a word before we go around.

DR. LLOYD-PURYEAR:I also have suggested changes to this one, and it's around the use of the word "legally." So when we put these out, when the committee staff put these out for committee consideration, I have an alternative for the use of the word "legally" and "accepted" to say, "All State newborn screening programs should have a policy addressing the disposition of dried blood spot specimens remaining after newborn screening testing is complete." And however, whatever the language will be for the remainder of that sentence, I'll leave that. But I would like to add this caveat, the State should consider review of the draft because these are recommendations to the Secretary for States to consider. And so, "The State should consider review of the draft policy by legal staff prior to finalization." And these are some of the things I'd like to work on with NCSL staff. What is appropriate? Sometimes it's the State attorney general. Sometimes it's some other entity within the State that would be reviewing and finalizing any draft policy. So I want to work on that language with people who are at the State level.

DR. HOWELL: We'll work on this first area. Can we have any comments about the two contrary opinions you've heard from these sides of the table so that we can wordsmith that a bit? So when you get it back, it will reflect the sense of the group here. Mike?

DR. WATSON:I think it would be worthwhile if somewhere in this document, you reflected on how this issue is addressed in a diagnostic laboratory setting because that's really what I think Piero's perspective is from. And it's different than a public health perspective, there is no doubt. In the world of genetics, for decades we were held to retaining specimens for the time period of a generation, which was like 20 years by New York State law. And the various professional organizations began to get back to reality and realize that not everything is stable for that period of time in the certain things. So it's leveled out I think around 7 years, but then started to get modulated by having to get some prior consent on a requisition form that you could keep it for

some period of time. So I think if you reflect on -- and that, I think, is what Duane said, is that there is sort of in the medical side, there are specific requirements about how long we retain things for that validation or verification thing to occur over a very long period of time. And just drawing the distinction between those two worlds might be useful in this document because they are very different perspectives, I think. DR. HANNON: When you look in the document, Mike, there are some information provided there that comes from ACMG, as well as CLIA, and also from CLSI's molecular document on issues about retention which is outside of blood spots in terms of good laboratory practice.

DR. HOWELL: Gerry?

DR. VOCKLEY: I guess if we're not pushing forward a formal acceptance or recommendation on this document, I'd rather have some additional discussion maybe after the meeting electronically -- or however is legal in this setting -- to wordsmith this. I'm a little uncomfortable, Piero, with your version of it simply because it's got too many "ifs" and "feasibles" and, you know, "when feasible." It's too -- it's too easy. I think you need a stronger way of saying it if we're going to decide to do that.

DR. RINALDO: I was trying -- against my gut feeling, I put that "if feasible," because I think that for some condition, I think the point was made earlier, yes, I would love somebody says take it out.

DR. VOCKLEY: I've never accused you of being wishy-washy before. [Laughter.]

DR. HOWELL: Chris has a comment.

DR. KUS: Mike, if you put a period after newborn screening testing is complete, what's the definition of newborn screening testing is complete?

DR. SKEELS: Well, it's different for each State, but I can tell you -- I think, and I defer to my colleague from Delaware, Dr. Getchell, who may or may not agree, but for me, complete means that you have verified the analytical performance of the screening methods and that all the quality management parameters were in control and that you have reported the results. And for me, that's what complete screening means. It does not mean taking it to the next level of diagnosis. And I think what we're wrestling with here is whether the sample should be retained for some future purpose of let's say long-term quality management to inform the program if it's got an underlying analytical problem. And I mean, there is really some truth in what you're saying there. But I actually think that you don't need the original sample to be able to tell whether a child clinically has a disease or not. So I think that's -- you mentioned this earlier, Chris, about the difference between diagnosis and screening. I actually think that's what we're kind of tripping over

here.

DR. RINALDO: But, Mike, of course, because at that point, a diagnosis has already been made. It's about the accuracy of -- remember, in my experience, when something goes wrong is 80, 90 percent of the time is post analytical. It's not how the number was generated, how it was interpreted. And that's really, I think it's -- to me, it's a fundamental, almost ethical, moral opportunity for quality improvement. I think no laboratorian -- and frankly, I don't make a distinction between screening laboratories or diagnostic laboratories -- any laboratorian, I believe that first and foremost order would be to verify what I have done if it turns out that what I did was not right. That's what I am talking about. Here, it seems to me that destruction, the premature destruction is an easy way out. So if I really were to follow Gerry's advice, I would say it's almost a conflict. You're protecting your rear end by making impossible to verify what was done.

DR. SKEELS: It's also making it possible to prove that we didn't make a mistake. In my experience -- and I've done a little bit of expert testimony on this -- if a child has a disorder, and the newborn screening program reported them as being normal at birth, it doesn't really matter whether the mistake was analytical or clerical. The point is we screwed up. We reported a false negative result. And so, going back to the sample and retesting it and saying see, look, it really was negative is really of no help. So we're not covering our butt in any way. That sample probably isn't even valid for that analysis anymore anyway. So I can assure you we're not discarding them for legal protection issues because quality management in my program is way, way more important to me than protecting the liability of the State of Oregon.

DR. RINALDO: And I fully respect that. You know, it always goes back to the point, the "what if?" To me, the only way would not be to ask the same person to verify what they did, but to have an honest broker whose word has been used before, that somebody speak around this blindly, not having any knowledge and see what they say. Because if a second opinion turns out to be, with all the caveats of storage and certainly they have a tougher job than the initial lab, but I really believe that it's not uncommon you encounter a situation where somebody will say, "Oh, gee, this looked like X." That I think, you know, this is not about exposing anybody. This is about providing an opportunity for meditating and reflecting on what happened and making sure it doesn't happen again.

DR. HOWELL: Brad?

DR. THERRELL: So one of the reasons that the word "validated" was there, Mike, has not necessarily to do with the laboratory, but validating that it was the right patient because many times there have been mix-ups in patients at the hospital. And so, that's why the word "validated" was put there. It went beyond the laboratory.

DR. HOWELL: We've had quite a lot of comments about the first recommendation. And the discussion, we've got all this stuff down in the transcript, and there will be some modifications before you see it again, hopefully, that will be agreeable to at least the majority of the folks in the table. We'll draw a line down the table and so forth here, et cetera. But are there further general comments? We have some -- perfect. We have some folks who have signed up from the public to

comment about blood spots, and you notice that we're going to have the public comments divided into two areas. And the first person that I would like to call upon is we have a report from the Alpha-1 Antitrypsin Foundation that wanted to make a comment about dried blood spots and they were unable to be here but sent a written material that Natasha is to read. And Natasha, will you find a microphone and read the public comment from Mr. Walsh from the Alpha- 1 Foundation.

MS. BONHOMME: Hello? It's on? Okay. Mr. Chairman, ladies and gentlemen of the committee, I would like to thank the committee for the chance to speak about the importance of retaining residual dried blood spot specimens from newborn screening programs. Alpha-1 Antitrypsin Deficiency (Alpha-1) is a genetic condition that may result in serious liver disease in infants and/or lung disease in adults. It is estimated that about 100,000 individuals in the U.S. have Alpha-1, yet less than 10 percent have been accurately diagnosed. Individuals with Alpha-1 formed the Alpha-1 Foundation in 1995 to provide the leadership and resources that will result in increased research, improved health, worldwide detection, and a cure for Alpha-l. I recognize and appreciate that this committee has engaged in conversation to explore the complexities surrounding the State policies governing the use and retention of residual dried blood spots. These blood spots are valuable resources that must be available to improve public health through technology development and validation and through research. The Alpha-1 Foundation strongly agrees with the American College of Medical Genetics Position Statement on Importance of Residual Newborn Screening Dried Blood Spots, issued April 29, 2009. In September 2008, the Alpha-1 Foundation initiated a dialogue with stakeholders to determine the appropriateness of including Alpha-1 on the panel of recommended disorders to be screened for at birth. As a result of a workshop that included participation of members of this committee and based on the recommendation of a follow-up task force, the Alpha-1 Foundation is committed to pursuing the development of technology and evidence required to be considered for the screening panel. In order for the scientific community to establish the level of evidence necessary to be considered by this committee, we must have access to banked blood spots. Within this calendar year, the Alpha-1 Foundation plans to initiate development of a rigorously reviewed protocol to use dried blood spot cards to develop specifications for newborn levels of alpha-1 antitrypsin. Without access to the blood cards, the testing methodology and validity would not be able to be established, and the potential health benefits to the Alpha-1 community will go unrealized. The Alpha-1 Foundation is committed to upholding the highest standards of ethical behavior, and we believe that, with the proper review and respect for privacy, the research as planned meets these obligations. In light of recent public controversies resulting in public misunderstanding and distrust of State storage policies, and recognizing that there has yet to be reports of any unlawful or unethical use of stored samples, we encourage the committee to develop strong recommendations that would ensure the continued availability of residual dried blood spot cards in State public health laboratories. The Alpha-1 Foundation is willing to assist the committee if requested. Thank you for the opportunity to speak to you today.

DR. HOWELL: John Walsh, who is president and CEO of the Alpha-1 Foundation. We have two other people who signed up on the blood spot section, but I think are really interested in speaking in the other section. And Jennifer Kwon is on the blood spot, but I think Jennifer would like to speak about Krabbe disease, unless I'm in error. Is that correct? Great. So we'll hold you, Jennifer, until we get into the Krabbe. And Andrea Williams is also I think interested in speaking

in the second session. Those were the public comments we had. So the -- Michele will outline what we're going to do with this document and so forth. But let's be clear. We are going to come back and expect the committee to review it and issue a document with what we think are the appropriate recommendations for dried blood spots. So that's the goal. That's where we're headed.

DR. LLOYD-PURYEAR: So I'm certainly going to review with staff the transcripts and the meeting summary. So this outline of next steps may vary a little, but in general, from my notes, I'm going to go back to various organizational and legal entities that I think maybe need to be requested formally to comment and evaluate this document. This would be the Office of General Counsel, Office of Human Research Protections. I would like ACOG and AAP to -- and AAFP, Dr. Chen, if you think a formal -- make sure they're actually seeing this document. The organizational representatives have not passed this on. ACMG, we'd like formal comments from them. NCSL, the Secretary's Advisory Committee on Genetics, Health, and Society, any others that you think -- the committee thinks a formal evaluation should take place. I'm going to work with Coleen to actually formulate a recommendation around use, to outline various uses, suggested uses by the committee for the residual blood spot. And I think that may take place of some the concerns that Piero has raised.

DR. HANNON: What about APHL?

DR. LLOYD-PURYEAR: APHL? Yes.

DR. THERRELL: What about the State health offices?

DR. LLOYD-PURYEAR: Yes. So just email me. These were off the top of my head.

DR. FLEISCHMAN: And the March of Dimes will

be preparing --

DR. LLOYD-PURYEAR: March of Dimes. Okay.

DR. THERRELL: You're going to have to have DoD also.

DR. LLOYD-PURYEAR: It's true.

DR. CHEN: Michele, just so I understand the process, you're going to consolidate these comments, make some edits and changes, and then come back out. And then is it at that point that you'd like our organization to respond, or do you want us to respond to this draft or --

DR. LLOYD-PURYEAR: Actually, except for the recommendation on use, I'm going to keep the recommendations in the paper as is and have comments based on the paper and the recommendations. So -- oh, so given that, my understanding there was general consensus that maybe you need a vote to delete the optional? If you want me to just keep that in, I will. I'm not going to make the changes going back and forth between various entities around that first recommendation because I don't think that -- I think language still needs to be refined so we can kind of come to a consensus, if that's agreeable with everyone?

DR. HOWELL: As the document goes forward, is there general agreement that the optional comment be taken out of the document? I see lots of heads nodding and so forth. What about you? Becky? So forth, it looks like nodding that we take out optional thing, et cetera. Any further comments? I think that one of the things that we're going to have to be very aggressive with is that as we look at the number of people that we're going to send this to, it could take a century, and it would be my intention that that not happen. And so, we will send it out to people with a very clear we'd like your comments, but if we don't hear from you by a certain date, you're off the list and so forth because, otherwise, we'll die of old age, and I'm not interested in that. Sharon?

MS. TERRY: To that end, to the process end, so would it make sense then to give the organizations -- because I'm thinking if I got this as an organization, it would be really wonderful to also be pointed to this transcript to say a very rich discussion ensued that won't cause me to make the exact same comments somebody already made here, but maybe to agree with or --

DR. HOWELL: The transcript is public.

MS. TERRY: That's public, right. I know. I'm not sure organizations always recognize that it's public and that, in fact, there has been a good couple hours, and they should read that as well as the document.

DR. HOWELL: We will -- we'll clearly make that evident and so forth so that they can acquire that.

DR. BOYLE: And I apologize. Michele, you added this group to your list, but two of the recommendations clearly involved ACOG in terms of prenatal care.

DR. LLOYD-PURYEAR: I said --

DR. BOYLE: I know, but I feel like they need to be somehow engaged in this. I mean, this is

not going to work unless --

DR. LLOYD-PURYEAR: -- sit down face-to-face with them.

DR. HOWELL: ACOG, of course, has membership on this committee, and so it will. Is there any further comment about this and so forth? This is an important document and so forth, and it's certainly not our intention to let it go away, but we also need to be sure that we're moving along so that we don't get into tremendous problems with various and sundry organizations about how we proceed. Any further comments before we go on our break? Harry? You better be brief.

DR. HANNON: I'm brief.

DR. HOWELL: Okay.

DR. HANNON: Has the workgroup completed their assignment? Am I free to move to other chores? [Laughter.]

DR. HOWELL: We would -- actually, the committee would like to thank you for this hard work and encourage you now to really push ahead with the

second spot program.

DR. HANNON: Okay.

DR. HOWELL: Okay, thank you. So we will soon -- Harry has told me confidentially that he has been consumed with this report, but now that he's off the hook that he is ready to go ahead and finalize the work that he is doing on the second spot issue that we've discussed in the past. As you know, certain States do two spots, and others don't. And they're going to come up with a recommendation that either everybody or nobody do that, right? So we'll look forward to seeing that.

DR. HANNON: We're going to put the data on the table. Again, this is not our decision.

DR. HOWELL: Thank you very much. It's break time. [Break.]

DR. HOWELL: Ladies and gentlemen, let's find your seat as quickly as you can, and we are now going to go into -- Dr. Perrin, if you would, please? We're now going to hear from Dr. Perrin, if we can distract him from his extremely interested conversation with Marina Weiss back there. You're supposed to be speaking, Monsieur Perrin. We're now going to have Dr. Jim Perrin from Harvard University, who will present his Evidence Review Workgroup, the final draft report on the candidate nomination of Krabbe disease. Unless -- Dr. Perrin, thank you very much. I think that, as you know, we had a preliminary report at our May committee Webcast meeting, an excellent discussion, and the final report was developed primarily by Alix Knapp, Alex Kemper, and Dr. Jim Perrin. And I might point out is that the purpose of this presentation today is to permit the committee to reach a decision about recommendations concerning Krabbe. You've met Dr. Perrin on a number of occasions, but he's professor of pediatrics at Harvard Medical School and Director of the Division of General Pediatrics at the Massachusetts General Hospital. And he has been very active in the area of evidence review and we're delighted to have him present this this morning. Jim?

DR. PERRIN: Thank you very much, Dr. Howell and members of the committee. Thank you very much for the opportunity to both present, but to do this work. We're really finding it quite fascinating and very rewarding work. If I can have the slides on, please? Or do I do the slides from here? This guy? My apologies. There we are. Great. Super. So just to remind you of recent progress and activities of the Evidence Review Group, we did present the draft report at the May meeting, and we submitted the final report to the committee in mid or late July. Today is the review. I would comment that we've also presented to the MCHB staff an overview paper that describes the work that we've been doing together with the Evidence Review Group. And I also would comment that we have a paper relating to our SCID review that has been favorably reviewed by a journal, and I hope we will be published relatively soon. The team members who have been involved specifically with the Krabbe work are listed here. And Alix Knapp and Alex Kemper are really the primary authors who were involved with this particular report, and I may, indeed, call on them as needed to answer question that I am totally blanking on when you ask me them a little bit later on. We have a fabulous team, and I just can't overstress the diversity of the team, the things they bring to the team, and it's been, from my viewpoint, quite marvelous working with this group as we understand the evidence behind these conditions and their

recommendations for inclusion. For the particular work on Krabbe disease, Florian Eichler, who is in pediatric neurology at the Mass General and has done a lot of work in lysosomal storage diseases, also helped us with trying to understand what there is about the neurological findings in children with Krabbe disease that have been published and to make some sense of what are some of the important areas of needed information. You all know, I believe, that Krabbe disease is an autosomal recessive lysosomal storage disease. It relates to mutations in the galactocerebrosidase gene. It causes or it's associated with progressive damage in the white matter of both the peripheral and central nervous systems. There are four main clinical subtypes -- early infantile Krabbe disease; late infantile, which is usually described as with an onset after approximately 6 months of age; juvenile; and adult. And there may be other forms that have not been well described in the spectrum of Krabbe disease. Our focus today is really on early infantile Krabbe disease, which is the one that may be related to newborn screening. From the nomination form for this condition, the rationale for review included the notion that without treatment, most individuals die within 2 years. The most recent data would suggest that untreated Krabbe disease has an average lifespan of about 23 months, that there are methods for newborn screening using measurement of enzyme activity and gene mutation analysis, that there has been population screening in New York State begun in the middle of 2006, and that pre- or early symptomatic stem cell transplant may decrease the morbidity and mortality from EIKD. So the methods that we've used in this evidence review are really the ones we've used in previous evidence reviews. First, a fairly traditional systematic review of published literature, going through literature search to come up with a list of potential studies. In addition to that work, we've also carried out an assessment of important unpublished data that comes from either key investigators or from advocates. And we'll describe both of these elements of the review as we move forward. The topics that we reviewed, the main topics we reviewed in the evidence review for Krabbe disease includes incidence, its natural history, means of testing both for screening and for diagnosis, evidence for treatment, economic evaluations at all levels -- cost of screening, cost of treatment, and the like -- and then we've tried, as we have in the past, to provide some discussion of what critical evidence does not exist and might be particularly helpful in decision-making in the future. What materials do you already have in the final report that we've provided in July and which is included in the agenda package? We have described in detail the methods that we used in our evidence review. We've provided a summary of the evidence. There are tables at the end of the review that highlight key data from the abstracted article, and we have a table of studies that we did not include because they were too small, basically, for our cutoff points. And then there's a bibliography of all the identified articles. The systematic literature review included reviewing papers published between January 1988 and July of 2009. We used Medline, OVID In-Process as our main search engines. We limited the studies to those in English, mainly because our staff are not really very competent in scientific reading in French or German or Japanese. We included human studies only, and we also reviewed references that may not have shown up in our searches from the nomination form and from the bibliography of review papers that we identified in the searches. We initially found 330 abstracts that were selected for preliminary review. From those abstracts, we selected 77 articles for more in-depth review, of which 29 articles met all the inclusion criteria for final abstraction. This is a brief overview of some of the characteristics of the papers that we did review, and it's worth noting that there are no experimental intervention studies in this set of 29, no great surprise in the context of very rare disorders like Krabbe disease. But again, for essentially all the diseases we're going to be looking at together, we're not likely to find randomized controlled trials where children have

been randomized to treatment or no treatment or to particularly different forms of treatment at this point. So most of the work that we have, in fact, are case series. Here, 15 of the not quite 30 papers are case series, and other designs of a variety of types has got a larger group, and we'll talk about this in a little more detail as we move forward. This is, again, a characteristic of the field that we're working in together on rare disorders. It's very different from how you might look at a new anti-hypertensive where you might have 20 or 30 or 50 randomized trials. We do carry out quality assessment methods for the studies we look at. We look at studies by study design, and we compare within rather than between study design categories, and we'll provide some of this to you. It's in much more detail in the actual report. And we also look at study goal to examine aspects of the quality of studies. Our approach to unpublished data was to contact Krabbe experts who are identified in three or four ways. One is from the literature review. Obviously, there are a number of names of investigators that come up frequently when you do a literature search. We also had discussions within the team, within the workgroup, as well as with members of the advisory committee. And then we also had people who were recommended by other experts, sort of a rolling addition of new names. As we talked to Expert A, she might say, "Well, you should also talk to Expert B and C," and we did that in a consistent fashion. And we included experts from different Krabbe disease domains, including both screening and treatment. We also talked with advocacy groups who particularly helped us by describing families' experiences represented in the Hunter's Hope registry. This is the list of people whom we contacted. I obviously am not going to go through in detail everyone on this list. It's in the report. It's in the slide. So you have two. Not everyone did respond to our contact, but we've had, frankly, extremely good response from people we've had contact with. People have been very open, willing to talk with us, wanting to help this process. We've found remarkably little hesitancy to work with ourselves and our staff as we've tried to gather evidence, and I think it's an indication of the passion that underlies people's interest in this set of topics and trying to do this right for children and families. So let me now talk a bit about some of the findings from the reviews, and I'll try to go through this in the order to which we raised some of the initial questions. The natural history of early infantile Krabbe disease is associated with extreme irritability, spasticity, and developmental delay, all appearing before 6 months of age, often with a decerebrate state in early infancy and, as I mentioned before, a very, very early death in these children. This is a terrifying and very severe disorder that affects children and, of course, their families quite dramatically early in infancy. Now, the natural history and incidence data that we have, this slide presents some information about the quality assessments of the studies available. So, first of all, for genotype/phenotype correlation, which we'll describe in a little detail in a few moments, we have no data from large population studies here. All the data come from systematic studies other than whole population screening or estimated from the clinical features of the condition as described in individual cases or short series. Similarly, of the incidence data, we basically have data from whole population screening or comprehensive national surveys in only the one case, and then all the other data come from more limited studies, which we'll describe shortly. What do we know about the incidence? And these are now most of the data that we have, most of these are moderately old studies, and they do not yet include the New York data, which I am going to present in a little more detail in a few minutes' time. These are data from Sweden, Germany, and the Netherlands, and they basically give us rates on the order of 1 to 2 children per 100,000 live births. That's the -- that has been the sort of going belief in the literature, about 1 in 100,000 for this particular disorder. And I'll get back to how the New York data do or do not fit that earlier rate in a few minutes when I spend some time in more detail on that particular set of

experiences. Screening for Krabbe disease is done by dried blood spots and initially by enzyme analysis, by MS/MS for the GALC enzyme. This is then followed by mutation analysis for GALC, essentially done in mainly one lab in this country. The genotype/phenotype correlations have been sought in a great deal of detail, but unfortunately, the data so far would suggest that while over 60 mutations have been identified in the GALC gene associated with early infantile Krabbe disease, the only genotype that is strongly predictive of EIKD, in fact, is homozygosity for the 30-kb deletion in the GALC gene. So only 1 of 60 or more seems to be highly predictive of disease. So let me talk a bit about the quality assessment with respect to screening test characteristics. And here again, we will present some data from screening programs in a U.S. population or similar, i.e., a population-based study, for sensitivity, for false positivity, for repeat rates, and for second-tier testing. So, one -- basically, the New York experience -- shows this population-based data here. Everything else comes essentially estimates from the known biochemistry of the disorder and, thus, a little bit less easy to extrapolate to population-based screening. Let me move now to the New York State experience and I know we had a good deal of discussion in the May meeting about this activity and what happened in New York and what data do we have currently from New York. We've had a series of extremely helpful discussions with the New York people about their results and their findings, and we'll try to present them as cleanly, as carefully as we possibly can. I hope you'll actually stop me if you have questions as we go through these next few tables because we have struggled to get them as carefully correct as possible. But these aren't easy to understand. New York began screening for Krabbe disease in August of 2006. By the middle of 2008, i.e., in the published report from the New York program in 2009, they had screened a bit more than 500,000 newborns for Krabbe disease. Among the steps that were taken by the New York group was to develop a rapid and accurate technique for assessing GALC activity and performing then thereafter DNA mutation analysis. They developed a standardized clinical evaluation protocol, based on available literature. They formulated criteria for transplantation. They developed clinical database and registry, and they developed a systematic approach for following developmental and functional outcomes of identified children. And the New York Krabbe Consortium addresses the need for such clinical evaluation and follow-up. As of June of '08, and I'll give you more recent data in a moment, of the 500,000 children screened, 4 were identified as high risk, 6 as moderate risk and 15 as low risk. We'll describe what New York means by those terms in a few minutes' time. Let me move now to a couple of very difficult slides and we've tried our darnedest to make these as accessible as possible. But this is an effort to go through the New York data. Is there a pointer, by the way? Red button on the boat. Good. This is a boat. So, as of I believe this is now June 30th of '09, but it may be a month or so earlier, New York had screened more than 750,000 children. And they had developed a mechanism for defining daily mean activity of the GALC enzyme in the first 7 months of the New York experience, where they looked at about 140,000 newborns and compared them with known unaffected and known affected controls. And using the data from the first 7 months, they essentially developed a daily mean activity percentage, which then affects how they described normals and abnormals thereafter. So, basically, they took first the children who were at less than 20 percent of the daily mean, which are, as of mid 2009, 4,000 children, thus excluding these 755,000 children. These children were retested in duplicate using the same dried blood spots. And if they were three samples on average greater than 12 percent, but less than 20 percent, which is really the bulk of this 4,000 -- about 3,800 of the 4,000 -- these were considered to be screen negative children. If they had an average of three samples that were greater than 8 percent, but less than 12 percent, which are about 200, they and the children with

even less GALC activity were all referred for DNA testing and to whether or not they had one or more mutations in the GALC gene. One hundred forty of that 236 did have, in fact, one or more mutations and were considered initially to be screen positive. This is maybe not the totally best term, as you'll see in a moment, but this was the first attempt to distinguish screen positive from the screen negative, i.e., these two populations all underwent DNA testing. Of this group, we believe all 28 had one or more mutations so that their lines actually go both directions. But this 140 then were the ones that were considered screen positive out of the 770,000 children evaluated by June of '09. We can certainly come back to these slides if you have questions as we go through them. This is now taking the 140 screen positive referrals. So all of the work up to this point was done with essentially the dried blood spots initially. Now at this point, physicians are notified. New blood sample is obtained, and the new blood sample is used to confirm the initial assay to determine GALC activity, and the second-tier results are sent on to the follow-up system New York has put together. Now what happened here, and I should have added one more box, which is of 140 children, 86 on this confirmatory approach were not in these levels of enzyme activity. They were all higher levels of enzyme activity, and in fact, you take this screen positive group and now define 86 of them as being screen negative, leaving these three groups. Now these three groups are based on the consensus of the experts in the New York group and their consultants in developing these strategies. So this is basically enzyme activity of less than 0.15, 0.16 to less than 0.3, and 0.3 to 0.5. And these are defined by the New York group as low, moderate, and high risk, and the high-risk group is really the only one that is recommended to be considered for stem cell transplantation. So this is now 7 children out of the 770,000 children who might be considered for stem cell transplant, and this is not quite visible on the slide. But there are two children who received stem cell transplant so far out of the New York State experience. That was true as of June of '08 and remains true as of June of '09.

DR. VAN DYCK: Jim?

DR. PERRIN: Yes, please?

DR. VAN DYCK: Peter van Dyck.

DR. PERRIN: Yes, Peter?

DR. VAN DYCK: About how old is the child during -- at this point in the procedure?

DR. PERRIN: A week or two. Very young. They can get this done within days, easily within days. They have set up the system that even a child whose abnormality might show up on a Saturday, there are mechanisms for flagging that child originally and getting the next steps done almost immediately. So I don't know that I know the outer bounds, but I think it would be well within 2 weeks' time for any of this. This now describes, again sort of overviews what I've just told you. They've screened, as of June '09, 750,000 children, 140 were referred for further evaluation. Of this group, only 7 are high-risk newborns, and this gives us a number that's approximately comparable to other previous studies, i.e., 1 in 100,000 children who are at high risk for this disorder. On the other hand, of the 7 who were defined as high risk and went on to further evaluation, only 2 were symptomatic enough or had evidence enough to be recommended for stem cell transplant. The other 5 were not, and I'll describe the current data on the other 5 in a

moment. The other 13 and 36 are moderate and low- risk newborns, and New York has a plan in place for following these children, not always successful because of the difficulty in following children for a variety of reasons. Yes, Piero?

DR. RINALDO: Can you confirm that none of the moderate and low-risk newborns had the 30-kb deletion?

DR. PERRIN:Yes. That is correct. Yes, all of these children went on to DNA analysis. None of them had the 30-kb deletion. Right. Right. Now this is the 7 children who were identified as high risk in New York State. These are their birth months. And you can see that cases 2 and 5 went on to stem cell transplant. One of these two had a 30-kb deletion. The other had another novel mutation not previously described in Krabbe disease, not an uncommon phenomenon in the context of children appearing with this disorder. That -- I don't remember now which one of these children was which in the 2 and 5. One child did undergo stem cell transplant -- both of them did, excuse me. And Number 5 died approximately 11 days post transplant. And -- right. The other ones have been generally followed up. Three of them have been followed up and have been asymptomatic or assumed to be asymptomatic. That really includes kids who may not have been seen in the past year as of June of '09. On the other hand, others were not followed up. One family refused follow-up. They didn't want to be bothered with the activity. They thought they had a child who was unaffected. Another child returned to a country of origin and was not able to be followed either. So, in fact, we don't have full follow-up data on all seven children. Again, the New York program diagnostically we've described already. The recommended follow-up schedule for screen positive infants is this. The high-risk children are encouraged to come back monthly for evaluations neurologically, to have neurodiagnostic tests every 3 months, which are listed below -- MRI, CSF, i.e., lumbar puncture, BAERs, visual evoke potentials, and NCS done. So not all the families in the high-risk group have been willing to go through this, and you can see what their process has been, what they set up at the beginning here for follow-up, which is, again, neurodiagnostic tests only for the moderate and low- risk groups if the exam is abnormal. And I don't have complete data on the total numbers of follow-up for those two populations. I do know that none of them have shown up to have EIKD as of June of '09, but I can't tell you what the total percentage was of follow-up. Alix and Alex may have that number. My understanding, it's in the 70 to 80 percent follow-up, but I don't have the exact numbers in front of me. That's the screening and diagnostic data that we have to present to you at the moment. Let me move on to treatment data, and the treatment for this condition goes back quite a while -- hematopoietic stem cell transplant, sources from both bone marrow and umbilical cord blood. It does require preconditioning with chemotherapy and it seems to be clear that damage relating to the process of Krabbe disease continues post transplant at least until there is full engraftment and new glial cell development. This is the data again on treatment, and I'm not going to spend too much time on this table, except to show you that we're really only talking about a small number of studies here, five. Five studies, which are mainly cohort studies, and then a little bit more, two of the studies that we looked at are, in many ways, opinion papers from respected authorities based on their clinical experience and so forth. Now these are two studies that came from Dr. Escolar's group at Duke. And I will go through them in some detail, but would be delighted to go through them in more detail if you would like later on. Basically, the 2005 paper presented 11 patients who were diagnosed prenatally or at birth, mainly because of a previous family history. Their age at diagnosis was between 12 and 44 days. They were transplanted pretty quickly, and there

was 100 percent survival in this group at a median of 36 months post transplant, which is in the paper the last data provided. In the 2006 paper, there were another 11 children now what they called Stage 1, which is basically these are children who appeared developmentally normal but they have inconclusive neurological findings. The paper actually doesn't tell us the age at transplant, but does tell us the stage at transplant, i.e., Stage 1. And here again, there was 100 percent survival rate with a follow-up between 24 and, in this case, 108 months of age. So, again, 100 percent survival for children who were asymptomatic essentially at time of diagnosis with early transplant. For symptomatic children -- this is a comparison 2005 paper -- 14 children who were diagnosed between 4 and 9 months of age, i.e., much later. They were transplanted between 140 days and basically a year of age, and the survival was only 6 of 14 at a median of 41 months post transplants, i.e., 8 of 14 children died in this late transplant group. And then for the 2006 paper, 4 Stage 2, 3 Stage 3 and 1 Stage 4 patient. The Stage 2 children had 100 percent survival with the follow-up at this point. Stage 3 had a 61.5 percent survival. The Stage 4 child died a few weeks after that child's procedure.

DR. CALONGE: Jim?

DR. PERRIN: So, in summary, this paper, this slide would suggest that survival is substantially higher among children with early transplant and substantially less among children with lower transplant.

DR. CALONGE: Jim? Is the death from -- the death from Krabbe or from complications of transplant?

DR. PERRIN: I don't think we have exact evidence there. We have been told that the death in the New York child was from transplant complications rather than directly from the Krabbe. And one might expect that the Stage 4 child who died quickly after transplant, probably also died of transplant complications.

DR. CALONGE: Thank you.

DR. HOWELL: Coleen has a question.

DR. BOYLE: Just a clarification. You may have said this. Just was there a genotype done? Genetic analyses?

DR. PERRIN: I was afraid you were going to ask that question, Coleen, because we have gone back to figure that out, and we do not have those data here, actually. Again, these were children -- the asymptomatic children were all there because of previous family history. And we don't have, from the published data or from the experts, the actual genotypes of these children.

DR. HOWELL: Fred, did you have a question?

DR. CHEN: Oh, I think that just clarifies that, in fact, of those asymptomatic early treatment children, then it's not entirely clear whether they would have fallen into a high or a moderate or a low- risk category.

DR. PERRIN: I believe that is correct. Do we have GALC levels on these children? No, we don't. So we don't know the absolute answer to that, but my guess is these would be predominantly on high risk or almost entirely on high risk. Piero?

DR. RINALDO: This is, indeed, a critical point. So to what extent have we tried to go back and retrieve this information?

DR. PERRIN: We have tried to retrieve some of this information, and we could still go back and

try to get more about the -- we did ask about the genotyping and did not have that accessible. I don't know the other question you're asking, which is would these all have been high risk by GALC activity? I don't think we've asked that. Is that right, Alix and Alex? I mean, it's a really good question.

DR. RINALDO: It seems, though, that while there is a strong genotype/phenotype correlation, the jury seems to be still out about the meaning of certain levels of enzyme -- residual enzyme activity?

DR. PERRIN: So the only strong genotype/phenotype relationship is a 30-kb deletion, which is relatively uncommon, and most children with early infantile Krabbe disease do not have the 30-kb deletion, okay? So I don't think the evidence would say that there is a strong genotype/phenotype correlation here. And the New York experience is really based much more on GALC activity and on clinical presentation. That isn't to say that they don't consider the DNA, the genetic evidence critical. They do. But the driving force behind at least these two children was as much their clinical state and the little bit of evidence of their having some abnormalities at the time.

DR. HOWELL: Coleen?

DR. SKEELS: Just to follow up, it's sort of the companion question, I think. In New York, there were 96 children, I think, who were initial screen positive for the enzyme activity and then who were DNA negative and were reported as screen negative.

DR. PERRIN: They were both DNA and GALC level higher. Both.

DR. SKEELS: Okay. So I guess I was going to ask about the heterogeneity of the different genotypes and whether there were some in there who might, in fact, be affected but weren't recognized because the wrong markers were in the panel? I'm just throwing that out. You probably don't have that information, it sounds like. But just curious.

DR. PERRIN:Again, I think we do know that the genotypes of these children did not include 30-kb deletion, with the exception of the one child in the high-risk group. And we do not know and could go back to the New York group and ask this question about of the, whatever it is, 30, 40, 50 children in the three groups, which ones had one mutation versus which ones had two mutations? We do know that they don't have 30-kb homozygosity.

DR. HOWELL: Chris?

DR. KUS: What was the difference between the ones that were confirmed versus the ones that are being followed up? What was the difference?

DR. PERRIN: So our understanding -- and Alix and Alex, please correct me if I'm not saying this correctly. Our understanding is those two children had fairly subtle indications of clinical abnormalities at the time they were evaluated. One of those two had the 30-kb deletion, which is known to be extremely highly associated with the disorder. So there wasn't any question about

that child. And the other child really had some minor, but identifiable neurological impairment or evidence thereof that led to that child's transplant.

DR. KUS: Was that -- I mean, the impression is that you're supposed to get these kids and treat them while they're asymptomatic. Was the findings
that they had -- and I've got to go back because I've looked at this. But were they studies that were done, brain studies or other studies? Was that the findings, or was it actual clinical exam findings?

DR. PERRIN: I don't know that. Alex Kemper, do you remember that?

DR. KEMPER:My understanding, from talking to Dr. Escolar, who is actually at the other institution down the road, the University of North Carolina, is that it's subtle findings on the physical exam that really pushed them over to recommending bone marrow transplantation. And one of the things that they're working on -- this is kind of jumping ahead -- is developing an algorithm that could be more generalizably used because there is concern that these subtle exam findings could only be picked up by those who are used to evaluating children with Krabbe disease to start with.

DR. PERRIN: I think it would be fair to say that the New York group did very much due diligence in coming up with criteria, both from examination and from imaging and et cetera, laboratory studies, to come up with as consistent a pattern of evaluation as possible or as is known in 2006-2007. I think, on the other hand, they and everyone else we talked with would say that it is not clear at this point what are the characteristics of children that consistently predict EIKD, either on laboratory or newborn examination? That's work to be done.

DR. HOWELL: Ben?

DR. LAVENSTEIN: So I think that's a masterful description. I would commend to this group there is an article in the journal Pediatric Neurology in April 2009, which is contributed by many of the people that you cited. It's an experience of the New York experience. And if you go back and you read that article, you will get the nuances because it really comes through in terms of the children who were transplanted and the children that weren't transplanted. And you certainly get the feeling of the lack of correlation of diagnostic studies. By the time the diagnostic studies become positive, whether you look at MRIs or evoke potentials, the horse is out of the barn. The patients are way down the road. The nonspecific findings on neuroimaging and on some of these other evoke potential studies are not very good predictors and the lack of correlation between the phenotype and the genotype is sort of the enigma of the disease. I think they also stress the need for consistency amongst the follow-up amongst people who are very well trained, as you alluded to, in seeing these patients serially, that they're not passed around amongst different pediatricians or different pediatric neurologists. Otherwise, you get a different flavor for the outcome in terms of their neurodevelopmental outcome. With regard to the two patients that were transplanted in New York, the one, I think, caveat is those that are transplanted below 28 days of age have a higher morbidity, and yet you want to transplant them early. The one that died, died of sepsis and multiple organ failure and multiple coagulopathy. And the other one did well.

DR. HOWELL: Chris had a comment before we go ahead. You can't hear you.

DR. KUS: I said the important point to know is that the kids that were transplanted all went to Duke, which underwent the evaluation through their program, too. So this whole issue about clinical findings is a critical one.

DR. HOWELL: Rebecca had a comment.

DR. BUCKLEY: I have a question on the ones who were not high risk. Has the long-term follow-up continued to show that they're asymptomatic?

DR. PERRIN: Our understanding is yes. The simple answer is yes, that not all have been able to be followed up. But that the ones that they have been able to follow up -- and they have a system in New York State for the follow-up of all these children where families have been willing to return for follow- up -- and I think it's in the 70-80 percent range of follow-up, the answer is yes. Let me move on and just say this is a way of really representing some of the data I said a few moments ago that, here, asymptomatic newborns have survival rates that are substantially better than symptomatic newborns. And these are data that actually come from the Hunter's Hope registry, which show even a less good outcome for untreated children compared to treated symptomatic children. This, again, is only mortality. I want to stress that. So we've already talked a bit about the mortality from the New York experience, and let's move on now to something about the morbidity rather than the mortality. And again, I'm using two papers that come from the Duke experience predominantly here. The 11 children who were diagnosed prenatally and the 11 Stage 1 children from this group here, these are probably the ones most important to look at. And here, basically, transplants prior to symptom onset maintained progressive central myelination, normal vision and hearing, and normal cognitive development except for gross motor development. And I'll show you some slides about this in a moment. These are basically, though, relatively short follow-up. This is basically approximately 3 years max follow-up for these children, whereas transplant post symptom onset did not appear to have any significant improvement in neurological status. So, for the late onset children -- I'm sorry, the late transplant children did not seem to improve neurologically as a result of their transplants. The later studies showed again pretty similar findings. A little bit of variation by the Stage 1 versus Stage 2 group, and I'll give you a little more data about that in a moment. But again, the sort of take-home message is that from the 2005 paper, the evidence would suggest that these children are doing well. They're not doing perfectly well, but they're doing relatively well as a result of the transplant. Now this is a far too complicated slide, and I'm not going to go through it in detail. But it does talk about cognitive development, adaptive behavior, receptive language, fine motor skills, gross motor skills and expressive language in children who were followed up. And I think what you can see here is this is, in general, the normal range and standard deviation here. These are individual children and the degree to which there was follow-up for these children here in the context of cognitive development. So these are the children who were in the early treatment group, and you can see that, indeed, there is normal development in certain of these children, but not in other of these children, as they go forward. And that's a consistent pattern throughout these kinds of slides. So among the early treatment groups, some summary comments from this would be that fine motor control seems to interfere with cognitive function testing, at least that's the view of the investigators as described in the publication. That motor

involvement that is persistent does affect expressive language. And during the second and third years of life, which is as far as this paper goes, during the second and third year of life, there is progressive spasticity in the lower extremities and some truncal weakness, and some significant fine motor and gross motor delay which, at least from the view of the investigators, affected the ability to measure cognitive and language function. So let me move now from the published studies to the evidence that we obtained from talking with experts who've had experience in stem cell transplants for this condition. And as you can see, the largest experience is the sample at Duke, but we have other samples from other places as well. And it is probably worth focusing here on the Duke experience. Now this is really conversations that we had in the late spring and predominantly summer -- well, late spring and early summer of 2009. So we have longer term follow-up than the 2005 level. Drs. Kurtzberg and Escolar have both been involved in the follow-up on the Duke panel. And here, basically, of the 17 surviving children, post transplant, the oldest is now 13 years of age. This was the New York child, by the way, who died post transplant was in the Duke population. No further progress in motor skill development, but no obvious regression was noted by at least these reporters. Two or three of these children can ambulate completely independently. Others need support for ambulation. Some use wheelchairs. There is some evidence that the peripheral neuropathy worsens over time. The less involved patients. I'm not sure we know exactly what we mean by "less involved" here. The less involved patients have normal cognitive abilities, and the more involved ones, as we noted before, some difficulty with speech processing. A third had normal motor function, according to Dr. Kurtzberg, who's really followed this more, through the first decade of life. Another third are ambulatory, and the final third are severe spasticity, use wheelchairs. And her view was that all have normal intelligence and communicate well. So, actually, difference of views by experts on the same population. All right. We have a couple of other children here for which we have not a lot of long-term outcome, but this is one, two children. Both were transplanted young. One, a second transplant at age 3 months, developmentally delayed for follow-up at age 3. This is a child who is younger, who is ventilator dependent now at 5 months of age or when we talked to the investigator. Again, one more child able to sit, not walk one year post transplant. Can vocalize but lacks understandable expressive speech. So --

DR. BUCKLEY: Do we know anything about the genotypes of these patients?

DR. PERRIN: As I said before, we don't. We do not have that information here. Right. That covers what we know to date about the outcomes of treatment for early and late treated children. These, I know, were questions that we discussed in the May meeting. Let me move on to a few final comments, and then we'll be able to have, I think, a very interesting discussion. Approximately eight centers in the U.S. seem to be experienced in the transplantation of infants with Krabbe disease. Duke and Minnesota are the ones with the largest amount of experience, but there are additional sites that do this. Insofar as the protocol is similar to protocols for other childhood diseases, centers that have stem cell transplant capability in general can likely deal with this procedure for children with metabolic disorders. Our economic evidence, I feel a tiny bit like a broken record when we present these to the committee. But there is no peer-reviewed publication that we could find relating to the cost or cost- effectiveness of screening or treatment and insufficient data certainly for any serious economic evaluation. So the key findings, let me try to summarize what we can say about screening and treatment. New York pilot screening, no evidence that they have missed any cases of Krabbe, early infantile Krabbe disease. So we would

say that the evidence would support a sensitivity of 100 percent. The observed prevalence of EIKD, at least if you use the two children who were defined as having the disorder by the New York State criteria, is substantially lower than that in the previous studies. Instead of 1 in 100,000 or 2 in 100,000, it seems to be 0.26 per 100,000 by their data to date. Overall specificity is greater than 99.9 percent whether you use either the 140 number or the, whatever it is, 56 or so number in the three risk categories. Treatment, the evidence would suggest that stem cell treatment in presymptomatic or early symptomatic children improves neurodevelopmental outcome. Motor function appears to show less improvement. The challenges to evaluating evidence are really quite extraordinary in this area. There is heterogeneity in how the disorder was initially diagnosed. There are differences in the age at time of stem cell transplant. There's variability in follow-up without necessarily consistent measures of follow-up and very few data extending to the second decade of life. There is some loss to follow up. So all of these are issues in trying to give you a complete sort of overview analysis of what we know about treatment outcomes at the moment. What are some of the critical pieces of evidence that are needed? Well, first is sort of the basic question is, are there appropriate ways to identify asymptomatic infants with low GALC activity who would benefit from bone marrow transplantation? And it gets back to the discussion we had a few minutes ago, which is, are there markers -- clinical or radiologic or other laboratory markers -- that can say this is clearly a child who will benefit from transplant? And at this point, I think the weight of the evidence would say it's a tremendously important area of investigation. We don't have the answers now. What are the harms of screening, especially the identification of asymptomatic children with low galactocerebrosidase levels, or middle or high but not apparently symptomatic levels? What are the harms associated with the chemotherapy used to precondition newborns for stem cell transplants? What are the long-term, really truly long-term neurodevelopmental outcomes and what is the cost-effectiveness of screening for this disease? So let me thank you very much for this opportunity to share our work. I want to thank Alix and Alex for being incredibly wonderful leaders of this effort and great partners in this work. And I think we're very much open for questions and for response.

DR. HOWELL: Thank you very much, Jim. One question I would have is I would assume that the data are available about the effects of chemotherapy in other conditions of transplantation? Is that not correct? Rebecca, you should know the answer to that.

DR. BUCKLEY: Well, in general, for people who use pre-transplant chemotherapy, they prefer to wait until the child is a little older for other conditions.

DR. HOWELL: Right.

DR. BUCKLEY: Because of the potential side effects long-term of the full conditioning regimen.

DR. HOWELL: And are there substantial data that would indicate that chemotherapy in the first month of life that's used for bone marrow

transplantation is harmful?

DR. BUCKLEY: I don't know the answer to that question, but I know that most people who do pre- transplant chemotherapy prefer to wait until they're older, unless the condition is something like this where early might be better.

DR. HOWELL: Are there -- Excuse me. Duane?

DR. ALEXANDER: The second bullet in your last slide talked about harms. Do we have any evidence on family functioning in the kids who screened positive but stayed asymptomatic?

DR. PERRIN: We do not for Krabbe disease. There are data, of course, from other disorders where that has been looked at to a degree, although even there, systematic data are relatively uncommon. This would be a fabulous investigation that would be very helpful to do with the New York State population, frankly, and I understand that. We do know, anecdotally -- Chris, you may be able to embellish this. We do know, anecdotally, a number of families were pretty annoyed with what was recommended for them and sort of said no way we're going to go through this. We don't know what other impacts there were on family functioning, beliefs, quality of life, et cetera.

DR. HOWELL: So that's clearly an area that needs to be studied, I would think. Piero?

DR. RINALDO: Actually, to follow up that question, is any evidence of adverse effects in terms of insurability?

DR. PERRIN: We don't know that. We've not heard that, but we have no systematic evidence.

DR. CALONGE: Jim?

DR. HOWELL: Ned?

DR. CALONGE: Yes. Jim, I wondered, I was just looking at the specificity of greater than 99.9 percent. So I know this is going to sound crazy, but how far out can you take that? Because 99.9 percent in a prevalence of about 0.25 per 100,000, you're going to find 400 false positives for every true positive?

DR. PERRIN: Yes, I don't know that we've done those calculations. Alex, go ahead.

DR. KEMPER: Yes. The 9s go out further than the first decimal point. And if you look at the New York State experience, depending upon where you consider -- what you consider to be a false positive. For example, the 140 that were referred or the 80- some that or the 30-some that ended up getting classified into high, medium, or low risk. It looks like the false positive rate is substantially lower than the 400 to 1. It's probably on the order of like 100 to 1 or 50 to 1, depending upon where you draw the threshold. Again, my concern about relying too heavily on these calculations is I'm unsure what to do with the medium and low risk. I'd also like to go back and address a couple of other points, Dr. Howell, in terms of the neurologic impact of bone

marrow transplantation. There are some recognized chemotherapeutic agents that are more harmful than others so that they're trying to go that way. But there are no data that we could find specifically related to the harms of those drugs. And then the other issue I wanted to address was the harm of being classified in that medium or low-risk categorization. The New York program certainly recognizes that and is attempting to minimize that so that they're lengthening out the kind of follow-up that's needed for the medium and low-risk groups. And the one thing that the people who ran the New York program emphasized to me is that they're still learning as they're going along. So they expect things to change in terms of what their cutoffs are. There's nothing that's written in stone.

DR. HOWELL: I think a comment that the people around this table understand is that when looking at the rare metabolic conditions that we've all been interested in, we all are aware of what we call the prototypic child with a given disorder. And when we start looking at the population for that, you'll find that, yes; there are those that have this disease that we've talked about as Krabbe or whatever. But then there's another group that might have a very different clinical presentation with other reductions. And so, I think that's one of the -- this is one of the important learning experiences and so forth, et cetera. Fred?

DR. CHEN: Can I follow up on this false positive discussion a little? I'm looking at the figure that describes the New York screening experience. And maybe it's a question for the public health lab members around the table. In fact, there were 4,000 specimens that had abnormal GALC activity, and then those were then retested in duplicate, and they took the average of three samples. And then 230 of those samples were then DNA tested before they came up with this 140 false positive number. Is that -- does that sound routine as part of the screening process for a public health lab, or are we really looking at a false positive rate, a number that's 4,000?

DR. HOWELL: Well, certainly, in New York that's done as a part of the routine procedure. Before they do any contact and so forth, they go through this algorithm and do the DNA testing

routinely.

DR. SKEELS: Are you asking whether that's similar to other conditions that we screen for? Well, it's a little more false positives than we get for the great majority of other things that we do. To be honest, I don't think it would be unmanageable, though, as long as most of those can be resolved in the laboratory without recalling the patient or requesting a second sample. I think it -- I don't know if you would agree, Piero or Jane, but it's not totally out of the question.

DR. HOWELL: Barbara?

DR. BURTON: Just, excuse me, want to make a comment on these infants and these even the ones in the low-risk category that are asymptomatic, but those in the moderate and high-risk category and make it clear that those designations are really very arbitrary of low, moderate, and high risk based on one laboratory's experience with where values fall for babies known to have early onset disease. So they occasionally see one in that high-

risk category. They a little more often see one in that moderate risk and most of them fall in that low- risk category. But in all of those ranges have been seen infants with early onset disease. And the other thing is most of the children in those categories have two mutations. Some have only one, but most have two mutations, and many of them are mutations that have previously been seen in some form of Krabbe disease, usually later onset Krabbe disease. A lot of them maybe not in that specific combination or they've got somebody who's homozygous for a mutation that's been seen with a more severe mutation, things like that. So many of these patients are ones that we would say in other diseases, based on the biochemical and DNA evidence, are affected, yet we don't know what the phenotype is going to be. Like we have patients, for example, with Gaucher's disease who have deficient enzyme activity, two mutations, who may never manifest the disorder. Others who manifest it anywhere during the lifespan. And I think this is what we're looking at with Krabbe disease. So I don't think we should be too led astray by this low, medium, and high-risk categorization, which has just basically been invented between the New York group and Dr. Wenger's laboratory for managing the patients that come out of this newborn screening experience.

DR. HOWELL: Gerry?

DR. VOCKLEY:I think this is enormously important that we have 56 babies that coming through sort of traditional definitions of genetic disease have a genetic shall we call it predisposition for ultimately developing symptoms. And that as far as we've been told thus far, the only way to decide which of those individuals, which of those babies are ultimately going to really develop early onset symptoms and need bone marrow transplant is the examination by not just a pediatric neurologist, but a pediatric neurologist who has experience in differentiating or following these early babies. So I'm really concerned here that we have a high-risk population that we have absolutely no idea how to subsequently handle them, except to say everybody's got to come and see one person who -- or two people who know how to follow these babies and identify them. And even then, they're being put through a fairly invasive follow-up protocol that involves monthly or every 3 monthly or as needed, whatever that means, lumbar punctures and scans. And you know, this is an enormously difficult problem to deal with at the level of screening and public health.

DR. HOWELL: Are there further questions? Let me make one comment. As I understand the situation, there is only one laboratory that's doing quantitative confirmatory enzyme activity. Did your group express concern about that as far as thinking of a national program?

DR. PERRIN: I would not label it as concern, Dr. Howell. Our group did discuss with that lab its ability to expand should there be a national mandate or national expectation -- not mandate, excuse me -- of universal screening for this condition, and we were told by the laboratory director that they felt that calculating on the New York State experience the numbers that would likely come through the lab, that they would be able to do this.

DR. HOWELL: I would think it's not really a very good idea to have a single lab, regardless of their capability, in the event of a national disaster or whatever and so forth.

DR. RINALDO:I agree. I mean, this is -- the point is not about if one lab could handle it. If it is a good idea to have just one lab, what about proficiency testing, comparison? It's --

DR. HOWELL: Right.

DR. PERRIN: I'm just saying I think we could not assess that question. That's really a question for the committee.

DR. HOWELL: Let me make a comment about where we are. We have folks, as you noticed, in our public comment section who have signed up to talk about Krabbe disease and general. I might point out Krabbe and general were lumped and so forth. And then what we're going to do, we're going to go to lunch. And after lunch, Piero is going to lead the discussion of this document.
So I would suggest that we try to wrap up

with Jim, if we could, with any specific questions. You'll be here after lunch, et cetera.

DR. PERRIN: Absolutely. For sure.

DR. HOWELL: But if there are no pressing things, I'd like to go to our public comment, and I would like to remind our public --

DR. KUS: Quick question?

DR. HOWELL: Yes, as long as it's brief.

DR. KUS: It's brief. Actually, if you go to the -- the concern I have is the presentation about the treatment evidence experts. When you go to that section, you've got Dr. Escolar reporting on neurodevelopmental outcomes and Dr. Kurtzberg, and my impression is that's their program. The developmental follow-up is Dr. Escolar, and you have the surgeon saying all are normal intelligence. And then you have the developmentalists saying no, no, no, no. So the way it's presented in the chart, it's concerning to me. Shouldn't there be a common result?

DR. PERRIN: Thank you. We would certainly be open to a device on how to present this as effectively as possible. We certainly agree with you

on the -- what we learned from our conversations.

DR. HOWELL: For those of you who don't know the set-up, Dr. Kurtzberg is the transplant person at Duke that has personally transplanted all these children, and Dr. Escolar is the developmental pediatrician at the University of North Carolina who has worked closely with her. If there are no further questions, let me zip ahead and remind the folks who are going to be speaking that we will be very aggressive in keeping you to the time. And the first commentator, I think, will not be commenting about Krabbe, but Andrea Williams from the Children's Sickle Cell Foundation has signed up to comment.

MS. WILLIAMS: Good morning. Thank you, Dr. Howell and members of the advisory committee. My name is Andrea Williams, and I am here speaking on behalf of the Consumer Task Force on the Newborn Screening. It is my pleasure to provide comments to you today on an issue that we know is of high priority in the newborn screening community and has become an especially relevant model during this time of health reform. The Consumer Task Force on Newborn Screening was established in September 2007 to ensure the integration of consumer perspectives in the planning and implementation of the Genetic Alliance's consumer- focused newborn screening projects. We are a group of non-consumers and parents who have experienced a range of newborn screening outcomes, carrier identification, false positive screening and outcomes of typical normal screening. Today, we examine the roles of players in newborn screening, specifically parents and families. We'll explore key features of family-centered solutions, the changing focus of long-term follow-up, and perspectives on funding and collaboration. We encourage the committee to revisit the work completed by the Subcommittee on Long-Term Follow-up, specifically two documents. First, a statement of long-term follow-up published in Genetics in Medicine in April 2008. Second, Supporting The Roadmap To Implement Long-Term Follow-up Treatment in Newborn Screening, the product of an April 2007 working group meeting. We appreciate the process you underwent in April 2007 to craft the roadmap. It is important to make roles and expectations clear so that families understand to whom they can turn as they navigate the medical system. As you continue your work to clarify these roles, it is important to know the balance between the responsibility as parents and advocates and the parents' need to cope with the unfolding medical situation. Many parents begin their journey as parents only, then progress to parents of a medically fragile child, and then may mature into the role of a parent advocate. This process takes time, and families need help and support along the way. Each individual parent's transformation is unique. The Consumer Task Force, composed of mature advocates can help facilitate this process and serve as a resource to the committee as we seek to craft a system together. Families typically do not anticipate neither emotionally nor financially having to deal with a health crisis with their newborn. It is essential that the entire family -- parents, siblings, and newborn -- have the support from the start. We agree that a medical home that is family centered and culturally sensitive is crucial to the implementation of long-term follow-up care. The Consumer Task Force is encouraged by the balanced approach in your April 2008 statement in Genetics in Medicine. A focus on patient-centered outcomes with an emphasis on treatment, rather than only on how data moves between various entities, represents a key shift in looking at the system through the lens of a navigator. The Consumer Task Force asks that you broaden your already forward thinking approach by expanding treatment to include information. By actively translating a wide array of information about the condition for parents and families, including features of the diagnosis,

treatment options, and support systems, we create a family-centered, holistic approach to managing the condition within the family. This is especially important in instances where the most effective treatment is uncertain. There is also a need to ensure patients and families have the tools to process this information. And the April 2007 meeting that resulted in the roadmap working group explored roles and responsibilities for affected individuals, primary care providers, specialty and subspecialty providers, and public health agencies. One role that was not addressed and must be included is the role of the provider responsible for helping families to digest and interpret information from a variety of sources, including companies, advocacy organizations, care providers, researchers, in a nondirective, nonjudgmental way -- for example, decision aid programs currently used in cancer. As conditions are added to the newborn screening and have no traditional treatment option or that do not have established support systems, such as disease-specific advocacy organizations, families need help wading through the information and understanding the likely outcomes before making those decisions. Such decisions made by parents overwhelmed with care demands can be incredibly stressful without support. We must work together to build structures for a transparent, honest system to promote and facilitate informed decision-making process for families. The Consumer Task Force recognizes that this discussion of stakeholder needs for long-term follow- up care can feel small as diverse communities outside the newborn screening system wrestle with the pains of a broken health system. These forces affect us, too - - access to health insurance, disparate access to quality and timely healthcare services, availability of tests, treatments, and cures. Coverage and reimbursement for those interventions provide just a small snapshot of the forces we all face. The newborn screening community can capitalize on a larger opportunity here. This discussion on long-term follow-up in newborn screening is a microcosm for considering the impact of a health condition on not just an individual, but on a family and understanding how we can build a safety net for all families affected by a variety of health conditions. Long-term follow-up care must be integrated into the health reform dialogue. The Consumer Task Force acknowledges that the long-term follow-up in newborn screening requires a greater Federal investment both in funds and support. Without a collectively renewed systemic Federal investment, we find it necessary to ask a very daunting question. Should we continue to expand the program if we do not have in place the services to support those who are already identified and affected? It could be a disheartening question, but it becomes less so when we acknowledge the opportunity that we have before us. Long-term follow-up care for newborn screening can be a model of crucial structural changes that positively impact all health systems. This can't be another -- simply cannot be another conversation about another program that lacks crucial funding. Seize it as an opportunity to transform health. The Consumer Task Force values collaboration across Federal agencies, advisory bodies, and establishing public and private partnerships. We applaud your collective effort to understand the work of these entities, and we want to underscore the importance of your continued collaboration and engagement in these agencies, as these agencies implement facets of healthcare reform. To move forward, we need an open, networked approach to long-term follow-up newborn screening that emphasizes shared infrastructure, interconnectivity, and systemic responses. As you continue to explore long-term follow-up care, we ask that you integrate parents and families, the true expert on these issues, into these discussions. Thank you for the opportunity to provide comments today. I'm happy to provide answers to any questions from the committee. The Consumer Task Force on Newborn Screening is ready to serve you as a system resource. Please let us know how we can help.

DR. HOWELL: Thank you very much, Andrea. [Laughter.] [Applause.]

DR. HOWELL: I think as most folks were aware, but all the public comments become a permanent

part of the record and will be a part of this report. The next person on my list is Ms. Jacque Waggoner, who is representing the Hunter's Hope Foundation.

MS. WAGGONER: On behalf of the Hunter's Hope Foundation, my entire family, and all Krabbe families of the past, present, and of generations to come, I would like to thank the Advisory Committee on Heritable Disorders in Newborns and Children, the Evidence Review Workgroup, and every person who has given of themselves for the benefit of helping Krabbe families. It is because of all of your efforts, however great or small, that I stand before you today with great hope. Twelve years ago when we formed Hunter's Hope Foundation, we began a journey to do whatever we could to stop this horrible disease from destroying children and their families, as it tried to destroy ours. At that time, very little was known about Krabbe disease and very little was being done to change the outcome for children and their families. Although it hurts deeply to know that most Krabbe children continue to suffer and die, it is amazing how far we have come. Today, there is treatment, if not a cure, for Krabbe disease. Early diagnosis through newborn screening is now possible. Furthermore, it is now possible for families to have vital health information to help them not only care for their affected child, but also for future family planning. Researchers and medical professionals have more information now than ever before to help them understand the nature of the disease and how to treat it. Of all the contributing factors to this advancement, the newborn screening program has been, and we believe will continue to be, the greatest. We have seen and will continue to see Krabbe families influence State newborn screening laws, starting in New York, Illinois, and Missouri. Newborn screening for Krabbe disease means life and death to these families. As they remain relentless in their pursuit to ensure every Krabbe child has a chance for life, Hunter's Hope will continue to support them in any way we can. We are often asked how families can have their newborns screened for Krabbe disease when they do not live in New York. At the Hunter's Hope Family Medical Symposium this past August, PerkinElmer Genetics presented their plans to add Krabbe disease to their supplemental newborn screening StepOne packet by the end of 2010. When this happens, Hunter's Hope will be able to tell families that they can obtain screening for Krabbe disease no matter where they live. We are concerned, however, that the advice given to families regarding their children's diagnosis and treatment may not be well informed if they come from States that are not screening for Krabbe disease. We want to ensure that in situations where there may be an absence of a full appreciation of the variables involved, children with the infantile form of the disease, specifically the 30-kb deletion, will be handled with urgency and the results immediately routed to knowledgeable specialists. We also want to ensure that children without infantile form of the disease will not receive unnecessary transplants. It is also important that all of these children are included in necessary short- and long-term follow-up programs. There is and will continue to be great momentum for the advancement of early detection and treatment of Krabbe disease. More and more infants with Krabbe disease will be diagnosed early. We must be proactive and begin now building an infrastructure that is designed to support not only New York, but Illinois, Missouri, and other States as they prepare to add Krabbe disease to their newborn screening panel, as well as for families from other States that will choose to use PerkinElmer's StepOne supplemental newborn screening. Given the imminent increase in the number of Krabbe infants diagnosed by newborn screening, we ask that the advisory committee take proactive steps and consider your leadership, your guidance, and funding support for the following: Establish a tri-State Krabbe consortium -- New York, Illinois, Missouri -- that builds upon the New York State Krabbe Consortium with the goals of establishing clinical/laboratory

correlations which will predict phenotype. Expansion to other States of the existing Hunter James Kelly Research Institute's New York State Krabbe Newborn Screening Registry, which tracks outcomes of children with positive newborn screens and correlates results of biochemical, genetic, and neurodiagnostic tests with phenotype. Continuation of the biannual meetings of the New York State Krabbe Consortium, during which the newborn screening program are reviewed and the evaluation protocol is modified as deemed necessary. Establishment of a mechanism in which results from the PerkinElmer are routed to appropriate specialists. In addition, these children should become integrated into the Krabbe newborn screening infrastructure, including the follow-up program in place for those States screening for Krabbe disease. Planning and execution of those projects identified by the Krabbe Evidence Review Workgroup deemed important for the expansion of Krabbe newborn screening. The Hunter's Hope Foundation realizes that the journey has just begun. We remain committed to the advancement of newborn screening for all children and all possible diseases where early detection may impact quality of life, especially Krabbe disease. We will continue to do whatever we can to help save the lives of children by advocating for expanded and universal newborn screening. We will encourage and support others in their efforts to do the same. Thank you.

DR. HOWELL: Thank you very much, Jacque. [Applause.]

DR. HOWELL: Our next presentation I would like to ask Dr. Jennifer Kwon from the University of Rochester.

DR. KWON: In New York.

DR. HOWELL: In New York, and not in that cold Minnesota.

DR. KWON: Yes, because Rochester isn't cold at all. I want to thank Mrs. Waggoner for her excellent comments, especially the suggestions about long-term follow-up and data collection. I think that her comments were so broad that it allows me to indulge myself in just pointing out some of the details of following high-risk patients. First of all, I appreciate this committee's careful review of the available literature and expert views on the New York State Krabbe newborn screening experience. I would like to address a phrase that was in the evidence review document. The statement on page 19 says that, "Of the seven high-risk cases detected in New York, two were considered early infantile forms of Krabbe disease and referred for human stem cell transplantation because of their GALC genotypes and the early signs of neurologic disease." So the suspense is building now, and then the following sentence says, "Dr. Wenger reports that the five remaining children who screened high risk had genotypes considered to put them at low risk for early onset disease." I follow one of these five patients. She was born in November of 2008. Her enzyme activity level put her in the high-risk group, and she is heterozygous for two mutations, each of which has been seen separately in children with early onset disease. I have the benefit, as you are aware, of being in New York State and being able to contact a number of experts on Krabbe disease to help me advise my patients. My understanding of the best information available at the time that I met with this family was that this patient was very likely to have early onset disease. When I met with the family, she was 3 1/2 weeks of age, and I outlined our protocol of investigation and referral to Duke University. She also met with our geneticist, as well as our own center's bone marrow transplant team, as well as the

electrophysiology team and the anesthesiologist. The family continues to be followed by me, but they are not followed per protocol. They were very upset at the diagnosis, as you can imagine. It's a heart-wrenching and horrifying diagnosis. Furthermore, the fact that they would go through this very invasive suite of testing in order to be categorized as possibly being eligible for a treatment that they felt was experimental and highly risky was very offensive to them. They were lost to follow-up for some time because, as they told their pediatrician, they were convinced that they were part of someone's research experiment, and they were uncomfortable in following up with us. Their pediatrician was able to smooth things over to allow them to at least follow up with me. It is this level of prognostic uncertainty, of how well our clinical risk levels actually work in practice that has made following these children and counseling these families very difficult. Thank you.

DR. HOWELL: Thank you very much, Dr. Kwon, for that informative comment. The next person on my list is Ms. Micki Gartzke, who is a Krabbe parent. And Micki has words to present.

MS. GARTZKE: Good afternoon. Thank you to Chairman Howell and all the members of the committee for all your hard work and the opportunity to speak here today. I would also like to say thank you to the two previous commenters for Krabbe disease. We need all the voices we can to move everything forward as quickly as possible under all the due diligence for the children. As Dr. Howell said, my name is Micki Gartzke. I'm the vice president of the Save Babies Through Screening Foundation, and I'm also the mom of a little girl that died of Krabbe disease. And I speak today as a parent and not a parent advocate, which is a role I've filled since 2000. As we know, newborn screening is available in New York for Krabbe disease, and with that comes along for the children who need assistance the residual health benefits of this early identification. For that, I am very grateful. Today, listening to Dr. Perrin's excellent talk, the key findings that he reviewed I felt clearly showed a strong case for newborn screening. The sensitivity and specificity seemed good enough. The existing treatment is good enough, although we want a much better treatment, still needs to be much better. I feel the availability of treatment is good enough. We want expansion of capacity in the future, and we all know that the collaboration will continue to grow. On the economic evidence, I was just wondering, I heard at the ACMG blood spot meeting the other day there were a number of States who have been screening the full panel, and for a number of years, they had not even found any patients with some of the disorders that were on the panel. So I wasn't really sure how the whole cost-effectiveness really worked when that is figured in. I'm not sure how you put a real dollar value on a life -- you know, on this life saved, as a parent whose family has survived a great loss. I do have a friend that knows. Her name is Gina, and she's just about to turn 10. She was born with Krabbe disease, and she was transplanted before she turned 1 month old. She wanted to come to this meeting. Her and her mom and I talked about it, and she thought about it. And then when she saw her schedule for this week, she was really disappointed that she couldn't come here to meet all of you because she was really looking forward to it. She understands all of this is going on, and she was really excited to show you her straight A report card from last year. She goes to a public school. She's in a mainstream class. She is differently abled. She is cognitively age appropriate. But we lost out because her schedule is busy from educational and social activities. She had a spelling test today at school. So she couldn't be here. The test starts in about 15 minutes. And she has after school soccer, like many 10 year olds. Hers is a little bit different. She has a motorized wheelchair. They play with a real big ball. Her team won the trophy last year.

And more importantly, tomorrow is Girl Scout weekend, where she will go with all of her 20 Girl Scouts who are all typically developed children, and they will all sleep in bunk beds in one big room with no adults in the room. She's never been able to do that before, of course, because of her different abilities. So as much as she wanted to come and share all of this, she felt sleeping in the bunk beds with the other girls was what she really needed to do. And she assured me through her speaker -- she does not articulate so well. She has a little talker. We call it her "ya-ya." She articulated through that that she would look on her schedule in the future once we get the next dates and see what we could put together. In light of all that, of course, I'm very supportive of the need for children born with Krabbe disease to have the chance to grow up and live their lives to the fullest, no matter their different abilities. In light of the fact that PerkinElmer is soon to add Krabbe disease to its OneStep, you know, for-purchase newborn screening program, I'm very excited about that. But then that puts us in a position where consumers who are able to purchase newborn screening can purchase newborn screening above what is available. That gives me a little bit of concern, but I always am hopeful, and I know that you guys are always dedicated to doing hard work. So I ask you today to please to continue moving forward at Godspeed with all of your hard work and your important work, to continually evaluate. And I look forward to the day when this disorder is added to the federally recommended panel. Many of the children are depending on you. Thank you.

DR. HOWELL: Thank you very much, Micki. [Applause.]

DR. HOWELL: The next commentator on my list is Michelle Fox.

MS. FOX: Hi, I'm Michelle Fox from the National Society of Genetic Counselors. And I just wanted to make a comment about what it's like to call out newborn screening results and having done that for a long time now when we really don't know what the answer is. We don't know what the prognosis is, and we don't know what the diagnosis means. My metabolic nurse tells me, "Tell everybody relax, reassure, and retest." But that's easy to say and hard to do. Thank you.

DR. HOWELL: Thank you, Michelle. I think that many understand that. And Dr. Diane Sawyer from the CARES Foundation would like to comment.

DR. SNYDER: Hi. I'm Diane Snyder. [Laughter.]

DR. HOWELL: Slight slip of the tongue.

DR. SNYDER: That's okay. People do it all the time.

DR. HOWELL: We actually had the TV cameras all ready and here you are. You're disappointing us.

DR. SNYDER: Thank you. Good morning. I know lunch is soon. So I'll be brief. Actually, my comments you all have a copy of.

DR. HOWELL: Yes, we do.

DR. SNYDER:I'm Diane Snyder. I'm actually a physician locally, but I'm also on the -- a board member of the CARES Foundation, as well as a mother with a child born with congenital adrenal hyperplasia. And I'm here just to -- and thank you for hearing me, as well as Dr. Therrell for facilitating my comments here. The CARES Foundation is about 9 years old, started by a mother of a child affected with CAH in her basement when she had a diagnosis and nowhere to go. And I'm here to tell you the very exciting project that we're working on. This woman, Kelly Leight, had a vision to establish comprehensive care centers, similar to the Cystic Fibrosis Foundation's, for children and families affected with CAH. And after years of planning, I'm happy to report this past Monday and Tuesday at the other Marriott, a group of us sat down, including pediatric and adult endocrinologists, pediatric surgeons, urologists, consumers, pediatric nurses, as well as our current sponsors from the New York Mid-Atlantic Consortium for Genetic and Newborn Screening, the National Newborn Screening Genetics Resources, and support from HRSA. It was a very exciting meeting for us to finally sit in a room. We've been working groups for the past 6 months on our vision for comprehensive care centers around the United States. Our initial project is going to be to try and establish a registry of children born and detected through newborn screening with CAH around the country, to be able to then have a place to refer them to of specialists quickly. We envision centers that have surgical expertise for female children born with ambiguous genitalia, as well as families to get treatment, especially in salt-wasting CAH before death. We are fortunate through the CARES Foundation to have already established newborn screening in all 50 States for CAH. So we're a little ahead of some of the other foundations. So our next step is to model after some of these other groups to have a place where we can then send these families, and not just for infancy and childhood, but now through adulthood. Just like cystic fibrosis, we know that these children grow up, and then where do they go and what happens to them? And then what happens when they get pregnant and they have children? And they need screening during pregnancy and treatment now during pregnancy. So as part of our goal, I have -- they are listed here of what we're attempting to do through the establishment of these comprehensive care centers after we start with a national registry, and this would be a win-win situation for patients, families, healthcare providers, and public health to provide a roadmap and model for children with heritable diseases from diagnosis on. Thank you.

DR. HOWELL: Thank you very much, Dr. Snyder. [Applause.]

DR. HOWELL: We have one more written commentary that will go in our record from Mrs. Rebecca Ruth, who is here from Missouri. And Mrs. Ruth has written a very thoughtful document. She's the grandmother of Brady Alan Cunningham, who died from Krabbe disease, and who has worked very aggressively in Missouri on newborn screening laws. And a law that was passed on July 8th of this year requires screening for Krabbe, Gaucher's, Pompe, and Neimann-Pick beginning in July of 2012. And Mrs. Ruth has written a document supporting, strongly supporting and advocating for newborn screening for Krabbe disease based on her own personal experience, and her note will go into our record and so forth. Thank you very much. Those were all the comments that I have written. And so, we'll stop for lunch. And after lunch, we'll come back and hear from Dr. Rinaldo and discuss this recommendation. So we'll see you in a little while.

[Break.]

DR. HOWELL: Let's take our seats. I think many of the folks in the back of the room still are not back from having lunch. It's hard to get to lunch and get back if you're having to go. But we need to sit down and start our discussion of Krabbe disease. And again, this will be led by Dr. Rinaldo.

DR. RINALDO: Should we start?

DR. HOWELL: Yes, please.

DR. RINALDO: First, I would like to start with really development and common understanding, and I asked this question to Dr. Howell just during lunch. Just what exactly are we supposed to achieve today? And I'm told that we are somewhat at the point where we have digested, if not ruminated, this evidence for quite some time, and we've got to come to a conclusion. With that in mind, first I want to start saying that I really -- my personal opinion is that what we heard today and in May through a conference call is that the evidence review system works. I think that Dr. Perrin and the group and Alex have done a phenomenal job in really summarizing the issue and providing us the tools to do the job that is expected of this committee. I would like to say that I don't think it's an easy job, and I was actually revisiting the slides that we considered in May. I believe they were given or distributed again as a supplementary, and in case you don't have them in front of you, but slide 28 is the one that summarized the following point. The slide is titled "Gaps in Evidence." The conclusion then was the testing algorithm may need revisions. The case definition is unresolved. The benefits of transplant are uncertain. That substantial harm is possible, and cost- effectiveness is undetermined. I feel I would like to start sort of saying that I don't think we have made much progress from that point. I think the issues are the same, and again, I probably -- we can sort of speculate that is unlikely to change any time soon. Now in terms of how to discuss it, I would like to propose that we do this just sorting the three elements, as we had done for the nomination form. But clearly, there are issues related to the condition itself, to the test, and to the treatment. And perhaps we can make the job somewhat easier if we focus on these three separately, starting with the condition. And I certainly don't want to really state an opinion to be discussed by others, but I clearly think that we are facing a condition that in the worst-case scenario is truly a devastating disease with little or no doubt of the seriousness of the consequences. So that's easy to say. There seems to be a tail that in terms of clinical manifestations and timeline of these manifestations that is clearly undefined. With that, I think my proposal, if that's my role, is to agree that clearly Krabbe disease, the infantile form, even with the uncertainty of the other phenotype, constitutes a disease that would benefit from early identification and intervention. And with that, I would certainly welcome any comments from the rest of the committee about this point. And again, if there is agreement, that we try to deal with the three aspects separately.

DR. HOWELL: Any comment about that? I think that certainly I would agree with the fact that it's obviously a very serious condition that would benefit from early diagnosis and treatment.

DR. WATSON: I'm trying to figure out what I call the disease. The clinical disease I completely agree with you. I have a lot of difficulty on the laboratory side of the disease. And I think that's something that for diseases like this, that we could probably provide more information in the evidence reviews on. I didn't understand the basis on which mutations were classified as

mutations versus variations, which contribute significantly to predict -- being able to predict anything. The enzyme assay, whether it's clear delineations between these categories or really tight, subtle differences and things like that, made it very
difficult for me to tie some of the laboratory components into the condition itself.

DR. RINALDO: Thank you, Mike, for jumping to part two because I'll consider that might be the end of part one. And so, is there anything else about the condition that we want --

DR. HOWELL: Would anyone disagree with the description of the condition as being a really serious one?

DR. ALEXANDER: No. I certainly don't disagree with it, but I don't know whether you consider it as part two or some expansion of part one,
which is that it's complicated by the fact of variations in the genetic phenotype, variations in the chemical enzymatic levels that are associated with the disease, and extreme variations in the severity of the condition itself. Now you prefaced it all by saying that the severe infantile form of the disease is serious, and that's fine. But it's not just the infantile form of the disease, and that's what makes it so complicated.

DR. RINALDO: It's really the transition between the two. I think that we clearly are dealing with the tail, the case definition, and the correlation, as Mike said, between a certain way to generate and assess laboratory data and correlate that to the clinical picture. I would consider that probably the key element of a discussion about the second part, and that is the test and the ascertainment process.
So following what Dr. Howell said, so I think that, overall, we agreed that this is a disease that at least at the more sort of better defined end of the spectrum clearly would benefit from early identification and early intervention. Do we agree with that? All right. That was the easy part. I think -- you know, I really think we should say that the New York program deserved to be commended for doing really trailblazer work in really considering all possibility and making sure that their sort of the collection of the evidence was done leaving no stone unturned. That said, I wonder if to what extent the protocol they had developed? I still think that there are some areas of uncertainty that at least are not clear to me, especially when you look at the beginning of their protocol where they talk about percent of -- my finger begins to hurt. But, no, I can handle it. [Laughter.]

DR. RINALDO: Thank you. All right. I play with pain. No, seriously, I am still debating what exactly that less than 20 percent of a daily mean means. I would like to know what's the variability, and I would like to know why at the beginning we make the decision. The decision is based on percents, and in the end, we are at absolute value expressed as activity. I think there should be consistency. I think I really would like to know what is the average? What is the mean? We're talking later of 8, 10, 15, and I think it's already brought up by Mike and personally I would be quite concerned of making decisions there seems to be clear cut in the assignments of phenotype. So 14 means something, and 15 means something else, 16. I don't know how you can really say something like that. I'm also troubled by the fact that there seems to be a protocol that leads to referral of patients who are likely to be a carrier with one mutation found. That somewhat is a major departure from most of the goals for most of established

conditions that we screen for. So, but with all of that, I -- again, it really depends where also you draw the line of -- I can really do it. Thank you. Where you draw the line about the performance of a test. If you take 140, I think that New York has clearly shown that the false positive rate is extremely low. It's exceptional, a point or 2 percent or less. But the positive predictive value is 3 percent. And I think that Dr. Skeels mentioned earlier, that is not -- on the other hand, if you consider true positive, all those 70, or it is more, all the patients including one of the three risk groups actually jumps to 43 percent. So depending what you consider the true positive, you have an order of magnitude of difference, two orders of magnitude difference in the positive predictive value that may even be much better. So, personally, I think that there is a test. It works. It could be improved, but I still have no idea how much it costs. And I know that we are not supposed really to dwell too much on the cost, but to say that Krabbe disease should be added as a singleton test to the standard newborn screening panel, it seems to me close to be an unfunded mandate. Dr. Skeels?

DR. SKEELS: Thanks. This is a little tangential, but I want to throw it in. It's terrific and highly instructive to consider these LSDs as separate entities, but in fact, when we get around to screening for them, we'll probably be using a multiplexed assay that screens for all of them at once and thereby lowers the unit cost. And we'll be sort of where we are with tandem mass, which is to say, well, we don't have to justify every new analyte that we want to look for, every new disorder, because it really doesn't cost us that much to do. And I'm not saying that's right or wrong, but that's a very likely evolution of this.

DR. RINALDO: Thank you, because that's exactly what I was planning to say as my next comment. I understand reference to the imminent availability of a commercial test. I know nothing about it, and I don't know if it's going to be a singleton, it's going to be multiplex, and how well it's going to perform. But I am uncomfortable sort of reaching a conclusion about the effectiveness and the value of a test where I have no idea one of the two elements will lead to the definition. One, again, is the quality of the product and the other one is the cost of it. Gerry?

DR. VOCKLEY: This is an immensely difficult discussion from a number of points. At a professional level, I take care of kids with rare diseases all of the time, and so, of course, I'm a strong advocate for doing whatever we can to identify these conditions early and treat them. From a personal level, I think if we made less bombs and took care of our kids better, we could afford this with no question. But from a public health level, I think we have to view it a little bit differently. And there are a number of nonlaboratory methodologic pieces that I think we have to consider. Number one, the incidence -- well, it depends on what we describe -- what we call incidence. But the apparent incidence of disease that the program is saying needs to be treated immediately is very low. The definition of who needs to be treated is right now very, very nebulous. There isn't, in the end, a test that allows us to take the 56 kids who passed through all levels of screen and were now viewed to be at risk -- mild, moderate, severe -- it doesn't matter, at risk. And there isn't a test that allows us to differentiate them. Even worse, the seven individuals that were in the most severe category, the ultimate determination as to whether or not they were at risk was one individual saying, "In my experience, this mutation doesn't put them at high risk." When, in fact, and I don't have those mutations in front of me, but we've heard that those mutations have appeared in individuals with Krabbe disease and in other clinical situations. We have a therapy, but it -- and it might have a wide enough availability to not be an issue. I

think it probably does. But we don't really have a lot of data on efficacy. We do see that patients are surviving. That's one very --

DR. RINALDO: Gerry, that's part three.

DR. VOCKLEY: That's part three. Sorry. Okay. And then, so I think we're looking at a number of methodologic questions that may or may not be solved by multiplexing, but I think probably that would eliminate many of them. But we still need a lot of additional data about what's coming out at the other end. What are we identifying and what's the likely outcome? I think rather than moving to a mandate to say we want to identify more of these kids so that we can figure out what to do with them, we have some States that, for one reason or other, have decided to be on the forefront of this issue. Let them. Let's help them. Let's fund them. Let's bring them into whichever alphabet soup of Mike's is appropriate and help them answer these questions so that they can come back in whatever the amount of time they need to be able to answer the kinds of things, the questions that we're asking here.

DR. RINALDO: Well, okay. I think we are sort of -- well, it probably is inevitable we jump back and forth on the different aspects because they are so closely entwined. I really would like to make a comment, though, that I'm always aware of the possibility of unintended consequences. And I think around the table here, there is enough I think awareness of the fact that in the last few years, a true major accomplishment has been the fact that we went from a system where even in this country, everybody seems to be doing something different to a degree of uniformity now. That is, I think, quite a remarkable achievement. In a sense, it's like we said, okay, we got to this point, and now things will start again. The hope was that we created a baseline where expansions or some people request reductions of the panel will be driven by a consensus process driven by evidence review like the one we just heard. I am a little uncomfortable that, basically, it returns to be a free-for-all where the power of lobbying and advocacy can influence the change of a landscape. I really think it should be based on evidence and expert review of the evidence and discussion of the evidence rather than out of the blue having States that said, "I'm going to add this or that," because it's only a matter of time where we will again end up having a very, very diverse patchwork of panels. And I really hope that the memory of those days where we were looking up MCAD families with a dead child and having to explain to these families that the only reason why their child was dead was born on the right or wrong side of the border. It's going to be inevitable that we will really cause the same kind of angst by stipulating that every State will be different and is really the luck of the draw where your child is born that will be picked up. I think that giving up consistency, uniformity as a solid foundation for universality is a slippery slope that, personally, I would -- well, it's really not about what I think, but it's more about watching, going back to where we were, and some of the things we were experiencing then were outright ugly.

DR. HOWELL: What specific recommendation would you like to make following that comment?

DR. RINALDO: Well, the recommendation would be to exercise some constraint and let the process,

you know, work. Let this committee and the Secretary, based on recommendations coming from this committee, make changes to the recommended panel and actually strive to have a fast implementation of things that have been deemed appropriate for expansion of the panel. I understand that some of the new States, I understand Missouri and Kansas -- and I personally have no really opportunity to see what exactly. I've heard comments. But it seems to me that if we now have States already are on track to add conditions that we didn't even feel appropriate to send to the Evidence Review Group, that really becomes a problem.

DR. WATSON: It's really a very highly nuanced problem. If you look, there's enormous variability among the States in what they can do when they're in a pilot environment. In some States, they actually have to mandate something to do a pilot where you actually can follow up the children. So it's not always mandating because you have all the data to say that everybody should do something, but it's often your law that says the way to do the pilot is to have to mandate and then I think do what New York did, which was a very, very careful data collection activity around that particular screening test and assess over time because you really don't know these. In fact, I expect this to happen a lot. You don't know a genetic disease until you start finding whatever it is in newborns and then following it. And so you have, even though you often say in these kinds of things "don't do that one," I think you're saying maybe don't tell every State to go do this today. But you don't want to shut down that piece where you're continuing to gain, to accumulate the data in that pilot setting that tells really in a very well-organized, controlled way that helps you better understand what the final decision over time ought to be.

DR. VOCKLEY: Yes, I think, Piero, that the way this process is constituted that we are -- we ask individuals or organizations, whoever, proponents to submit something to add to the panel as opposed to prospectively going out and saying, okay, now we're going to look at this disease. Now we're going to look at that disease. It essentially dictates the kind of process that we're talking about. That is, there will be an inevitable ebb and flow of interest in one disease or another because of personal, political, and honest-to- goodness public health kinds of issues. I don't actually think that's a bad idea. I think that it is okay to have a State say, well, for whatever reason, we've decided we want to move this forward. If New York hadn't started this, then this would have never come to us. And it's circular argument. So I think to say that we have to maintain uniformity at the level of the States, it eliminates some of the hybrid vigor of the program perhaps? However, I do think that once we get to a point where there is enough accumulated experience to start talking about the strength of what's happening, then this is where this panel has the opportunity to come in and be a little bit more -- provide a little bit more guidance. So I think that the guidance that we need to provide is that -- the question that we're being asked right now is to add this to the recommended panel. I think that the data provided don't support the adding it to the recommended panel and that we can list those reasons. Now the programs that are involved in looking at this disorder can look at those recommendations and -- that recommendation and those reasons, and they can decide, "We disagree. We're going to find more data. We're going to study this better, and we're going to be able to come back to the committee at some point in the future with the revised application." More power to them. I think that's the way the system -- I just don't see any other way for the system to work, given that we cannot drive the agenda for the diseases to be studied.

DR. HOWELL: Let me elaborate a little bit. I think the question before the group today is based on the evidence that we have presented, that has been presented and discussed here. What would we recommend about adding this to the panel? And I think we need to make a specific comment about that. We can go through what we've heard, and does the evidence that we've heard about the condition, the test, and the treatment at the current time support the addition or not support the addition? I think, at the same time, again, to elaborate on what Gerry said, let's assume that we say, well, it doesn't support it. Then I think it's incumbent upon the group to say these are the areas where we need additional information or what do we need to do and so forth? And then we would strongly suggest that that information be gathered, and we'll have some specific recommendations about how to do that. And then once that's gathered, hopefully, come back and say, you know, well, now we know this. We know this, and we would have a different recommendation. But I think we should go through systematically, Piero, if we can, and make a decision about whether or not it supports adding at the current time.

DR. RINALDO: Okay. Before passing to Dr. Skeels, just remember that, technically, we're not supposed to say -- it's more complicated than the choice between add and do not add. There are three other possible. There is a total of four possible options. And some of them may have some fairly significant consequences because, remember, one of the options here is to say that the evidence says that it really shouldn't be added, that the evidence is already there that it shouldn't be done. So, as long as we are all on the same page with that. Dr. Skeels?

DR. SKEELS: I was going to say almost exactly the same thing. We have four categories, I believe?

DR. CALONGE: Yes.

DR. SKEELS: And I think for Pompe, we voted for category three, which was, this may at some future date be ready for newborn screening, but it isn't now, and we need more information or something like that.

DR. RINALDO: I agree, and I think I recognize Dr. Calonge's voice on the phone, and I really -- Ned made me a believer of a process of the

key questions. But I'm taking really exactly his words. One is that translating evidence or lack of into recommendation, we have to do three things. Pass judgment regarding the magnitude of net benefit, and that's benefit minus harm; judgment to the adequacy of evidence in answering the key questions; and then judgment of the certainty of net benefit. So, and just to continue along that line, remember, I just want to remind everybody of the four possibilities. Recommend adding the condition to the core panel. Recommend not adding the condition to the core panel. That's option two. Recommend not adding the condition, but instead recommend additional studies, which is I think known as option three. And the fourth one that perhaps is a bit redundant is recommend not adding the condition now. Well, perhaps that's what we did with SCID, where it was somewhat a growing body of evidence suggesting addition, but it was not quite ready. So I would say that's the fourth one. Now if I take Gerry's comment made earlier, I think you have stated that you don't think we should add Krabbe disease to the panel now.

DR. VOCKLEY: No, no, no. No. I think we shouldn't add it based on the data that we have, and I find it difficult to believe that they'll provide the data that will make it reach that level. But if they want to try, it comes back as a new -- essentially as a new application essentially. So I would say not add it.

MS. MONACO: I just -- I wanted to question at what point do you decide that those -- that data would be sufficient enough? I mean, because we're asking for pilot studies to provide more data. But I think in these instances, I don't think with the rarity that we'll ever really ever get the kind of numbers that we want to see. And if you are that family that's affected and your baby is screened and detected, that's 100 percent. So, and the way the budget is and everyone is going to say the lack of funding to do their studies, but by having these few States add it to their panel and whatever information you gain I think would be information helpful.

DR. RINALDO: Actually, I think it's a very important point because I don't remember on top of my head the number of births. I know in Illinois it is 185,000. So smaller, but a large State. I think it might take Kansas 10 years to add any meaningful data to this process. Missouri -- well, Kansas, I don't know how many.

DR. BURTON: Missouri has about 80,000.

DR. RINALDO:Eighty thousand. So, but Kansas, I think, is less. And I understand, was told that Kansas also has reached the same sort of legislative mandate for testing for it. Maybe I'm wrong, but I've heard that being said. So I really think that they need to have an appreciation of the fact that these are not 6 months and you're done. So you're making a commitment to really contribute data that goes beyond the analytical validity, you know? You can quickly come up with data about false positives and specificity, but the clinical validation will take a long time. Now that's a point that Mike has made earlier and others about, well, hopefully, this could actually be an important point to make that people have to start working together rather than doing independently, which historically is what I believe happened in most cases with MS/MS expansion.

DR. HOWELL: I think that as we move ahead thinking, it seems like there's a sense of the committee -- and again, we've not polled the committee -- that the information at the current

time would not support adding to the core panel today. And the next question is that what sorts of information would you want? What are the deficiencies that could be conveyed to the people that will be proceeding at this point? And hopefully, they will be working as a group.

DR. RINALDO: Well, I guess we'll go back to -- well, we clearly have to say, I think we haven't talked yet about the treatment and the effectiveness of that and the harms related to the treatment. Duane?

DR. ALEXANDER: Yes, I certainly agree with the position that based on the information that we have at the present time, I'm uncomfortable with recommending that on a national basis we recommend adding this to the routine panel. However, I think we have the good fortune of what I will call not an experiment of nature, but an experiment of government, if you will, where we have in place, several places and probably an increasing number of places where this is being done. And it can be done in a more effective way than it is being done if we pool resources and reach agreement on a common protocol to answer the questions that were left hanging from the report. It wasn't that the report didn't try to get them. They did try. They asked the questions, and the answers weren't there. And we do have the opportunity to do an effort of putting together the States that are doing the screening, probably in the Translational Research Network that Mike has put together, and gather that information in a systematic way that will assure that we get the answers sooner than we would if the States went ahead all completely on their own. So that would be the course that I recommend. We have almost a parallel to it with the SCID recommendations, where we believe that we don't have the information yet because we haven't picked up a patient yet in the screening. But we believe that eventually that's going to come, and it should come fairly soon. And the sooner we go about putting these together and doing it in a systematic way, the sooner we'll get the information that will allow us to make a decision. So that would be my thought that we ought to try it and go ahead in a systematic way to gather the information to answer the questions that remain after the report today.

DR. HOWELL:So Dr. Alexander is supporting recommendation number three on the slide, which recommends not adding the condition, but instead recommend additional studies. And furthermore, importantly, that New York and Illinois and Missouri that we know are committed to do this, that they combine their program so that they have a common pathway and so that information can be gathered systematically. And obviously, that's what the Newborn Screening Translational Research Network was established to do.

DR. RINALDO: Before I give it to Mike, I assume this would be a funded recommendation or an unfunded recommendation?

DR. HOWELL: There is funding in the Newborn Translational Research Network. I can't comment about how much is there. But the point is the Newborn Translational Research Network is funded.

DR. WATSON: When I look at the differences between not adding now, but wanting to get more information -- sort of the category three versus category four -- category four to me really brings the whole "harms" piece in. And if you see real harms from whatever is taking place that can't be managed, then that's a very different kind of no than, no, the data just is kind of not good

enough to say yes. DR. RINALDO: Actually, Mike, sorry, I don't mean to interrupt. But four is what we did with SCID. I think four was --

DR. HOWELL: Three. We did three with SCID.

DR. RINALDO: Well, remember, we set four conditions that my understanding with the discussion

with SCID was four conditions have been met -- detection of a case, maintenance of the performance metrics, availability of quality reference material from CDC, and addition of at least one or more programs.

DR. HOWELL: That's the recommendation.

DR. BURTON: That's the recommendation.

DR. RINALDO: So, well, then somebody has to explain to me what's the difference between two and four.

DR. BURTON: Three and four.

DR. RINALDO: Two and four.

DR. BURTON: Two and four, you would never add it.

DR. GREEN: That's not the wording that's in the formal recommendation. The problem is that Piero has the formal --

DR. BURTON: Piero, these are your slides, I think?

DR. RINALDO: I cannot hear you.

DR. GREEN: I think that part of the problem is that this is not the wording that was formally recommended by the committee. And so, what I gave to you in spots that maybe is difficult to read on the fly is the wording that the committee had approved. So I'm just suggesting that you might want to quote that. That would be helpful. So the slides are wrong.

DR. RINALDO: Okay. Ned, it's your fault. [Laughter.]

DR. CALONGE: Well, I'm glad that I get credit for something.

DR. HOWELL: Absolutely. Absolutely.

DR. CALONGE: I think the basic idea was that the number two was kind of what Mike was saying that we felt there was sufficient evidence where we had enough certainty that the test either provided zero benefit or net harm that we would recommend against adding it. The other two categories are for the insufficient evidence. And one of the categories is insufficient evidence, but we're kind of optimistic about this, and I think that's where SCID was. We felt that the test looked good. There is good reliability. We had a treatment. The treatment looked like it worked. If you didn't get the treatment, you did very poorly. Early treatment made a bigger difference compared to waiting until the child became clinically evident. But we kind of had this gap in the evidence of we actually hadn't detected any. So the idea is while we're kind of optimistic about this and we think supporting in terms of reporting pilot studies, we would put it in that category. The other category is just insufficient, and you know what, we don't know enough to say any more than that. So it's not a death knell. It's still insufficient. That's not going to say it would never be added. It just doesn't have that sense of optimism, we're almost there, that we wanted to kind of push it from the standpoint of we really need to find ways of supporting the research to fill in the evidence gaps. Does that make sense now?

DR. RINALDO: It does to me.

DR. HOWELL: Yes. Yes.

DR. RINALDO: I just want to be sure we are all on the same page. So, basically, number four is not now, but looks like you are beginning to see the light at the end of the tunnel. Three is still not enough information to really decide either way.

DR. CALONGE: Right. You got it. Perfect.

DR. RINALDO: Okay. So I guess I don't know if the fact that one of the three categories really steps into category three, which might probably be all we need. But what about treatment? Who wants to say something about -- I understand there was this first meeting in August, and I don't know. I know, Mike, you were there. I don't know if we can summarize the discussion or something, but it's concerning to me, listening to the evidence review presentation, that there is disagreement. And now also we had Dr. Kwon making extremely, to me, impressive point about the fact that if people cannot agree on what they are seeing, it's a problem in itself. Gerry?

DR. VOCKLEY: Yes, I actually -- we were trying to figure out which number I was recommending. So I think I was actually recommending number two. And the reason is there, at this point, is just nothing in the application and nothing in the evidence review to suggest that we're remotely ready for this. There are way too many questions, and I am worried that identifying kids who are "at high risk," seven individuals who if somebody other than David Wenger looks at it, says, "Yes, we'll transplant them," that we could actually be causing harm. So I think that what we have to send back is a clear sign that you have a much higher level of hurdle to overcome to bring this back to us than if you were in category three or four. And in fact, you better look at your program very, very carefully because we're concerned that you might actually do some harm. And I don't -- we can't say don't do this. That's not our -- that's not our mandate, as I understand it. But we can send back a note that says -- I mean, we can send back very clear guidance that here is you've got to be very careful here. If you want to bring this back, here are some things you need to address, but be very careful because we're worried about it.

DR. RINALDO: Chris, before I let you -- basically, the difference between two and three, two it really begins to step into the territory of evidence of harm. Three is, again, it's still a mixed bag and it is not clear. Chris?

DR. KUS: Just to be clarified, so four is even less clear, right?

DR. RINALDO: I think that four is what we did for SCID. We said there are four things that need to be achieved.

DR. HOWELL: That's number three.

DR. RINALDO: Ah --

DR. GREEN: May I speak? Can I refer to the bench that we've agreed upon? Is that okay?

DR. HOWELL: Speak briefly.

DR. GREEN: Yes, I'll speak briefly. So one

we agree upon. Two is no, is evidence of net harm. Gerry's right on that. Three is what we did for SCID, which is that there are additional studies -- there are additional data that need to be generated, but the group is optimistic that that can be accomplished. And four is we just don't know.

DR. HOWELL: I think that's my understanding also. Barbara?

DR. BURTON: Yes, I want to --

DR. KUS: Could I just finish? I mean, I want to just finish a comment because of Gerry's comment. I guess if I see number two that comes out of this group and I'm in New York, I'm saying this group says that we're doing harm, and we should really seriously consider stop doing it now. Now, I don't know that I would agree with that, but I just want to be clear that's how I would take it. Okay.

DR. HOWELL: I would take it the same way, and I would also disagree with it, clearly. Barbara?

DR. BURTON: Yes, I just want to say that I strongly disagree with that because even though there has been much presented that suggests that the possibility of harm needs to be explored, I have seen nothing that really shows that harm is being done through the screening. I also think there are compelling reasons that have been brought forth in support of screening. I mean, there are clearly children with Krabbe disease alive today that would not be here had it not been for early diagnosis through a sibling and even one case in New York through newborn screening, where the parents had been, had the benefit of choosing a treatment that we have seen clearly changes the natural history of the disease. There is no question that most of the kids who are surviving are not normal, but they are surviving, and you cannot argue with the survival statistics. So the treatment issue I think is that there is a treatment. It changes the natural history of the disease. Should parents of affected infants have the opportunity to make a choice as to whether they get that treatment or not? And so, I think that is a compelling argument. I think we've seen lives are saved. There certainly may be laboratory issues, and I think there are those remaining to be fine-tuned. And I think we need additional studies. But I don't think in any way, shape, or form you can say that there hasn't been some evidence presented of benefit to some children from the early diagnosis that would come from screening. So I think it would be a huge mistake to just say that this should stop now, as opposed to we need to get more data.

DR. HOWELL: Mike?

DR. SKEELS: I'm sort of vacillating between two and three, and I have to say I'm really impressed with the New York data. There is a large number of children. It was very elegantly done. I think I understand the data, and I think if you continue to do additional studies, even if you replicate it 10 times, you're going to have exactly the same information in front of you. I don't think that continuing to study another 750,000 or 7.5 million children is going to contribute new information. And based on what I saw, I'm with Gerry. I don't think that New York should be screening for this, and I don't think the rest of us should be either until we can actually do a good job of it. And if that offends New York, I apologize for that. But it was the legislative body that made that decision, not the newborn screening program.

DR. HOWELL: Jana?

MS. MONACO:I'm sorry. I have to disagree. I have to agree with Dr. Burton because, again, however small the numbers are, they are validated true cases. And as she said, there are children that are surviving and thriving because they were screened, and it doesn't appear that New York is running a gamut and trying to accomplish as many transplants as they can. I mean, it seems like the evidence that they've provided, that they are truly trying to separate these cases and discern which mutation they have and not really jump the gun with how they're treating these children. And I think we have to respect and not dismiss that information and use it as a foundation to further grow with the studies. I mean, if we squash anything now, we'll never get anywhere.

DR. HOWELL: I think that I disagree with Mike on one point, and that is that it's clear to me that if you study additional patients carefully, for example, I would think that Barbara's group

that's getting ready to do this will probably be using a different confirmatory, diagnostic test. They'll be using different technology and they will find something different, I believe. At least I would I certainly hope so. Chris?

DR. KUS: Yes, I guess part of the thing here for me is that when you're looking at the recommendation, it's whether it's going to be a national recommendation. This right now is how does what you say affect a State that's already, for governmental purposes, doing this? And the folks who would recommend two, I'd like to hear more specific evidence about the harm that has been done or would be done so I can understand that. Because, again, I think I agree with Barbara that there is evidence that the natural history is changed with treatment. Screening could lead to that. So I'm trying to see -- I want to hear what specific harm aspects are you proposing or where is the evidence?

DR. SKEELS:I'm not a clinician, and so I defer to those who are to talk about clinical harms. And I also want to say that even if we categorize this as a number two, that doesn't mean that you could never reapply, as Gerry pointed out. That just means that based on the application before us, which is really the only thing we have to deal with, I think that's the right position. Now, in terms of harms, cost is a harm. Money, tax dollars spent is a harm that if they could be used for something else that's clearly beneficial. So from a public policy point of view, there's more to harm than just clinical harm as well, and I'll stop. DR. KUS: Well, two things. One of them is the reapplication thing is correct. But again, clarifying with you that making that recommendation seems to say you're implying that harm is being done and you should stop now. So I think that's -- you can't do it. The cost thing, we haven't been able to handle that any way. So I don't know how I deal with that aspect because I think, again, the benefit is a kid that would have died will live. There are problems with it, but there are some -- there is definitely -- there is evidence of benefit to treatment.

DR. RINALDO: Gerry -- but Chris, you make a very cogent argument. I still don't understand why we cannot get a dollar figure on the table for us to at least understand what we're talking about. Gerry?

DR. VOCKLEY: My concern about, first of all remember two is zero or net harm. My concern about net harm is there but for the grace of David Wenger, there were five kids who could have had bone

marrow transplants who clearly, now in retrospect, would not have needed them. That's -- how are we going to decide at the end of that algorithm who gets those bone marrow transplants? I'm extraordinarily uncomfortable identifying a handful of kids and saying we're going to rely on the opinion of one person to tell us that those kids either do or don't need a bone marrow transplant, and that's the thing I'm worried about.

DR. KUS: Well, I'm not sure that's a correct presentation in terms of one person. I wish I knew more specifically about the decision. I know the decision is somewhat is a team decision. So I'm just -- I'm not sure that's the correct presentation.

DR. RINALDO: Okay. Let's -- Dr. Perrin obviously has something to say.

DR. PERRIN: If I can just make a point of clarification. This is not based on David Wenger's comments at all. This is really there is a protocol in New York State that involves a number of clinicians and investigators who really came up with a protocol for the determination of which kids merit transplant versus which ones do not. That is not based on a single nonclinician's viewpoint of the mutation. So I think that's just -- I apologize if we gave that impression at all. But that was simply not accurate for what goes on.

DR. RINALDO: Jim, can you also comment on the degree of consensus in that group?

DR. PERRIN: I don't know exactly the consensus on those five or seven children. My understanding is pretty good, but I honestly don't know that.

DR. RINALDO: So you see, that's the point. We are missing some really important information here. There are several hands, and I don't remember who has been waiting the longest. So is that you, Mike?

DR. WATSON: I would only say that harms are going to come in different forms, and it's going to be important that we distinguish clinical harms from cost harms because if we have clinical harms, I'm going to be hard pressed to think this should even be in the Translational Research Network. We get funded for clinical investigation. So that can ameliorate a financial harm to get those studies done. But if there's clear clinical harms, then you're a little less firm on even investigative grounds of going forward.

DR. CHEN: Just a brief, I mean, bone marrow transplant is -- one of two of the children transplanted died. No one could tell us whether it was from transplant complications or from the disease. So that is not something to be undertaken lightly. And so, if we're talking about clinical harms, there's one right in front of you. But I think what we also heard today from Dr. Kwon was something that this committee doesn't usually hear, which is about the harms to the family and the diagnostic cascade that happens even when the child isn't sick or when the family doesn't agree with or is quite uncomfortable with the level of uncertainty that we're hearing about and that's faced with this disease. And so, I think that was quite valuable testimony.

DR. HOWELL: Barbara, you had a comment?

DR. BURTON: Well, my original comment had to do with what Dr. Perrin said that certainly the differentiation between a patient who is a candidate for transplant and not in New York was based on more than David Wenger's assessment. There was clinical assessment. But again, I want to stress that I've seen no data here, I have seen nothing to demonstrate any clinical harms. We have heard a suggestion of psychological harms to patients and that may be something that occurs with other forms of newborn screening as well, but it has to be balanced by the benefits to the affected infants identified. And we know there is at least one child in New York surviving who would not be alive had it not been for newborn screening. And we know that for siblings who have been identified in these early diagnosed cases as well. So if you're going to say zero or net harm, you have to balance those harms or those potential psychological harms against the benefits. And there clearly are benefits here. So I don't see how you can say that you've got the data showing net harm. I just haven't seen it here.

DR. HOWELL: Let's -- we'll have a brief comment. Then we need to come back, and I think we need to be a little more systematic in going down the list and coming -- of the things that we need to consider because we've been -- we're talking around a lot of the things. Duane?

DR. ALEXANDER: I just want to point out that we had the information that was presented to us today only because there was an attempt to get some systematic data collected from the New York experience. The only way we're going to build upon that is to continue that effort and also to fill in some of the holes, some of the gaps in the data that were identified in the presentation here today. That will allow us to be more sure about whatever decision we have to make about this process when it comes back to us presumably within a couple of years or whatever. Only if we try to get that additional

information are we going to be on firmer grounds so that we feel comfortable about whatever we decide when we see this again. And I just can't see voting against gaining knowledge about a condition like this, where this looks like the best way to go, the only hope that we have in the near future for dealing with this serious condition.

DR. HOWELL: Piero, could we go -- it seems to me that before we can come -- we need to come up with a specific decision of the committee. But I think it would be helpful to go down the list of the test, the condition, et cetera, quickly and outline what is the information that we lack in those areas.

DR. RINALDO: I think for the condition, again, it goes back to slide 28 about the gaps. For the condition, I think there is an issue of case definition. We may disagree to what extent there is missing information or confliction information, which, by the way, has a different weight in my mind.

DR. HOWELL: That's one.

DR. RINALDO: And so, with that, I think that we even can give -- oh, it's nice to have that. You can give a category to each of the three elements, and you might want to do this by asking the voting members of the committee --

DR. HOWELL: I would suggest we go through and try to identify the lacunae in the information, and then when we're all done, we will come up with a single look at this thing and come up directly --

DR. RINALDO: Well, it's case definition, testing algorithm, and benefit of transplant, if you really want to narrow it down to three probably most significant --

DR. HOWELL: Great. Key areas of information that must be garnered.

DR. RINALDO: The key areas. Is there agreement?

DR. HOWELL: Is there general agreement with that, and so forth? Yes, Barbara?

DR. BURTON: I mean, I agree that more information is needed about the specific benefits of transplant, but I actually believe that the evidence is unequivocal that it changes the course of the disease. So that it is a treatment in early infantile Krabbe disease in the presymptomatic or early symptomatic patient. Does it cure the disease? No. Absolutely not. Do they still have significant problems? Yes, and we have disagreement about the degree of those problems, the extent, and the cause that needs to be further investigated. But I want to point out that there are many other diseases in the newborn screening panel for which we have treatments, but yet we have continued morbidity and mortality that's very significant. So the fact that a treatment isn't perfect shouldn't be our criterion for deciding whether or not the patients benefit from newborn screening.

DR. RINALDO: And Barbara, we clearly take note of your position. But we have to be prepared that probably there are people here that will not agree with you. I think there is a fourth point.

DR. HOWELL: Okay.

DR. RINALDO: And that is if this is going

to be a standalone or part of a multiplex testing? Because that, although we don't have information about the financial impact, that really goes back to are we going to add this as a test for Krabbe disease or a test -- you know, I was thinking after all SMA is the one actual deletion and so perhaps somebody can come up with a combined assay to look for the deletion in SMA, the deletion in Krabbe, in this gene and basically have two conditions tested. So that's another way. But I think it's important to really at least know that we're talking about what kind of scenario at the testing level. This is a single test for a single condition and with extensive secondary, second-tier testing.

DR. HOWELL: Is there members of the group around the table, are there other areas of information that you see that would be needed, that are needed, or has Piero captured it? It seems that you have -- Rebecca?

DR. BUCKLEY: I think that one of the gaps that Dr. Perrin pointed out was that in the summary of literature articles about treatment that we don't know

the actual mutations in the patients who've received transplants. And I think if that could be filled in, that would be very helpful.

DR. HOWELL: Okay. Great. So we have a series of things that we need information about and so forth. And then I guess the key thing is that those are the things we need to know now. What we need to do now is to look at this list that's up on the board and come up with what we would recommend. Now Dr. Alexander has, I think, spoken quite eloquently. I believe, Duane, your category would fit in number three?

DR. ALEXANDER: Yes.

DR. HOWELL: And that Dr. Alexander would recommend not adding the condition, but recommend additional studies. Those additional studies have just been summarized in a very brief thing, and the level of certainty?

DR. RINALDO: I don't know if the word "compelling" applies here, personally.

DR. HOWELL: Well, the survival is pretty compelling.

MALE VOICE: Life is compelling.

DR. HOWELL: What? I was going to say being alive is pretty compelling.

DR. RINALDO: Being dead, too.

DR. HOWELL: What? Yes.

DR. RINALDO: The child that died probably would be alive without transplant.

MALE VOICE: Up until age 2.

DR. HOWELL: Well, not likely. But anyway, the patient died of a complication of transplant, died of sepsis, which is a recognized complication of transplant. But I might point out, as you saw that they had transplanted, unfortunately, one of the two New York State persons happen to have died. But that's the only death that they've had in all the Krabbe's they've done. So that's a little bit misleading. Okay. Magnitude of net benefit? Rebecca?

DR. BUCKLEY: I was just going to say that I thought that in the latest summary that there had been several deaths.

FEMALE VOICE: They were from Krabbe?

DR. BUCKEY: Yes, there's been several deaths. Well, there were 22 that were done initially, and there were only 17 alive in the follow-up, I
believe. Is that right, Dr. Perrin?

DR. HOWELL: Jim, what was your comment?

DR. BUCKLEY: They were talking about deaths in the transplanted patients, and I thought at your latest follow-up that there were 22 initially who had
been transplanted, and then in your latest follow-up, there were 17 alive. Is that correct?

DR. PERRIN: I just want to verify the data.

DR. HOWELL: What was the answer to that? I'm sorry. They do not know. Okay.

DR. RINALDO: They're checking the data.

DR. HOWELL: Jana?

MS. MONACO: In relation to that, I guess we also don't know the cause of death in any of those patients, and the fact of the matter is with any of these disorders, no one can predict the ultimate lifespan of these children, even the ones that are screened.

DR. HOWELL: I don't think we have enough information to have a sensible comment, but perhaps others have died from a variety of potential reasons. Would someone like to comment additionally about Duane's recommendation?

DR. RINALDO: Is that a motion?

DR. HOWELL: Well --

DR. RINALDO: Basically go with --

DR. CALONGE: Could I?

DR. HOWELL: Ned, by all means. Are you there?

DR. CALONGE: Oh, yes. So I think what -- I understand the argument around the to-do and the concern that we may be doing zero net benefit or more harm than benefit, which is if we subtracted that and the psychological issues and everything else we put on the harm side of the equation, we think that it overtakes or it weighs more than the lives that we know or that we have been told have been saved. So that's the issue is that zero point doesn't say people haven't been helped. It just says that there are either more people harmed than helped or we see this kind of

net benefit that we think is very close to zero or we would call zero. So I want to make sure that people recognize you can get to a don't add without -- even though some people have been helped by screening. So that's one issue. The certainty issue is before we assign the two, we want to be at least moderately certain that we're at that zero or net harm place. And at least from where I sit, that's where I'm having the most problems because there aren't enough cases of either benefit or harm for me to be totally confident with that area. I would want to point out that in the insufficient categories, you can actually do more research that convinces you not to do it. Not all research -- we shouldn't ever go into we should do additional research with the idea that that's always going to have us add the condition because then we actually bias the research and we're not objective as we go forward.

DR. HOWELL: Well, obviously, the purpose of

doing the research is the information, which obviously it could move you in one way or the other.

DR. CALONGE: One way or the other.

DR. HOWELL: And I think that's clearly the case.

DR. CALONGE: So then I get to this area of where we created the special "I" category, the kind of I-optimistic. And that's where I have a little trouble with the motion because I haven't heard enough to be optimistic. I think this is an "I don't know." I think it's a category four, and by putting it in that category, we don't necessarily push this as one of the diseases we want to spend a lot of precious resource -- national resource, research resource -- I'm sorry. Because we just don't know. That's kind of a different category than three, which says, boy, we think this is close enough that another couple of studies are really going to lop us over into the positive "let's add it" category. So I guess my recommendation, for what it's worth, is that this looks like an out and out "we don't know at this time," not ready for prime time. Even though there have been some benefits that are compelling, there have also been some harms that are compelling and we just don't know.

DR. HOWELL: Jim Perrin has some comments, I think, on that particular subject.

DR. PERRIN: The only comment to add is that of the 17 and 24 or 22 really represents not -- it represents the ones that were actually followed actively in the Duke-UNC connection. So our understanding is that of the newborns or approximate newborns early transplant group, only one child died who was the child who was referred from New York. And all the others have survived is our understanding of the data.

DR. HOWELL: Could you comment about evidence of net harm? Because I must confess I fall in Barbara's camp, and that is that we know that treatment is complicated and so forth, but I've not heard much evidence of serious harm.

DR. PERRIN: I think the conversation has really raised the question of the potential harm of clinicians who aren't sophisticated in the diagnosis of this condition making judgments asking for or bringing about the transplants, which are dangerous. And so, I think that has been raised. We would say in our evidence review we did not find any evidence of that harm taking place.

DR. HOWELL: So that's been discussed, but there's no evidence that you identified.

DR. PERRIN: There's no evidence, right.

DR. HOWELL: Coleen?

DR. BOYLE:I was just going to make a comment on that as well. For me, it's trying to understand the sort of net benefit in the context of screening, newborn screening. I don't disagree with you at all, Barbara, in terms of the clinical practice, in terms of there being clearly net

benefit. But it's really trying to take it into the world of the newborn screening where I think we get into really challenging interpretations.

DR. HOWELL: Chris?

DR. KUS: But I guess, I mean, I think it's important to talk about that, but you've got to have some evidence about that, too. I think part of the reason the way the thing is designed in New York State is to follow that along and be clear about it. So I mean, it's not -- it's potential harm, but I don't see that there is evidence to say that there is harm.

DR. BOYLE: I think, just as Ned nicely outlined, I think there are harms and there are benefits within the context of newborn screening.

DR. KUS: Where is the evidence of the harm? That's what I'm trying to get clear here. People have said harm, and the harm is the -- and I agree. There is one death in the New York case, and in cases that have been treated that are asymptomatic and treated early, there have been no deaths. There is always the risk of harm when you're talking about doing transplant, but we're talking about a condition where kids die by age 2 most of the time.

DR. RINALDO: I think part of the harm here is sort of that scary lingo that the families of those patients put in the intermediate, moderate, and low risk. Frankly, I don't think that should be really completely dismissed.

DR. KUS: I'm not dismissing it. But if we're talking about evidence, you've got to have evidence. And I think Jim just commented in going through and reviewing the progress relative to his evidence, there wasn't evidence of it. I think we can talk about these things, and I think they're important, but if we're doing an evidence-based review, you've got to have the evidence.

DR. RINALDO: I thought that Dr. Chen, Chen I think is the name, gave a pretty compelling description of what the harm would be to that --

DR. KUS: That's anecdotal information.

DR. HOWELL: That was a single. That was not evidence.

DR. RINALDO: I understand there is at least another family that said --

DR. HOWELL: Tracy?

DR. TROTTER: I think what -- Chris's comment actually moves us along here because there is insufficient evidence, period, on both sides. I don't think any of us can come down obviously on either side. I don't think anybody is very much doing that.

DR. HOWELL: I think that's correct.

DR. TROTTER: And I would like to second Ned's thought or I hope recommendation that it's number four and see if we can move ahead and figure this out.

DR. HOWELL: Well, we -- let's back up a bit because we had a motion that Dr. Alexander made for number three, that we did not consider a second for that. And so, I guess the question is, is there a second for Dr. Alexander's motion from the voting members of the committee that we consider it as a number three?

DR. CALONGE: Three or four? I'm sorry.

DR. HOWELL: Three.

DR. BURTON: Not your motion.

DR. HOWELL: No, it was Dr. Alexander's. Not yours, Ned.

DR. CALONGE: Okay. I'm sorry.

DR. HOWELL: Is there a second for that motion? I would second the motion. Jana second. Okay. Those favoring number three, can we see the voting members raise your hands for Dr.

Alexander's motion. [Show of hands.]

DR. DOUGHERTY: Hi, this is Denise. What's -- I'm trying to find number three here.

DR. HOWELL: It's recommend not adding, but recommend additional studies.

DR. DOUGHERTY: I raise my hand.

DR. HOWELL: Okay. So let's see the hands again. [Show of hands.]

DR. HOWELL: I'm sorry. We have one, two, three -- Can we count? What was the count?

DR. BURTON: Five.

DR. HOWELL: Five. Okay.

DR. LLOYD-PURYEAR: Is it five? Who's five?

DR. HOWELL: Denise. Okay? Okay, and so we have five persons there. How many voting members are present?

DR. LLOYD-PURYEAR: Who is five? Oh, Duane is five?

DR. HOWELL: Yes, Duane is. It was his motion.

DR. LLOYD-PURYEAR: Kwaku, who else?

DR. HOWELL: Kwaku, me.

DR. CALONGE: Do you just want to call for the names and count them?

DR. HOWELL: We've got -- the people who voted were Dr. Alexander, Kwaku, me, Jana, and Denise. That's five. Okay. How many members, voting members of the committee are here?

DR. LLOYD-PURYEAR: Everybody.

DR. HOWELL: Well, how many is that?

DR. LLOYD-PURYEAR: That's 15.

DR. HOWELL: Fifteen. Okay. All right. Here we are. We even have a voting sheet. Good heavens. We're getting formal. Okay, that motion does not carry because there are 15 voting members present or on the phone and so forth.

DR. TROTTER: A member can abstain. You should ask for a no vote.

DR. HOWELL: Anybody abstaining? [No response.]

DR. HOWELL: Nobody, okay. Would you like to make another motion then?

DR. TROTTER: Well, I will second Ned's original motion. This is number four.

DR. HOWELL: Okay. Okay, we have that. And so, those favoring Ned's motion for number four, please raise your hand. [Show of hands.]

DR. CALONGE: I vote aye.

DR. LLOYD-PURYEAR: For Ned and Denise, category number four is recommend not adding the condition now. The evidence is insufficient and additional evidence is needed to make a conclusion about net benefit.

DR. DOUGHERTY: Well, okay, I thought I was voting for that with number three, but -- [Laughter.]

DR. HOWELL: Well, it --

MALE VOICE: Vote again. Vote again.

DR. DOUGHERTY: If three went down, can I now vote for four?

DR. HOWELL: Yes.

DR. DOUGHERTY: Yes. I vote for four. I vote aye.

DR. HOWELL: Do you have -- we have -- What's the number?

DR. LLOYD-PURYEAR: So it is -- what did Duane say?

DR. HOWELL: He did not.

DR. LLOYD-PURYEAR: He did not.

DR. HOWELL: Any abstentions?

DR. RINALDO: Ask who is against and who abstains.

DR. LLOYD-PURYEAR: So any abstentions?

DR. HOWELL: I abstain. Any abstentions? We've got -- you either have got to vote yes, no, or abstain.

MALE VOICE: You didn't ask for it. You haven't asked for nos.

DR. HOWELL: Oh, no. Okay. Excuse me. No? Are you going to vote no? Well, I'll vote no, too. [Laughter.]

DR. LLOYD-PURYEAR: And Ms. Monaco?

DR. RINALDO: Jana? Okay. I think she

raised her hand previously, but I think she wants to change her vote, right?

MS. MONACO: We can vote again?

DR. HOWELL: Yes.

MS. MONACO: But we have the option to -- can I change my vote?

DR. LLOYD-PURYEAR: Yes. Were you for or abstention or --

MS. MONACO: I'm still for number three.

DR. LLOYD-PURYEAR: No.

MS. MONACO: Right. Okay. I'm a no.

DR. HOWELL: Are you in business then?

DR. LLOYD-PURYEAR: Yes.

DR. HOWELL: That motion passes and so forth, so that the committee will make a recommendation number four and we will send forth to the nominators the areas of information that are deficient. That will come into the evidence, okay? Are there further comments about this? Kwaku?

DR. OHENE-FREMPONG: Really just a general comment. I mean, we sometimes talk about stem cell transplantation as if it's a simple curative procedure. It has its own transplant-related risks and mortality, and it's not clear to me in many of these discussion as to what sort of donor was used. That pretty much determines the risk category. These are unrelated matched donors or unrelated and not fully matched donors, they all carry different risks. And I just want us, as we talk about these conditions and talk about transplant, to be sure that the transplant conditions may not all be uniform. The donor selection may not be all uniform, and the risk categories are quite different.

DR. HOWELL: Is there anything else to do on that?

MS. MONACO: I wanted to make one comment, too. In the future, as we review it, I hope that no one would look at the neurological outcomes of the patients that are transplanted, and although they may have their development delays and so forth, to not deem that as a failed transplant by no means because these children do have a quality of life defined by their own families. And it's not up to us to define quality of life, but for the fact that they are thriving to the best of their abilities is significant, important in the context of their lifespan and what it means to the family.

DR. HOWELL: Thank you very much, Jana. Any further comments before we leave this particular -- Chris?

DR. KUS: I mean, going to the transplant, it's in the slides that it's an allogeneic hematopoietic stem cell transplant. So we're talking bone marrow and umbilical cord. So I don't know how that relates to this, but I don't think it's the matching that you're talking about.

DR. OHENE-FREMPONG: It still will be you don't know whether it's a sibling or unrelated. So right -- well, it could still be cord blood. These are little babies. Cord blood assumes that it's somebody else's. So I just wanted people to know that it's not a uniform therapy.

DR. HOWELL: This committee has to prepare a report for Congress, and we now will hear from Ms. Alaina Harris.

DR. LLOYD-PURYEAR: No, it's Alissa Johnson, isn't it?

DR. HOWELL: No. I have Alaina next.

DR. LLOYD-PURYEAR: Alissa should go first.

DR. HOWELL: Does Alissa want to go first? [Laughter.]

DR. HOWELL: All right. My agenda has --

DR. LLOYD-PURYEAR: Oh, you're right. It is Alaina first.

DR. HOWELL: I have Alaina first. Are you Alaina? Are you going to go first? I don't think it's critical that we go one or two, but let's roll it. Alaina is -- I think many of you know Alana. She's a public health analyst in the Genetic Services Branch. And it's Alaina and not Alissa. All the As are talking this afternoon.

MS. HARRIS: Are we in business? We are. Great. Thank you. All right. So, how do I do this? Sorry. So, as many of you are familiar with, the Newborn Screening Saves Lives Act of 2008 Section 1111 reauthorized and expanded the activities of this committee. Here are the different areas. Today, we're going to talk about Part E, which is the annual report. Here are the legislative requirements, and again, we're going to just focus on this part here that the committee publish a report on peer-reviewed newborn screening guidelines, including follow-up and treatment, in the United States. It goes on to say that the committee is going to submit this report to appropriate other committees of Congress, the Secretary, the ICC, and that this report is going to be disseminated on as wide a basis as practicable, including posting on the newborn screening clearinghouse, which was established under Section 1112. So I did some searching around, trying to find out what the legislative intent was for this committee report because that's pretty much all that we have on what this report is supposed to look like. Here is what I found. That the report is to be published by April 28, 2011, and the intent was for the committee to report on what it has done since reauthorization and its plans for the future. So we've done a little bit of brainstorming for you today on what that content for that report could look like, and here are some ideas for you to discuss. We can revise the evidence workgroup reports and provide a report to Congress on what we've looked at adding to the recommended panel or not. We can provide updates from the subcommittees. Another thing we could include in the report is information on the heritable conditions that the States require and offer for their newborn screening programs. We could look at the incidence and prevalence of conditions on the recommended screening panel when we have that data and, if available, information on the health status of individuals with these conditions. So no means is this an exhaustive list. You guys may have other ideas as well. So I'll turn it back over to Dr. Howell to lead the discussion.

DR. HOWELL: Any comments about what you

would like to see in this report? My gut reaction, you should probably include all the things that you can get data on. The number five, I think the data would be very meager, to say the least, frankly, as we've just learned from the New York State experience, which has been very carefully done. Any comments about this report? Kwaku?

DR. OHENE-FREMPONG: Some of these do not lend themselves easily to being referred to as peer- reviewed. I'm not sure whether the peer-reviewed was referring to the report before it goes out or whether the content is from peer-reviewed sources.

MS. HARRIS:It would seem here on peer- reviewed newborn screening guidelines. This would be articles that -- without knowing what Congress intended exactly, I am assuming this would be articles that have been published in peer-reviewed journals like Pediatrics, Genetics in Medicine. And so, we do have a few things that the committee has published in peer-reviewed journals.

DR. RINALDO: Like the nomination paper,

financing --

MS. HARRIS: The long-term follow-up report.

DR. RINALDO: Long-term follow-up. So there should be plenty.

MS. HARRIS: We're asking now because we have to start preparing the content and writing the report and getting it cleared.

DR. TROTTER: Yes, I think that's the point. I think we -- as a committee, we should be kept informed on what's going on and sort of this is going to be an iterative process between all of us, and we can be helpful, hopefully, to you and your staff in preparing this report, as long as we know what are you looking for, what can we add, how can we be helpful?

DR. HOWELL: Is there anything else that we need to comment about this?

DR. VOCKLEY: I have a quick question, Rod. I mean, peer review, I actually think we ought to try to define that a little more broadly. Peer-reviewed publications and we have some examples of output from the committee that have gone to peer-reviewed publication. But I think our evidence-based reviews of these conditions are, in fact, peer review. And so, every one of the decisions that we've made I think is a peer review activity.

MS. HARRIS: It was on the list.

DR. HOWELL: Yes. Yes, and so forth, and there will be some publications coming out of that.

DR. VOCKLEY: We can call it peer review.

DR. HOWELL: Yes. Alan?

DR. FLEISCHMAN: It strikes me that the issues that we're talking about now, those peer-reviewed things would be very helpful. I think we ought to be able to identify the number of children who've been identified by this national program and share that with Congress, and I think we ought to be able to identify best practices of informing families and primary care physicians and linking kids to follow-up services, both for confirmatory and then treatment. So I mean if we can help Congress think through the program with the potential for what the future needs might be, that would be very helpful in this annual report approach.

DR. HOWELL: Any other comments or suggestions for Alaina? [No response.]

DR. HOWELL: We'll look forward to seeing -- thank you. I think that you'll have a lot to do, but there's a lot of publications and so forth that you can do. We're going to focus our attention now on a policy paper about newborn screening and healthcare reform, and that's -- we'll hear from Alissa Johnson. And she has prepared a policy paper on newborn screening for the committee regarding healthcare reform for the committee. Alissa?

MS. JOHNSON: Can you hear me?

DR. HOWELL: No.

MS. JOHNSON: So now can you hear me?

DR. HOWELL: Yes.

MS. JOHNSON: Okay. No?

DR. HOWELL: Yes.

MS. JOHNSON: All right. Very good. So I am here today to present a paper that Michele and I prepared for you. It's actually a committee briefing paper that, if used, is intended to provide information to the Secretary on newborn screening and how that intersects with the current healthcare reform debate. So just to give you some idea of the process that I went through to do this, by no means do I consider myself an expert in newborn screening and healthcare reform. I relied heavily on the literature that was there. So it was basically a literature review of what's out there on healthcare reform and then doing a literature review of many of the committee papers that have been done and other articles that people on the committee and in the audience have written and trying to draw some parallels with changes that some advocate should occur within the healthcare system generally with changes that some advocate should occur within the newborn screening system and highlighting how some of those concerns are similar. So the basic theme of the paper is that as with the healthcare system overall, there is unequal access to newborn screening services across the country. So we actually have unequal access to healthcare within our system and as we have unequal access to newborn screening services as far as the system as a whole. The reasons behind the disparities in newborn screening often mirror problems that are cited within the broader healthcare system, and the things that sprouted up as I was reading through the literature over again were public financing, payment systems, other administrative inefficiencies, and insurance coverage issues. And some of these issues I understand do overlap, but this is a way to divide up the discussion I approached it and approached it working with Michele. So the slides that I'm running through will go through those four issues. And they're broken up in what do we see in the current newborn screening system, and how do we recommend that reform might make a difference and correct these disparities? I'm not going to go through all of the parallels in the healthcare reform literature because I don't really think that that's your focus. This is what I've highlighted in the newborn screening system, and if there's something I can point out in some of the broader healthcare literature that I think makes the case more compelling, I will, although we don't have a whole lot of time and I know you people need to get home. So the three key things that we pointed out as features of the current newborn screening system are that there is a combination of funding streams generated from fees, Maternal and Child Health Title V Block Grant Funds, State appropriations, and general revenues and about the latest figure that Michele gave me was about $10 million in appropriations just to that from the Federal Government. Also, existing support only provides for some educational efforts, screening, diagnosis, and initial confirmation of treatment in half of the States. And that figure is based on an NNSGRC's National Newborn Screening Information System that was reported. Fees do not correlate with the number of

mandated tests. That's actually also based on a prior -- I'm not sure if it was a working group presentation, but that involved Brad and someone else he was working with, too. So you'll see it's heavily cited, all of the material in here. And so now, as far as public financing, the reform -- the one recommended reform that came out of that is to ensure stable funding for core and critical public health functions such as immunizations and screening. So that's the first recommendation that is in the paper. I would like to note that that's actually an adoption of a recommendation that's been made by the Trust for America's Health. So I don't know if we want to highlight that more in the paper. It's quoted in there. But I also did want to note we didn't put as a recommendation, but something you might want to consider that it's suggested that developing national guidance for -- and that sounds actually repetitive, but national guidance for developing public health budgets is suggested in the paper. We don't have that as a recommendation. Maybe that's something you want to consider, and that actually comes from a paper that I think Brad, Michele, Kay Johnson, and others worked on. As far as payment systems, features of the current system that are pointed out in the paper are billing and payment practices vary from State to State, and this section of the paper does rely heavily again on work from Brad Therrell and Michele Puryear and Marie Mann and Donna Williams from that paper. And that there's lack of financial incentive to coordinate care. The reform that is currently in there as a recommendation -- this is the second recommendation -- is to convene an expert panel to examine the billing and payment practices for the cost of screening services and to put forth recommendations that enhance the standardization of healthcare transactions. We do have actually an additional recommendation that speaks to, if you go back here, the coordination of care. The third recommendation, which is also under payment systems, is to work with CMS to develop and pilot a bundled payment method for providers treating the same child with a disorder diagnosed as a result of screening that can serve as a model for all children with special healthcare needs. And we do mention in the paper that CMS has piloted bundled payment systems before. So that's where that came from. As far as other administrative inefficiencies, features that we point out in the current newborn screening system are lack of funding to support e-health activities for State public health departments and efforts to promote electronic exchange of newborn screening information, also the way that some of those inefficiencies are being handled. So, on the one hand, the lack of funding to support e-health activities, we do realize that there are activities that are ongoing, but also we cite a survey that found that State health departments that were noted as serving as the primary entity responsible for pushing forward e-health activities reported that lack of funding was still the major barrier in the majority of States. So with the recommendations, what we really want to do is to -- what we've proposed is encouraging what is already happening. So that's the fourth recommendation, and that's further define and adopt the meaningful use case for newborn screening for health information exchange endeavors by the department. Next, we cover insurance coverage issues. Features of the current newborn screening system that we point out are State policies that require insurance coverage for medical foods varies and are not comprehensive. And you all obviously know all of this very well, having gone deeply into this issue. And gaps in coverage of necessary medical foods and foods modified to be low in protein result in financial burden for some families. And I would say that one change I would suggest to the paper, if possible, if you decide to move forward with it is the information coming out of the survey of parents and adults that was discussed in the subcommittee meeting. That would be really helpful to have because in writing this paper, I was trying to come up with figures for what people may end up paying above and beyond the cost of regular foods even if they live in a State where they -- and have a health insurance policy that's

covered by the mandate, what they still may face. So those figures would be really helpful to have. Right now, it says hundreds or thousands. But if we could be more descriptive, that would be good, I think. So this is fairly straightforward. This recommendation, which I believe is the last, but close gaps in insurance coverage for medical foods and foods modified to be low in protein as recommended by the committee in April, and then the exact recommendations are footnoted in the paper. So, really, it's just another opportunity to get that out there. I think that pretty much covers it. We did send the paper out. Michele sent the paper out the beginning of August. So, hopefully, everybody had a chance to read it. We did receive a few comments back and made some minor changes, but I guess if anybody has any questions?

DR. HOWELL: Any comments for Alissa about the paper? Alan?

DR. FLEISCHMAN: You know, I think there are some very good points here. But you've conflated public health screening and healthcare delivery follow-up and I think you either are going to have to define what a newborn screening program is and either include the follow-up aspects or not because you're talking about a lot of apples and oranges. They're all fruit and they're all very important, and the solutions are different. And the methodologies for solution are different. So your recommendations really are very different. So you talk at one point about immunizations and screening, but the report, which I've read, screening is about the public health laboratory screening and confirmation. That's what I think you were talking about.

MS. JOHNSON: Right. But, well, in the report, the report does talk about newborn screening as a system, which includes all of that.

DR. FLEISCHMAN: Correct. And you're going to have to define that up front and then say what part of the newborn screening program as a system are you talking about when you're talking about the public health funding for the laboratories --

MS. JOHNSON: Right. Okay.

DR. FLEISCHMAN: -- and financing of that. And then you're going to have to say there's another part of the program, which is the follow-up, which is healthcare delivery for chronically ill and complex children and you want to talk about how we want to fund that and develop models for that.

MS. JOHNSON: Right.

DR. FLEISCHMAN: So I mean, you really have to be crystal clear if you want to actually make these recommendations meaningful.

MS. JOHNSON: Right. And maybe I'm not sure if I mentioned it there, but -- well, first of all, maybe immunization should not be in there. That's just adopted from the Trust for America's Health quote that we have in there. So I don't know. People can leave that up to them. But also maybe as an alternative, you want - - if you think this recommendation should be more detailed by outside of this process, maybe developing national guidance for public health budgets for

newborn screening programs, not saying this is how you should do it is what you what to do instead of that.

DR. LLOYD-PURYEAR: Can we see if the committee wants to go forward with this?

DR. HOWELL: Indeed.

MS. JOHNSON:That's up to you all if you're comfortable with a general statement about improving, ensuring stable funding for poor and critical public health functions like screening or not.

DR. HOWELL: And we need a sense of the committee's interest in having this letter go forward from the committee. Can we have some comments about that? Kwaku, would you like to comment on that?

DR. OHENE-FREMPONG: I think we assume that every baby has access to screening, whether they can afford it or not, and probably the best way to assure that is to not make it be funding dependent. I mean, in that Government public health sources covering the screening should probably be the more uniform pattern than one that could be subjected to loss of private insurance for some period of time and, therefore, not all of a sudden being exposed and not being able to get screening. But I'm not sure whether any babies actually fall through the cracks because of loss of insurance.

MS. JOHNSON: Right. Well, not with the actual screening and maybe we want to be more clear that it's funding for the newborn screening system as a whole, which is the point that we brought up. So I mean, do we want to address all of the components of the system in the recommendation?

DR. HOWELL: Alan, you had a comment?

DR. FLEISCHMAN: Yes, I don't want to be taken wrong. I think there are a lot of good recommendations here. I don't think we've been clear --

MS. JOHNSON: Right.

DR. FLEISCHMAN: -- in the aspects of what we're asking. And then my question to maybe Peter or Michele is will this be useful or helpful if we do this, or are there other opportunities to solve these issues? I mean, will this committee's work in this regard be a useful adjunct inside the department? If it would be, then I think we could clarify these things and make the policy recommendations fit the problems. I mean, there are no bad recommendations here.

DR. HOWELL: Any thoughts? Michele? Peter?

DR. LLOYD-PURYEAR: He agrees.

DR. HOWELL: What does he agree on? [Laughter.]

DR. LLOYD-PURYEAR: I can't. It won't go any further.

DR. VAN DYCK:I think that it's something that can go forward for the committee that can be useful because I think that anything that's stated clearly can be useful. But I agree that there is -- I think something going forward from the committee is useful because it keeps the issues current. But I think there needs to be -- I agree with your comments on the clarification of the level of the items that are discussed in concert with the recommendations.

DR. HOWELL: And I think that comes back to Kwak's comment about the fact at the current time all babies in the U.S. are screened, regardless of their ability to pay. And so, that part is kind of one of the few things we have that is taken care of by whatever mechanism. And so, it would be important, I think, to separate out the other part of that recommendation so that it's clear.

MS. JOHNSON: Right. So separate out the other components and say that you're not talking about that. You're talking about the system.

DR. HOWELL: So I gather that from the bureau's point of view this would be valuable, and we need to separate out some things. Kwaku, you have some comment?

DR. OHENE-FREMPONG: Yes, but I think it's an important point that if the State takes the responsibility to establish a diagnosis, does the State carry the responsibility through by making sure that that child who is diagnosed with that condition mandated to be screened for by the State, the State ensures that the child will receive healthcare in the short term and, as we're talking about long-term follow-up, also in the long term?

MS. JOHNSON: Right. And I think one of the things that we tried to do in the paper is point out that there is disparity in what happens, as you all know, after short-term follow-up. Using the information that we had from the National Newborn Screening Information System, we could see what States were self-reporting on how much they were doing. There were places that had annual follow-up with people, and other places that merely had a confirmed diagnosis and referral and made sure that they followed up on that referral, but then that was it. So --

DR. HOWELL: So I think that you've got a number of comments to refine this document and try to get something together to go out, and the sense of the committee is that it would probably be worthwhile to go ahead and send it.

MS. JOHNSON: Right. And maybe we need to have -- and I don't know if you all want to think about if we need to have more on long-term follow-up in here than we do? But you've already got things going on there.

DR. HOWELL: Our long-term follow-up guru is sitting to my left. What do you think, Coleen?

DR. BOYLE: I think we could include a few more things. Maybe I'll give you some specific comments. Oh, sorry. I was just saying I think we can, based on the work we did on Wednesday and Thursday, include a few more items.

DR. HOWELL: So that would be worthwhile and so forth. So we look forward to hearing further about you, okay?

MS. JOHNSON: Okay.

DR. HOWELL: Anything else for Alissa? [No response.]

DR. HOWELL: The afternoon is growing dim, and ladies and gentlemen -- thank you very much, Alissa.

MS. JOHNSON: Thank you for having me.

DR. HOWELL: Let me point out to put these on your schedule. Our next meeting is, it will be a face-to-face meeting January 21st and 22nd. Then there's May 13th and 14th and September 16th and 17th, and so forth. And obviously, they will, as usual, be in this neck of the woods. We have received a nomination to consider about universal predischarge bilirubin screening, which has been nominated, and that will have to have an internal review. And so, we'll anticipate that that internal review will take place and then a recommendation about what to do with that that will come at the January meeting. As I think those who are actively involved in pediatrics are aware, we still have a substantial problem in this country with Kernicterus, which is totally preventable. But it's a devastating disease, and so there is a great deal of interest in how to approach that so that we get rid of that very serious condition.

DR. CALONGE: Rod?

DR. HOWELL: Yes?

DR. CALONGE: The task force is on the eve of releasing a new recommendation with the new evidence review. So as the committee looks at that topic, they'll have a recent EPC funded and performed evidence review to evaluate.

DR. HOWELL: Oh, outstanding. When will that review be available, Ned?

DR. CALONGE: I just reviewed the press release this week. I think it must be coming out next week.

DR. HOWELL: Outstanding. Well, that will be tremendously helpful for the committee and so forth. Is there any agenda items you have for the January meeting? We'll look forward to your sending those forward to Dr. Puryear. Are there any other items of interest that we should hear about on this Friday afternoon, which is probably still drizzly outside? [No response.]

DR. HOWELL: Hearing nothing, can I have

motion to adjourn? [Motion.]

DR. HOWELL: Outstanding. And I see unanimity in everyone's eyes. Thank you very much.

[Whereupon, at 2:56 p.m., the meeting was adjourned.]