28TH MEETING OF THE SECRETARY'S ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

Friday, September 14, 2012

MORNING SESSION

8:30 a.m. - 12:15 p.m.

Humphrey Building

HHS Headquarters, Room 800

200 Independence Avenue, S.W.

Washington, D.C.

APPEARANCES

COMMITTEE MEMBERS:

JOSEPH A. BOCCHINI, JR., M.D.

JEFFREY BOTKIN, M.D., M.P.H.

CHARLES HOMER, M.D., M.P.H.

FRED LOREY, PH.D.

DIETRICH MATERN, PH.D.

STEPHEN MCDONOUGH, M.D.

ALEXIS THOMPSON, M.D.

CATHERINE A.L. WICKLUND, M.S., C.G.C.

EX-OFFICIO MEMBERS:

COLEEN BOYLE, PH.D., M.S.

CHRIS DEGRAW, M.D., M.P.H.

DENISE DOUGHERTY, PH.D.

KELLIE B. KELM, PH.D.

MELISSA PARISI, M.D., PH.D.

DESIGNATED FEDERAL OFFICIAL:

SARA COPELAND, M.D.

APPEARANCES (Continued)

ORGANIZATION REPRESENTATIVES:

NATASHA F. BONHOMME

FREDERICK M. CHEN, M.D., M.P.H., F.A.A.F.P.

JANE P. GETCHELL, DR.P.H., M.T. (ASCP)

CAROL GREENE, M.D.

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BETH TARINI, M.D., M.S., F.A.A.P.

MICHAEL S. WATSON, PH.D., F.A.C.M.G.

MARY J.H. WILLIS, M.D., PH.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

CHAIRMAN BOCCHINI: All right. Good morning. Welcome to day two of our meeting.

First order of business is to take attendance. So we'll go ahead and do that.

Jeff Botkin?

DR. BOTKIN: Here.

CHAIRMAN BOCCHINI: Coleen Boyle?

DR. BOYLE: I'm here.

CHAIRMAN BOCCHINI: Sara Copeland?

DR. COPELAND: Here.

CHAIRMAN BOCCHINI: Denise Dougherty?

DR. DOUGHERTY: Here.

CHAIRMAN BOCCHINI: Welcome.

DR. DOUGHERTY: Thank you.

CHAIRMAN BOCCHINI: Melissa Parisi?

DR. PARISI: Here.

CHAIRMAN BOCCHINI: Charles Homer?

DR. HOMER: Here.

CHAIRMAN BOCCHINI: Kellie Kelm?

DR. KELM: Here.

CHAIRMAN BOCCHINI: And I think Fred Lorey

is still on his way.

Chris DeGraw?

DR. DEGRAW: Here.

CHAIRMAN BOCCHINI: Steve McDonough?

DR. MCDONOUGH: Aye.

CHAIRMAN BOCCHINI: Dieter Matern?

DR. MATERN: Here.

CHAIRMAN BOCCHINI: And then Alexis Thompson?

DR. THOMPSON: Here.

CHAIRMAN BOCCHINI: Cathy Wicklund?

MS. WICKLUND: Here.

CHAIRMAN BOCCHINI: And Andrea Williams is not here. Don Bailey is not here. I am here.

Okay. All right. Thank you.

Because Fred has not yet arrived, we're going to change the order of the presentations from the subcommittees, and we're going to start with Beth Tarini giving the report on the Subcommittee on Education and Training.

Beth?

DR. TARINI: Thank you, Dr. Bocchini.

Okay. Perfect. No, I'm okay.

Okay. So the subcommittee charge, as many of you may be familiar with, I'll review, is -- oh, and by the way, I'm channeling Don Bailey. He's in Turkey. You will see him. Don't be worried. You'll see him return for the next meeting.

So the subcommittee charge is to review existing educational and training resources, identify gaps, and make recommendations regarding five groups. And those five groups subdivided into two categories are parents and the public, as well as health professionals, which include health professionals, screening program staff, hospital/birthing facility staff. And that is the makeup we try to mirror of the membership.

So our goals for this meeting were to review ongoing activities and updates from member organizations and to review progress to date and identify next steps and goals regarding our priority projects for the January 2000 -- actually 2013. We're not going backwards in time.

But lest you think the time devoted

relates to the font size, we spent the majority of our time focused on our priority projects. But briefly, not to forget the member organization updates, these updates were done. We didn't discuss them at length. They were submitted to the committee, distributed, and then questions were asked, pointed questions as they arose.

But just to review some, the AAP has released an EQIPP newborn screening quality improvement course, entitled Newborn Screening: Evaluate and Improve Your Practice. Actually, registration is closed, I believe. But to let you know that that course was open until August 30th. And that course is to help providers with training of how to document, record positive newborn screening results and also how to discuss them with families.

The Genetics and Primary Care Institute continues. This was a 3-year collaborative agreement between Maternal and Child Health Bureau and the American Academy of Pediatrics. Those ongoing projects are the Quality Improvement

Initiative, which is to start in the spring -- late winter, spring in the network practices that are part of the QuIIN network of the AAP.

There is an upcoming Genetic Literacy in Primary Care Colloquium that Dr. Bob Saul is spearheading in October at the AAP. And work is being recently started on the development of a pediatric family history tool in collaboration with NCHPEG and HRSA.

And NCHPEG also alerted us to their prenatal history tool, updated us on this. You'll hear more about this today, I believe, from Dr. Scott.

So priority A is to track, provide input on, and facilitate integration of national initiatives and committee-initiated activities. Our priority A project, the aim of which was to conduct a scan to determine major education and training needs that extend into areas other than newborn screening and to do so using a prototype condition through which would identify major education and training gaps.

So our specific objectives were to identify or our ongoing were to identify one heritable condition that is not part of the RUSP and for which screening and treatment most likely would occur at a later point in child development. Later as in reference to newborn. In partnership with professional parent organizations, we will identify major education and training needs for that condition.

So our first step has been to create a list of possible prototype disorders, the characteristics of which are the following: not currently on or previously considered for the RUSP. It's a specific heritable condition, i.e., not under the larger rubric of developmental disorders, as opposed to Rett syndrome itself.

Has a specific genetic etiology known. We try to avoid a complex condition that has a multitude of genetic and environmental components. There's availability of screening procedures, and the effectiveness of screening will prevent costly diagnostic odyssey.

You'll notice that treatment effectiveness is missing because we define that loosely. These are not meant to go strictly along the Wilson-Jungner criteria.

So from May through September, we solicited input from members of the Education and Training, Long-Term Follow-Up, and Laboratory Standards Subcommittees, as well as SACHDNC members and the regional collaboratives. And at this meeting, we created a list to present to the committee for additional input. A list of 10 or less was our goal, which we achieved under time. Well, 8 minutes, but that's pretty close. That's within a competence interval.

So here is our list of possible prototype conditions in alphabetical order -- thank you, Emily -- so as to not imply that there is a value judgment in the order. We have Duchenne muscular dystrophy; Ehlers-Danlos Type 4; familial adenomatous polyposis, FAP; Fanconi's anemia; fragile X, Friedreich's ataxia; long QT syndrome; Marfan syndrome -- there should be a D there; Turner

syndrome; and Wilson's disease.

So this is a preliminary list that we'll present to the committee in the hopes at the next meeting coming down to one within the subcommittee to come back and present. Input from the subcommittee at this time or later would be helpful as to particularly the values which types of disorders, or which particular disorder in this case as well, would provide useful direction as to the needs for education and training and gaps to address that might also overlap with newborn screening conditions that are considered for the RUSP.

So, on the one hand, the goal being to specifically improve education and training for a specific disorder, but along the way, the process will identify procedures, gaps that are probably generalizable as well to newborn screening conditions.

I don't know if we want us to have discussion here? Particularly about what kind of impact we're looking for as regarding the disorder about treatment versus quality improvement of life,

et cetera.

CHAIRMAN BOCCHINI: Thank you, Beth. That was a good presentation and a good summary.

And so, at this point, this goal, as Beth said, was really to give this committee an opportunity to sort of test looking at a condition for which we would be potentially making recommendations outside of newborn screening. So to meet the full spectrum of the requirements of the committee or the charge of the committee to look at heritable disorders in both infants and children.

So it gets us from newborn screening to screening at an older age. But to use this as sort of a model for what sort of things we might run into if we were to look at a condition and make recommendations for screening at an older age.

So this is the list, as Beth said. And I have to say I didn't realize Beth could be so tough in trying to get this done in time and cull the list from I think we started with --

DR. TARINI: We started with 12. We went up to 15 and then down to 9.

CHAIRMAN BOCCHINI: And she got us down pretty nicely. So now we need input from the committee to sort of look at these 10 conditions and consider, give additional thought to and perhaps some additional recommendations that we can go back to the subcommittee with and kind of argue for one or another of these conditions to be considered as the final condition.

So we'll sort of open it for general discussion. Charles?

DR. HOMER: I like thinking about the criteria that you said the committee didn't use, which was thinking about is there an effective -- I said I like thinking about the criteria which the committee didn't use, which was this idea of whether there's effective therapies.

DR. TARINI: Didn't use exclusively.

DR. HOMER: Didn't use exclusively. No, I think great for getting that on the list, but then in culling this list and thinking of if part of what we're intended to do is make recommendations for things that should be screened for clinical practice

or through a public health system, it seems to me that that criteria would apply.

I would then ask the expertise in the room. I mean, for me, long QT syndrome jumped out, but that's because there was just an article in the Globe about the problems with treatment thereof if your pacemaker gets all messed up.

So that makes me think we should screen and identify it because then we could treat. But again, that's really based on my USA Today level of clinical knowledge, rather than --

(Laughter.)

DR. HOMER: -- more sophisticated. But I'd suggest that be a filter for which we might use looking at this.

DR. TARINI: So that's particularly the discussion point that we'd like the committee's input on because during -- what we did was not exclude some disorders on the list for which there was not extremely compelling evidence that a treatment would lead to improved medical outcomes for the child.

Because there was discussion that we would first solicit input from the committee as to whether or not they felt they would like a broader list or to consider a condition for which treatment would provide access to services, knowledge ahead of the disorder coming, access to support emotional services for which there may not be a substantial evidence base.

So the degree to which the committee feels that should or should not be considered, we'd be happy to oblige.

DR. MATERN: I don't know how you did this, apparently, since I wasn't there. But I guess you could either choose a condition that has already been brought forward to the committee for consideration into the inclusion into RUSP. And few years ago, the Friedreich's Ataxia Research Association was here not to propose it at the time, but suggest that it might be coming.

And obviously, one of the conditions that we are testing right now is Friedreich's ataxia. Another one on that list is Wilson disease. Then we

had the 22q deletion people here, and I assume they will come back at some point. And what other conditions? MPS1 was here as well, too. So that would be one way.

And the other way, if you look at the incidence of these conditions, would that help you in picking one out?

DR. TARINI: That's on the docket as a possible issue.

So I just want to go back to this actually was discussed, Dr. Matern, the idea of whether or not something was on the RUSP. Because the committee, the subcommittee is sensitive to not being perceived as giving a "leg up" to disorders as they come up for either immediate or potentially immediate review, or those that have passed through the evidence review, we don't want it to be seen that we're showing favoritism. That's not our goal. Even if that's not our intention, we're sensitive to that perception.

That being said, we realize that there are some disorders for which it may not be imminent that

they're added to the RUSP, but it may be in the next few years. And so, it becomes a slippery slope of how one -- how deep one goes into potential for being added to the RUSP.

So, for instance, that came up with Duchenne's and, as you say, with Friedreich's. So we kept them on, but we also wanted to point that out. And I think if we're bringing it up to the committee that at what point is -- also fragile X. These have been discussed in terms of newborn screening, and we would rather focus on another disorder perhaps that's rarer, perhaps that's higher in prevalence.

DR. PARISI: So is one of the considerations the potential utility of being added on to the newborn screening panel? Because it sounds like your criteria really are looking for things that have more of a pediatric onset, but I notice there's a pretty broad range of age of onset for these conditions from infancy for about a third of girls with Turner's syndrome through adolescence for some of the others like Friedreich's, et cetera.

So I'm curious about what the committee thinks in terms of age of onset and whether the goal is ultimately to promote something that could be added to the RUSP or whether that's not part of your consideration?

DR. TARINI: So the goal is not to promote anything that could be added to the RUSP. "Could" being a word you could define -- I feel like I'm in a Senate hearing.

"Could" being a word you could define a number of ways. At least not immediately being considered was one strict definition we used. So we are trying to get out of the newborn period as best we can, focusing on later times.

Sometimes those disorders will roll back, and there will be an infancy presentation, which will then roll you back into the potential for having a newborn screening disorder. That being said, to your second point, we did have extensive discussion on, for instance, Marfan syndrome as an example of we have a disorder presentation that seems also to roll into adolescence, and in some

cases, diagnosis will be elusive until adulthood.

So what we did was a gross assessment of do the majority of cases present in the pediatric age range? They can span the pediatric age range using loosely like 18. But if it was starting in adolescence and nearly all spilling over, a majority spilling over into adulthood, we tended to shy away from those disorders.

So that was another discussion point we had.

DR. LOREY: Just a comment on Turner syndrome. We, in addition to newborn screening, we do all of the prenatal screening for the State of California. And although our targets are 21, 13, and 18, you pick up a lot of Turner syndrome in prenatal screening.

DR. TARINI: Right on. So this was another discussion point. If some of these disorders are being screened and prenatally -- fragile X, Turner -- then what is our value added, A, of beginning a campaign of sorts to improve education and training, and B, also then what is its

proximity to them perhaps soon coming onto the RUSP?

So this was also another point that came up.

DR. BOTKIN: Yes, I think my understanding of this exercise, too, was to say that newborn screening is, by definition, sort of population based. We take all comers.

With these other sorts of screening modalities, we might well be targeting and perhaps targeting broadly just girls or targeting more specifically based on family history or that sort of thing. So I want to make sure I have that understanding correct with how the screening might work with these other types of conditions.

DR. TARINI: That's correct. There was this particular emphasis on the fact that there do not have to be a test interpreted as one takes blood and sends it through a machine. A test could be a procedure or process like family history screening, could include that, or could be clinical evaluation.

And it could target -- and it was not necessarily, as Dr. Botkin points out, it was not

necessarily that all, it was not necessarily universal screening. It could be targeted screening.

CHAIRMAN BOCCHINI: Carol?

DR. GREENE: It's all fascinating. I would -- I want to point out that long QT has -- there's already been discussion about long QT screening in the neonatal period because there is a mechanism, and there's lots of arguments for it. But I think it might be one that's relatively close to being proposed for the RUSP.

And I would be -- I think it might be important to look at something that is fairly common because, otherwise, it might not be a so useful experience to study it. And I keep coming back, looking over the list, to Turner because there's such interesting questions. What is it useful for? What is the mechanism?

I think you should screen boys. I think the majority of the Turner's cases that I see are not picked up on newborn screen. They're picked up too late to go on growth hormone therapy. What kind

of screening should they actually be having?

If we knew they had Turner, they'd be -- so there's actually a protocol and a management protocol, and it introduces utterly different questions. Of all the things on the list, it seems to be probably the most common and the one that introduces the most novel questions to explore.

CHAIRMAN BOCCHINI: Other questions, comments?

(No response.)

CHAIRMAN BOCCHINI: Well, if not, this was a good discussion. I think it adds some good depth to the considerations and I think that -- Steve?

DR. MCDONOUGH: Mr. Chairman, procedurally, would it be between now and the next meeting, could the committee do some voting, top three picks or something like that, so we can narrow this down to a couple for the next meeting to perhaps discuss what our priority would be?

CHAIRMAN BOCCHINI: Yes, I think that the subcommittee is going to start looking at with each of these disorders considering some of the

suggestions made within the subcommittee and now by the full committee about what criteria to then apply, to apply them to each of these and sort of look at each of these conditions with those criteria. Perhaps cull the list a little further based on those things, and then bring it back to the full committee for either a vote prior to our meeting or at the next meeting so that we can.

So I think that's the -- those are the next steps.

All right. Alexis?

DR. THOMPSON: Can I also ask that as we look at creating a matrix for these, if we can actually look at whether or not there are advocacy organizations for each one of those to look at where our opportunities are to work together?

So if we actually knew that, not only things like frequency and treatment or no treatment. But if I actually knew that there were additional resources that we could consider for getting more information.

DR. TARINI: I think that's a good point

that was brought up at the end of the discussion. Thank you. The idea of having the potential to -- so let me actually ask then.

Some were saying, some were arguing it either way. Some said, oh, if there's advocacy groups, they already have attention shined on them. What you're saying is if there are advocacy groups, they could be used as sort of a mechanism and leverage to disseminate information.

So it was actually discussed the opposite way in the subcommittee meeting. So I want to make sure I understand what you're saying.

DR. THOMPSON: I think simply knowing that they exist, without necessarily saying how one will use them.

DR. TARINI: Okay. And then moving quickly through. Priority B was to promote newborn screening awareness among the public and professionals. And these were our overall objectives. We'll focus on this one because, as you can see, we had a robust discussion about conditions.

So we focused on supporting and providing input around the 2013 newborn screening awareness campaign plans and activities, how we could be involved in each of the various activities being planned. The star of the show was the CDC and APHL, Carla and Jelili came and briefed us on the impressive progress they've made to date.

To summarize briefly, there will be an APHL newborn screening symposium meeting in May 2013. There will be a book, coffee table book documenting achievements in newborn screening over its lifetime.

There will be a D.C. celebration event to coincide with the September 2013 SACHDNC, and it will include a day on the Hill, I believe, preceding it. There will be a traveling exhibit of newborn screening historical artifacts, as well as social media messaging being developed.

And the next steps that we discussed at the subcommittee were the value of adding advocacy groups, involving them in spreading awareness, and the need for messages, press releases, specific

statistics that can be used by member organizations to increase awareness of newborn screening and in particularly in a standardized way. So we're all using the same messages and the same facts, both for improving awareness and being standardized.

And then next steps for after 2013 so that it doesn't die with the 50th anniversary would be one idea was creating a toolkit for individual States to use when they themselves celebrate their 50th anniversary.

And finally, priority C, to provide better guidance for advocacy groups and others regarding the nomination and review process. The problems here to be solved, as we see them, are to increase public transparency for what we do and the rationale behind the decisions made and to provide feedback to nominators regarding next steps and support future nominators in preparing successful application packages.

So this priority is being worked on in collaboration with the condition review group to develop a public-friendly Web site information and

to start specifically with a public-friendly summary of evidence review.

Next, so we understand the issue of the Web site in general, but we start specifically with one task, that being the evidence review summary. And we know, going forward, this is also going to be a priority for the condition review group.

So that being said, we'd like to use it as a test case sort of looking back at ones that have already been completed. And to help -- also that will help the condition review group going forward as they develop their future lay summaries.

So our next steps in discussion were to seek clarity on technical constraints on revisions to the SACHDNC Web site, what we can and can't do. And work on harnessing potential of SACHDNC and newborn screening clearing house Web sites to disseminate public-friendly material. And as I said, to create a subcommittee to assist with the creation of public-friendly documents, starting with a past evidence review.

That's all.

CHAIRMAN BOCCHINI: Thank you, Beth.

Any additional questions or comments? If not, thank you for -- oh, we got one? Sorry.

DR. BOTKIN: I wonder if we're currently providing a lay language-friendly summary of what the committee's decisions are on conditions so that people understand what the nature of the concerns were, what needs to be done as part of next steps? Are we doing that?

CHAIRMAN BOCCHINI: That is part of it, yes.

All right. Dieter?

DR. MATERN: Is that a concern that we have proactively, or has somebody said, "I don't get it." I mean, there are the letters from the chairman on the Web site, indicating why something was not accepted. I understand them, but that doesn't necessarily mean anything.

But has anybody complained that it's not clear?

DR. TARINI: I know of no specific complaints, but general discussion that some of the

material is difficult to digest for the public without -- but I know of no specific complaints.

MS. BONHOMME: Hi. Yes. I mean, we've had some phone calls of people saying, "Oh, can you walk me through this?" Just people who are wanting to understand with the nomination process and things like that. So it does seem like there is that need.

DR. TARINI: Thank you.

CHAIRMAN BOCCHINI: Thank you.

Other comments?

(No response.)

CHAIRMAN BOCCHINI: If not, Beth, thank you very much. Appreciate your report.

Next we'll have a report from the Subcommittee on Laboratory Standards and Procedures. Fred Lorey will give that report, or is he -- oh, Fred, can we call on you to give your report at the present time?

Sorry about that.

(Pause.)

CHAIRMAN BOCCHINI: All right. So we have technical difficulties. We'll go ahead and change

the order again and then put Fred as the final.

So, Carol, are you ready to give your report? We have the Subcommittee on Follow-Up and Treatment. Dr. Carol Greene will give this report.

(Pause.)

DR. GREENE: So, good morning. And do I advance the slides? Yes, I do.

So thank you very much to the committee -- subcommittee for an extremely useful discussion and also to a lot of work that has happened since I made the attempt to step into Coleen's shoes. And we have to report on some work that was done as part of subcommittee activities or spinoff from subcommittee activities that's all owing to her leadership. And then we'll talk about some of the new things.

We started our meeting with some changes in the membership. We said a farewell and thank you to Michelle Fox, but we also reminded her that once you're on the subcommittee you never get to stop working for it, which is where a lot of the volunteers come from.

And we welcomed two new members, State

Health Department -- State Health Department of Maryland, Debbie Badawi and Kathryn Hassell, who's -- Debbie Badawi, you may remember a presentation last meeting about CCHD implementation in Maryland. And Kathryn, Kathy Hassell has been working a lot on the sickle cell project that we've started.

We should also say that -- I'll talk in a minute about what we've been doing. So we had some updates. Some of these, again, are a direct result of subcommittee efforts. We heard from Brad Therrell that the work that had been done on the sort of points to consider or review of connecting newborn screening blood spots and birth certificates is published.

Sue Berry reported on revision in process for publishing the manuscript on the work on coverage of medical foods and supplements that was started in the committee and then involved multiple regional collaboratives.

And Rani Singh reported on -- and this is not an activity of the committee, but definitely important -- that Newborn Screening Connect, which

is, I think, an activity of a regional collab, has gone live and has started to get some interest connecting families and patients as a voluntary registry, and they envision knowing where people are and having people connected with each other and making sure people have access to -- it's a two-way access for the metabolic healthcare provider and research community to have access to talk with the parents and parents to talk with each other and vice versa.

Sue Berry reported, and she sent me another email this morning, but I didn't get a chance to include it. So if there are any important comments we can add. But she's been working, and Kathy Hassell is part of that project as well, on newborn screening long-term follow-up data, a project that's gone to REDCap to start to enter data. And there are quite a number, I understand from the email this morning, of cases already being entered.

Nancy Green, who spells her name wrong, reported on --

(Laughter.)

DR. GREENE: -- publication of the paper on the key considerations for point of care screening of newborns, which will be important when we talk about one of our upcoming projects.

And I really want to single out for upcoming especially Nancy Green and Kathy Hassell and Cindy Hinton, who've been doing a lot of work, And Alexis Thompson, who's been doing lots and lots of work on the sickle cell project, which I will talk about last because I think there's likely to be the most discussion.

So we have been working. We've been having regular phone conference calls monthly and some added on for subgroups, workgroups working on specific projects. We're focusing on the priority areas and products previously -- our marching orders by this committee that we had reviewed with Sara to make sure the projects that we develop are in line with the -- Sara and Joe to make sure they're in line with the plans.

And subcommittee members and volunteers

have formed workgroups, and we're good at roping in volunteers. So we've just roped in Sylvia for the EDHI group as well.

And I'm going to talk about our priority A project and our priority C project. But I am first going to remind folks that our priority B is not a freestanding project, but it is a reminder to us, as we discussed in May, that as part of our case studies, the project A and the project C, we are wanting to include an interest in learning what are the current and what are the variable roles and responsibilities and make sure that all of our case studies look at that question. It's not a specific separate project.

So our project that goes with our -- and A, B, and C, it's not like ranking which one's more important. They're just so we can name them.

So our project focusing on implementation of point of care testing, assessing the challenges of new point of care tests and start by asking what we can learn from the experience with EDHI and what ways is it different from, similar to, what can we

learn that will help us in the real time of implementation of CCHD?

So this project is in early stages. It's not yet clear what our outcome is going to be. Well, that's true for the other one, but it's even less clear here what the end product will be. But we're also moving very fast because to start with, we have a limited time that we've got Brad Therrell, who started -- and sorry, I went with Therrell and White because I don't remember -- it's Karl White, right?

Brad has been working on some relevant information, and he reported on it. And we have a limited time to access that work. So we need that stage at least completed before the end of December is my understanding.

So they reported on the status of -- the current status of really focusing on reporting and communication among other questions. Does the information go on the blood spot? Where does the information go? How is it handled? What are the laws and regulations in the various States that

govern that?

And you know, whatever are the laws and regulations, what is actually done? Because sometimes what's done, as was pointed out, is much more than is required by either law or regulation. And Alan discussed issues of -- does anybody besides me have the experience that when you type "EHR," it always wants to make it "HER"? It's really annoying.

(Laughter.)

DR. GREENE: So I kept changing it back. Discussed issues of electronic health records and point of care screening. And the incredible potential for help there and what are some of the current limits. And reminded us, and this will come round again, that we want to both use the electronic health record in any visions of future studies that might be carried out, but we also want to study the question of how EHR is being used and how it can be used.

So that led to general discussion around the issues, project goals. And really reminding

ourselves that the focus of this one is on what does the EDHI experience offer? Since it's been up and running, what does it offer to understand as we look forward to implementing other point of care screening?

And after the meeting, but I thought this was important enough to capture, we did mention during the meeting the paper that was recently published on key points or key issues in point of care screening. And at least one idea for future development of this is starting with that paper, which has laid out a lot of the issues as maybe one of the contributions of this committee would be to begin to explore a roadmap of what are some of the issues?

Now, again, that's reaching far down. We haven't yet decided what it's going to look like because the first question is what lessons did we learn from EDHI that would be relevant to others?

Because we're wanting to be sure we take advantage of the resources we have available to us, that will be the subject focus entirely of our next

phone call. Any questions about that?

DR. COPELAND: I would encourage not just the regional collaboratives be included, but also the CCHD grantees, the six States that were funded or, actually, it's more like nine States that were funded. So please enlist their knowledge, too, since they're actively being paid to do this.

DR. GREENE: Okay. Obviously, I wrote it down so I don't forget. I think my inclination might be to start to loop them in early and make sure we have some folks on the workgroup.

But to really -- we have been focusing on EDHI first and then CCHD, and we have that resource. But I think we want to loop the CCHD people in early so we know we're asking the right questions of the EDHI folks.

So, Jill, if you could and if the EDHI workgroup could start to think about how we make sure we have somebody representative involved early, if we don't already. Okay?

Priority C, real-world impacts and outcomes. I split this into two slides. This is

we're calling for shorthand our sickle cell case study. And this is the -- there are three bullets. The next one will be on -- the third bullet describing the study will be on the next slide.

And our goal is, and we're just -- there's so many ways we could do this. There's so many important questions that one of the things that we kept doing during our discussion is reminding ourselves. What are the goals? What have we agreed with this full committee to do?

So our goals are to explore the extent to which -- you can read it. Are we doing a good job, you know? Have we been successful? Are we improving health? And there was a very strong reminder during our subcommittee meeting it's not just health. It's development. It's psychosocial. It's long-term outcomes.

And that there are a number of things they were specifically interested in looking at, but it's by no means a complete list. But very specifically, we are looking at the question of variable notification in trait, and we are specifically

looking at issues to do with electronic health records. And we're definitely looking at the variability of impact in difference in clinical -- sorry, impact of variability in clinical care.

Question?

DR. COPELAND: My understanding was that you guys were going to take the public health long-term follow-up goals and apply sickle cell to see how that works?

DR. GREENE: Yes, we are.

DR. COPELAND: Okay. Because that is more like what our demonstration and treatment projects are funded to do, as opposed to having --

DR. GREENE: Right. That's the next --

DR. COPELAND: Okay. As opposed to having a subcommittee of an advisory committee do the outcomes evaluation.

DR. GREENE: That's the next bullet.

DR. COPELAND: Okay.

DR. GREENE: That's why I said this one was too long to put all on the same slide, okay? So as Sara just said, we had to keep on reminding

ourselves that as tempting as it is to actually try to --we're not -- first of all, we're not going to do the project. And the idea is that we should not duplicate. We should work on thinking about harmonization.

Our goal, what we could add as value as this committee, the subcommittee bringing ideas to this committee, is to bring the wisdom and the concerns and the experience of the newborn screening world to make sure that the efforts carried out to collect long-term data actually answer the questions of the newborn screening community. Okay?

And with that in mind, does that -- need to add something?

DR. COPELAND: No, I think it's going to be an ongoing discussion because there's a potential for duplication of effort, and I really want to make sure that the focus is more on the long-term follow-up and the system and how it looks, as opposed to what sickle cell is doing. Because those are two separate issues.

DR. GREENE: Right. And we did

continually also remind ourselves that the committee asked us to look at sickle cell as an example to make sure that this ends up being a model for how you can look at any newborn screening condition, and does the system succeed in improving outcomes?

So, with that said, we started with a presentation, and that is -- there was a very lively discussion, especially of, well, both matrices. And the first matrix, just again to focus everybody's attention on what Dr. Copeland just said, which is to apply our long-term follow-up systems analysis -- that's work that was done when Coleen was chair, and we were all very, very, very proud of it. And that first matrix, everybody remembers who was in the room, down the left side are the four different parts of the system that we had laid out in that paper.

And then on the other axis, the matrix looks at the different populations who are interested in different questions, how those fit into those four elements of newborn screening. And begin to use that matrix to make sure that we have

captured the questions that are important to us. Okay?

So that's the first matrix, and that was presented by Cindy, populated as a first draft with information that we took from Alexis Thompson's presentation before.

And the second matrix looks at the -- some of the questions crossed with or looking at where the data sources are. And not to say, and this was, I think, a nice breakthrough from Cindy and Nancy, we had initially started thinking about individual data sources. But instead, they started breaking it down into what kind of data is available from primary care providers, from individuals and families from the public health, from the specialty care providers.

And then we can begin to populate that with an understanding of who's doing what work and use this whole landscape to see exactly what kind of product we're going to end up with that will help the people doing research to make sure that outcomes research answers the questions that are important to

this committee.

Always remembering avoidance of duplication, focusing on harmonization. There were some key points that came -- or some interesting points that came up with a lot of passion during our discussion, and that was a reminder to include concerns about privacy.

A very strong reminder to -- I think this would be on the next slide would be to remember to include not just health and medical outcomes, but outcomes of importance to family and the individual, and also to remember that we, again, can look at the use of EHR and to study the use of EHR and to envision -- not to use because we're not doing the project, but to envision the use of EHR in projects looking at outcomes.

We also reminded ourselves about some of the very different issues in terms of what are the questions and where are the data sources in sickle cell and sickle trait? We talked about whether this would include other hemoglobinopathies, and the answer was S cell, but not the others because we

want to make this manageable. And the psychosocial outcomes, and we talked about where the data is.

After, just to give you an example, and I really -- please forgive me. I really did change the slides a lot. But just to give an example that people are quite passionately interested in this, and folks were working very late last night and working together as a group. And then Nancy sent me some slides, and here's just a modification and culling of them.

This would be, because one of the very key points that while we want to keep this rich and capture everything and make sure that we're looking broadly, in the end, if you're going to help somebody to envision a project, that project is going to have to be simple and doable.

And we are looking at a tension between getting roped into the, well, we're going to study this because that's what data we have available, where our marching orders say let's ask what are the important questions. And if there are gaps in the data available, let's identify those gaps and say

people need to start figuring out ways to collect that data because it's important.

But with that tension there, it's still this is some late-night and very cool and interesting efforts by a small part of the workgroup thinking about how you would envision way down the line what could we be informing and thinking about selecting a key indicators. And we know there's lots of people working on what are the key indicators and what are the outcomes.

And there are people who are working on guidelines and lots of projects. And so, one of the keys here is going to be understanding who's doing that, and that's going to be one of the first things that we do on the next phone call, one. But in the meantime, people are going to be pulling together information because, remember, we have that matrix to populate to say where is the data and, therefore, where might be the gaps?

And thinking about in the end what might be practical, but also we're identifying gaps. And already thought about what are some of the key

indicators and what are some of the key outcomes if you really want to look down the road. And so, thinking then back to the subcommittee, looking at next steps, we're still envisioning what the final product would look like. We have some ideas.

It has to be useful in future decisions about implementing newborn screening. So the goal is to -- it's a case study, and we care about sickle cell. There is a lot of work done about sickle cell. The goal is to take advantage of what's happening about sickle cell to see if there's an opportunity to make it better and also to learn how to do work understanding outcomes of other disorders.

It should be useful in designing future data collection, useful to promote development of future simple projects that would actually look at the effectiveness in newborn screening. We might end up with a white paper. We might end up with HRSA or somebody else writing RFAs.

It's all sorts of possibilities, but we have a lot of work going on. And I think our next

steps are clearly -- our immediate next steps are identifying other groups and ongoing efforts to understand what are the available data sources, who's doing what. Identify the gaps in information that's currently tracked. In other words, what key questions are -- cannot be answered with current existing data sources or strategies for outcomes evaluation?

We really want to be thinking about harmonizing key questions and looking at harmonization of outcome indicators, data element strategies. We can't do it, but that's what we're thinking about, how to help facilitate that.

And not the next meeting because that one will be EDHI focused, but the meeting after that will be sickle cell focused. In the meantime, some work will be done, and we will be reporting back at the next Advisory Committee meeting. And I hope I didn't mess up anything.

CHAIRMAN BOCCHINI: Thank you, Carol.

Questions and comments? Denise?

DR. DOUGHERTY: Well, while I'm thinking

of it, and Charlie mentioned it to me, the CHIPRA quality measure development effort has Gary Freed at University of Michigan working on some quality indicators for sickle cell care. And one of the issues is even though that program, because it's under the Child Health Insurance Program Reauthorization Act, is focused on measures for Medicaid and CHIP. It's clear that those measures may not be adopted by some States because they just don't have enough sickle cell patients.

So we're actively looking for other opportunities for implementation of these measures. Plus, the meeting I was at yesterday, Gary was there. And he was saying we have so many possible measures and, as you're saying, so many possible questions and topics, which are the most important ones?

So I'd like to put the committee in touch with Gary so that we can start working together. But what would be helpful is to have sort of a one-paragraph description of what it is the committee is trying to do. Because I see lots of possibilities

here, but I'm not sure I could actually summarize it in, you know, the old one-pager.

DR. GREENE: We can work on that. It's -- it's pretty much those -- it really is those first three bullets, and beyond that, we're still working on clarifying. But I can work on that with Sara and Joe.

DR. DOUGHERTY: That'd be great. Thank you.

DR. COPELAND: I would propose that probably our grantees are a more appropriate place to take that, as opposed to a subcommittee. Because our grantees are the ones that are implementing the quality measures and working with Charlie, and they're the ones doing the work.

It's not a -- sickle cell follow-up is not -- sickle cell treatment is not a State program. It is a clinician program, and I think that there's when you look at a Federal advisory committee trying to tell clinicians what to do, you run into some problems.

DR. DOUGHERTY: Well, but I thought the

whole purpose of the Long-Term Follow-Up Committee was not for the States or a committee to tell clinicians what to do, but what is State role in facilitating and monitoring the successes and failures of the clinical community in doing the follow-up and treatment?

Certainly, the State can monitor. If the State can see where the gaps are, then the State could possibly help facilitate some amount of the treatment and follow-up. But I thought that was the goals. So I'm not --

DR. COPELAND: We can discuss it offline. But I think that we need to make sure that we put the burden on the appropriate people.

DR. DOUGHERTY: Well, just for purposes of these quality measures, I just want to make sure that there is -- that people are aware of what each other is doing. There's some expertise on this committee and subcommittee that I think could be helpful to Gary out in Michigan developing these measures and trying to figure out which ones are the best ones.

So, you know, I mean, there was an effort in the Office of the Secretary that was trying to coordinate across everything that the department was doing, all the different entities. CDC, you were involved in that. And that seems to have dropped off, but I don't think we should forget that those of us who were involved in that effort to coordinate, collaborate, should not continue to try to do that.

CHAIRMAN BOCCHINI: Coleen?

DR. BOYLE: I was going to elaborate just a bit, and I guess I would love the committee's reaction to this of our discussion yesterday. And this is just one piece of it.

So in my mind, building on Alex's or the committee's matrix from yesterday, you know, where we were talking about the evidence, the scientific evidence for the efficacy of screening. And then we were imposing that reality base of readiness and I guess it was feasibility was the other aspect, I guess I was thinking of a fourth dimension, and I know we don't want to go into the fourth dimension

here.

(Laughter.)

DR. BOYLE: But thinking about availability, not so much availability of services. So that's not right. But more what needed to be, and again, that's more readiness and feasibility, it's like what are the treatments and how you would monitor the uptake of those essential treatments for children?

So as part of the committee's work and part of sort of structuring the recommendation, I was thinking that there could be this fourth dimension, which was sort of the treatment piece of it. And then in a real crisp way so you're thinking about what those necessary treatments were and then perhaps how that information would be captured and by whom to make sure that that was happening.

So sort of laying this framework out as you were going about implementation. So that's what we were tossing around a bit. I don't think it's sufficiently developed or gelled. But I actually do feel like that's the committee work.

It's sort of setting that I don't know if it's the floor or the ceiling, but setting the bar.

DR. HOMER: And just building on that and tried to integrate some of these other comments. We did start with the framework that the previous committee, Coleen's committee had worked on. And it was very helpful, and I think the process also in running through that with the example of sickle cell disease is not only informing whether the world at large and how the extent to which sickle cell has fulfilled that, it also, I think, is informing the model.

Because we then looked at that model and say is there enough clarity in that model or not? So, for example, it says medical home. Well, that's important and hard to assess. It says evidence-based care. Well, you know, that's sort of everything that was on that list.

So I think -- and it also says research as though that were separate from evidence-based care. So I think, actually, Sara, this goes both ways. In other words, by using this model, using the case

of sickle cell disease, we're not only saying to what extent has newborn screening for sickle cell disease fulfilled this promise, but it's also reflecting on to what extent does the model that we've already developed as a committee actually is it complete, or does that model itself need some tweaking?

And I think we're going to come back and inform that model through the conversations.

And just to build on Denise's point. One time there was substantial discussion in the committee, and it may or may not be our committee's role. But an acute awareness that there are multiple Federal efforts right now, which are related to establishing measures of whether the system of care and research and monitoring for individuals with sickle cell disease is functioning to the way that it should.

And we were conscious that we did not want to contribute to the cacophony of creating a different voice, but we also were aware that we may have a potential voice as an advisory committee to

encourage unity amongst those voices. So if we could use our good offices to encourage the multiple parties that are involved to become more aligned, I think the community at large would be appreciative.

DR. COPELAND: I understand that, and I would emphasize that I would much rather than it informed the model than tried to inform sickle cell disease because you don't have all the players on the subcommittee. You don't have NHLBI there, and you don't have the blood disorders group, per se. Althea Grant isn't there.

And I mean, they're in your center. But I still think that the project officers that are at the base level, I just think there's more players than are necessarily included in your subcommittee. And so, I want to make sure that we don't -- don't start stepping on toes.

DR. DOUGHERTY: Could I? One of the things that subcommittees used to do and this committee used to do was to have the different players come and have a set of presentations so the subcommittee or the whole committee could find out

what everybody was doing and then be more informed about what the role of the subcommittee or this committee could be.

And so, that's rather than say we need to limit what we're doing -- we couldn't even inform the framework and build upon, I think, without hearing all these other things that are going on. So I would suggest that we have -- you know, we have had workshops before on different topics. I would suggest that just because the Office of the Secretary isn't telling us to coordinate, I think it is an opportunity for this committee.

DR. THOMPSON: This is just a question for information. Sara, the trans-Federal efforts to collaborate with sickle cell, is there actually an advisory component to that effort? I mean, it seems to me that if we're working under the auspice of the Secretary that it would be useful to have some advisory group somehow interfacing with these different Federal partners that are seeking to coordinate efforts across sickle cell.

Does that entity, does that trans-Federal

-- I don't know, I'm not sure if it's called a collaborative or exactly what the name of that entity is, does it actually have an advisory component to it?

DR. COPELAND: It used to, and -- well, I don't know about advisory. But right, it was never an official advisory group. But that being said, we can't -- we can't autonomously develop an advisory committee to the Secretary. So we need to be -- we can advise the group, and we can use the tools we have.

But there is a trans-agency group that's not meeting currently. My understanding is it'll start up again soon. So --

DR. THOMPSON: I mean, it just seems that if -- it's just connecting the dots I think is all we're asking for without necessarily asking for any change in the actual structure of things. I see your point in terms of avoiding this drift to taking on things that legitimately are being taken care of and probably even more effectively being taken care of by other entities.

But it also -- it would seem that wanting to have some opportunity to create a clearing house so that, in fact, we are clear on what's already going on, as well as being able to provide the opportunity for input in terms of how those projects are coming together.

The other question is, is that in sickle cell, there are a variety of reasons why there has been this effort to collaborate across Federal agencies. One of the questions in my mind is that wouldn't that be wonderful if that happens for even more disorders?

And if we anticipate that happening, us clarifying how those different agencies will work together on behalf of citizens who are affected by these diseases. It seems to me that understanding how that model will work, including how they would interface with either a subcommittee of this committee or exactly how we would avoid duplication in the future to the extent that that would happen for other conditions.

DR. GREENE: I think that that was very

well articulated, and this is getting to the tension between is it a sickle cell project or is it the implications of sickle cell for newborn screening outcomes projects in the future? And perhaps one of the points here is that this is an advisory committee for heritable disorders, and the question is not just the role of the committee, but also what's the scope of the project?

So we'll continue to work on that. And I realize I did forget to say one thing that was very important. I mentioned privacy, but not up on the slide was a report on or an update on another project because -- I forgot to put it on a slide because I gave that report on behalf of Mike Watson, who gave me some information.

And this sparked some interesting discussion on the issue of privacy that the NCC with Alissa -- I'm going to blank on her last name -- looked at the existing laws and regulations that govern the ability of the public health system to access individual records, which is where some of the data for outcome studies comes from. And the

concern raised that certain types of privacy advocates for certain individuals might have discomfort about that process and then the importance of transparency.

And that's another one of the projects that's already been funded and carried out by HRSA that needs to be considered as we go forward and thinking about future studies.

CHAIRMAN BOCCHINI: Questions or comments? I think this has been a good discussion, and I think with the insights of Sara and Denise and I think we have a good opportunity to kind of coordinate things in a better way to sort of focus down on the right questions for this committee, as well as to contribute to the overall efforts to coordinate things.

So I think that's good. And thank you, Alexis, for your comments. That's good.

Okay. Thank you, Carol.

All right, let's bring Fred up. Okay. Now Fred Lorey is going to present the report from the Subcommittee on Laboratory Standards and

Procedures.

DR. LOREY: Good morning. We actually covered quite a bit of material yesterday.

(Pause.)

DR. LOREY: Excuse me. We started out with Dr. Chen giving us a presentation on the CDC recommendations for good laboratory practices in biochemical genetic testing for newborn screening for metabolic disorders.

The intent of the recommendations, and I believe one of the slides may have a Web site if you want copies -- if not, we can provide it -- to provide quality management guidance for genetic testing -- excuse me -- performed for screening, diagnosis, monitoring, and treatment of heritable disorders.

Consider biochemical testing and newborn screening separately when practices differ.

Clarify the CLIA requirements and provide additional good laboratory practice recommendations.

And complement the 2009 CDC guidelines for molecular testing.

Some of the recommendations for good laboratory practices include the following intended audiences: laboratory professionals, surveyors, inspectors, users of laboratory services, standard-setting organizations, professional societies, and IVD manufacturers.

Expected outcomes are to improve the quality of laboratory genetic services and improve healthcare outcomes for genetic testing.

We had a discussion afterwards, and I think the subcommittee felt it wasn't quite ready to go forward to the full committee. But we're going to request additional information on how this would impact State programs.

Next Jelili Ojodu gave us a presentation similar to yesterday, but he gave us more detail and actually showed us some of the actual examples of data collection. I'm sorry. This is Harry Hennon went next to discuss the CLSI document on newborn screening for SCID.

This document, it's not completed yet, but addresses the detection of SCID by population-based

newborn screening using the TREC assay. And they are asking for volunteers to review the draft. It's gone through several reviews, but they would like additional comments, should anybody want to volunteer. There's quite a distinguished list of authors on this document.

And it looks like it will be a particularly valuable document to States that haven't yet begun the screening because it's really going to cover everything about SCID testing and the disease.

Moving on to Jelili's presentation. Priority B is one of our subcommittee's priorities to provide guidance for State newborn screening programs in making decisions about lab integration, follow-up, and quality assurance. It's important to confirm the quality of the data, as you heard yesterday, provide feedback to the States based on data received.

And he made it clear they were very interested in getting feedback from the States. The States could use the new data repository and

NewSTEPs. That's their new program he spoke of yesterday. And it's important to discuss with the States what do States get back?

In other words, it's a workload for States to provide data input to several different groups. How will this data be meaningful to the States? And what would this be valuable to States?

Some of the input from State reps on the subcommittee or among the guests is just asking them to remember not to duplicate efforts and don't reinvent the wheel. Because a lot of times, those of us in State programs end up entering basically the same data in several different datasets. And so, that was just our input, and he was very receptive to that concern.

And then, again, Jelili talking about case definitions, as he did briefly yesterday. Also supports priority B for this laboratory subcommittee. Several States have volunteered to beta test this NextSTEPs document on test definitions.

And discussion on how to get outcome data

back to the States so they could improve their programs, something the ACMG is already looking at.

So these are -- in a previous slide, you saw priority B. These are our priority projects. Priority A is to review new enabling, innovative technologies. And the first example that we've decided to look into is the succinylacetone assay. You might remember a couple meetings ago, there was some discussion about this and how it sort of evolved, replacing tyrosine as the marker for tyrosinemia type 1.

And the question was raised why aren't all the States using this now? Because they did not -- all of them are not. So we had several volunteers to form this workgroup that this was just decided yesterday. Carla Cuthbert and Victor at CDC, Dieter, who worked extensively on developing this assay and putting it into the primary screen, and Stan Berberich from Iowa.

And this may be rosy, but we proposed to present something at the May 2013 meeting.

Also, providing guidance for State newborn

screening programs and making decisions about lab integration, follow-up, and QA. One project is comparative performance metrics, which is already in process. We would like to develop a slide deck for State labs so when a new condition is added to RUSP -- and emphasizing after it's added, a decision has been made -- what types of information is it helpful to the States to provide to, I don't know, I'll call them decision-makers, which include CMOs, legislature, hospitals, et cetera?

And we decided that since it's already being worked on and Amy's done quite a bit of work on it with SCID, we'll use that as our first example or our template. And then we had volunteers to work on this as well.

And this last one was an interesting discussion. Establish a process for regular review and revision of the RUSP and recommend specific changes to technology when indicated. Work with the condition review group, who I think is taking the lead. This was something they wanted to do, and I think all of the groups, all of the subcommittees,

to be a joint project.

And we just had a small discussion about how nothing has really been reviewed since the initial thing, other than the addition of SCID and congenital heart defeats. And do we need to periodically go back and reexamine what's there? Do we need to talk about moving anything from one category to the other, and what is the process?

We're also having a membership drive.

(Laughter.)

DR. LOREY: So the HRSA folks have agreed to help us out with an email distribution list and mailing out a self-nomination form. I think we only had about six people there yesterday on the subcommittee. We had more guests than committee members.

And these are some of the areas we've identified that we feel we need more strength. State lab people, particularly those States with molecular expertise. Which is actually very few when you're talking about newborn screening.

Commercial labs, clinicians, and

pathologists. So you'll probably be seeing this. I'm guessing you're on their distribution list.

And then we had an update on the health information technology. The new version of the LOINC newborn screening panel is available at this Web site. I'll leave that up for a while so you can copy it down.

And they would like feedback. Are there new codes needed for second screen tests? And what they mean by that is the mandatory second screen tests, do we need -- what happens when there's a positive followed by a negative or vice versa?

And as we all know, that sort of depends on what the disorder is. But that's what they're asking. Do we need codes for that?

And how are newborn screening laboratories reporting mutations found in mutations testing for newborn screening where they do the genetic testing themselves?

I'll turn it back to Dr. Bocchini.

DR. COPELAND: I just want to make a clarification on priority C. The consensus then was

to let you all lead the way in terms of the condition review group and the other subcommittees, and we'll participate once something comes out. Wasn't that the consensus that we had?

DR. LOREY: Yes, absolutely.

DR. COPELAND: I just wanted to make sure.

DR. LOREY: Sorry I didn't make that clear.

DR. MATERN: I just wanted to clarify again about the membership. Pathologist is a very broad term, and I think we want a board-certified molecular geneticist and not just a pathologist.

CHAIRMAN BOCCHINI: Okay. And as I understand from Sara, those efforts are already now underway to begin to develop the request for the new members in the categories that you've defined. So - -

Any other questions or comments?

(No response.)

CHAIRMAN BOCCHINI: Okay. Fred, thank you very much. Appreciate it. Looks like you got a lot of work done yesterday.

We are now scheduled for a 15-minute break. We're a couple of minutes ahead of schedule. So we'll just get started, reconvene at 10:15 a.m.

Thank you.

(Break.)

CHAIRMAN BOCCHINI: All right. Next on the agenda is a presentation by Dr. Stuart Shapira on multistate analysis of single tests or routine second testing in newborn screening for hypothyroidism and congenital adrenal hyperplasia. This is an update.

Dr. Shapira is a medical officer on the pediatric genetics team in the National Center on Birth Defects and Developmental Disabilities. His research activities include birth defects, epidemiology, dysmorphology of autism, gene and nutritional interactions for adverse reproductive outcomes, and newborn screening.

Dr. Shapira received his Ph.D. degree in genetics and his M.D. degree both from the University of Chicago. Completed residency in pediatrics, a clinical fellowship in genetics and

metabolism at Boston Children's Hospital. He also completed dual research fellowships in genetics and metabolism and allergy and immunology at Harvard Medical School.

Dr. Shapira is board certified in clinical genetics, biochemical genetics, and molecular genetics. We welcome you to the committee, Dr. Shapira.

Thank you.

DR. SHAPIRA: Well, thank you. And good morning.

It is a real pleasure to have the opportunity this morning to share with the committee an update for this study, to talk about the results that we have so far, as well as some of the challenges for the future in this area.

I'd like first to go through the acknowledgments. There have been a very large number of individuals who've been involved in this study. There are a number on the study development and data analysis group from APHL, the CDC, and from the Wisconsin State Laboratory for Hygiene listed

here who've been integral with moving this -- the analyses forward. As well as we've received database development and support from APHL.

And then each of the laboratories have been involved in providing case information from the States, from the laboratory as well from the follow-up programs. And so, all the individuals who've been involved in these aspects are listed here from Alabama, California, Delaware, Maryland, Oregon, Texas, and Wisconsin.

And then Brad Therrell from the National Newborn Screening and Genetics Resource Center, the NNSGRC, was involved very early in protocol development and support for this study.

So, very briefly, some background. When newborn screening began in the 1960s, specimens were obtained typically at 48 to 96 hours after birth, and the reason for waiting this long was to decrease the proportion of false negative results or essentially missed cases that would come either because the infant didn't have adequate nutritional intake to diagnose the metabolic disorders or

because of delays in the elevation of TSH or thyroid-stimulating hormone, which is the pathognomonic abnormality that's seen for primary congenital hypothyroidism.

But there were pressures over time to decrease healthcare costs, and this resulted in early discharge of mothers and newborns before 48 hours of life. And although the American Academy of Pediatrics and others have addressed this issue, these early hospital discharges still occur frequently, and this has impacted the newborn screen.

And therefore, there are nine States that have mandated a second screen be collected at 8 to 14 days of age on all newborns, and this is thought to reduce the chance of missing cases of clinically significant disorders particularly related to this early discharge. This second screen is collected on all infants, regardless of what the result was on the first screen.

And these are the States that have this mandated second screen. And Oregon also screens for

the last three -- Alaska, Hawaii, and Idaho. So a large proportion of infants in those States receive a second screen. And births in these States, so the infants that have the second screen account for about 17.3 percent of all U.S. births.

Now in addition to these States that have a mandated routine second screen, there are three States that have a recommended second screen, and it does occur on at least 85 percent of all newborns in those States. And the three States are Alabama, Maryland, and Washington. And that accounts for an additional 5.1 percent of all U.S. births.

So the total percent of the U.S. population with a routine second screen is about 22.4 percent, and those States with the mandated screen are shown here in mauve. And those with the highly recommended second screen are shown here in yellow.

Now a number of questions had been raised over the years as to what is the utility of doing the second screen on all newborns? So, for example, is a required second screen the appropriate means to

detect cases that would otherwise be missed? Because almost 80 percent of infants born in this country do not receive a routine second screen, and yet it's felt that the States that don't do the routine second screen and may do some targeted second screen and are not missing infants.

So is this the most appropriate means? Are there biochemical or are there laboratory-based practices that impact whether or not a case is detected on the first screen versus the second screen? And does the second screen really detect treatable cases and prevent negative outcomes?

In some sense, it's felt that maybe the infants picked up on the second screen are not really -- don't really have clinically significant conditions. So it doesn't matter whether or not they're picked up by screening or picked up later on clinically.

And finally, is the second screen a reasonable, cost-effective public policy? It's expensive to screen every single baby twice.

So a number of these questions we could

look at with this study. We can't look at some of these. For example, this was not a cost-effectiveness study. So the last question, in particular, could not be addressed.

Now I wanted to give very brief history of this study. In February 2006, the project was proposed to the Laboratory Standards and Procedures Subcommittee of the Secretary's Advisory Committee, and this is directly from the minutes of that meeting, stating that scientific literature indicates that all cases of congenital hypothyroidism -- indicates that cases of congenital hypothyroidism and CAH are missed on the initial screen but are detected on a routine second screen. And most newborn screening programs do not support the operation of a routine second screen.

So in order to better understand the justification for a second screen, we are proposing a study to investigate the effect of the routine second screen.

This is the timeline that was developed at that time. And during the first year, the timeline

was fairly well adhered to with initial subcommittee approval, draft proposal, further committee review. APHL and the NNSGRC were involved with the planning of a meeting with stakeholders and with State screening programs. And then the initial project was to begin in early 2007.

So this meeting in 2000 and in 2006 did occur on December 4th and 5th. It was called Issues in Requiring Routine Second Testing in Newborn Screening, and I mentioned who the sponsors were.

The newborn screening laboratory and follow-up representation were there from all of the States, almost all of the States that have the required second screen, as well as the three States that have highly recommended, high numbers of second screening that occur, as well as three States that do just a single screen -- California, Massachusetts, and Wisconsin.

There were endocrinologists present from all of the States listed, as well as a number of Federal representatives, as well as the Secretary's Advisory Committee, Pediatrix, and CARES Foundation

had representatives at this meeting. And during the meeting, there were presentations by panels of endocrinologists on their experiences from newborn screening in the areas of second screening for hypothyroidism as well as for CAH.

And there was a discussion of participation by State newborn screening laboratories and follow-up programs in two studies. One would be a 1-year prospective study, and the second would be a 5-year retrospective study where the 5 years would occur between 2003 and 2008.

Now I'll get to that in a little more detail. So during the meeting, and subsequently by email and conference calls, the group decided upon data elements to be reported and collected to include demographics, laboratory data, and clinical data. And every State present at the meeting verbally agreed to participate and to provide data elements on confirmed cases of hypothyroidism and CAH, but this would be pending IRB approvals.

So with regard to the data elements, the demographics included information such as sex and

race/ethnicity. There were data elements related to factors that might affect the newborn screening test results, such as the feeding status of the infant at the time of screening, the birth weight, whether or not the infant was transfused prior to screening.

Also laboratory testing factors, such as algorithms, the actual laboratory screening test results, the cutoffs, and how long the period of time was between sample collection and testing. And then a number -- then whether the infant was identified on the first screen or on the second or subsequent screen or also whether it would include infants that were not detected by newborn screening that were picked up later clinically.

And then a number of clinical factors such as confirmatory test results, whether or not the infant was treated and how the infant was treated, information on family history and on clinical characteristics as shown here for CAH.

So these were the data elements. APHL was responsible for developing a Web-based data repository for the data. And individual-level

anonymous data were to be submitted to APHL for analysis.

Now the Laboratory Standards and Procedures Subcommittee was updated on the project toward the end of December 2006, and these are from the notes. It was planned that there would be a retrospective study with 3 to 5 years of cases. This was expected to begin in February 2007 with data collection and submission over a 6-month period.

And then, based on that, there would be a protocol developed for a prospective 1-year study of cases refined based on the retrospective study results.

Now although there was unanimity at the big stakeholders meeting in December 2006 about proceeding with the study, when everyone left and went back to their jobs, enthusiasm waned. People became busy with other tasks. There were changes in laboratory director and staff changes.

And the IRB approvals really bogged down the process. In fact, not enough States could

obtain approval for the prospective study. So this was scrapped, and what I will discuss today is just the results of the 5-year retrospective study.

There were also problems with development of the data repository. It took more time and effort than expected, and there were no dedicated resources for data collection, although APHL did ultimately provide some funds to State programs to support the activity.

So these were the States that were eligible for inclusion in the study based on their participation in the stakeholders meeting. And the States shown in mauve I will call in the future two-screen States. The States shown in green are one-screen States. But after all is said and done, these are the States that contributed data for the study.

So the two-screen States being Oregon, Texas, Alabama, Maryland, and Delaware. The one-screen States, California and Wisconsin. Massachusetts is shown hatched here because we don't have data yet from them but expect to receive that

in the near future.

Now a presentation of the initial data analysis and results occurred at the Laboratory Standards and Procedures Subcommittee this past February. And since that time, the analyses have been refined. Additional variables have been evaluated. Multivariate analyses have been performed. The cases from Alabama were included in the study just this past August, and we're working toward including the cases from Massachusetts.

Now I'm going to get to the actual data and analyses that have been done, and in future slides, any table that's shown in green is in reference to hypothyroidism, and most of this will be in reference to primary congenital hypothyroidism. Anything shown in orange is related to congenital adrenal hyperplasia.

So these are the years covered by cases that were submitted for the study. The only thing of note is that Alabama was not able to submit cases for the 2003 to 2007 period. So all of their cases for both hypothyroidism and CAH come later.

The only other difference is related here for California. Only half a year of CAH in 2005, compared to a full year for hypothyroidism cases.

Now there are differences in the States in relation to screening algorithms and the primary analytes screened. And the main difference has to do with hypothyroidism as shown on the next slide. So the one-screen States use TSH here, thyroid-stimulating hormone, as their primary screening analyte.

The two-screen States, for the most part, use T4, a thyroid hormone, as their primary analyte and then, basically, for abnormals, then check TSH. Delaware is the only one of the two-screen States that uses TSH as the primary analyte.

So the differences that we observe may in part be due to the differences in screening. It will be helpful to have Massachusetts as another one-screen State because they use T4 as their primary screening analyte.

And now on to the data. These are the cases that have been submitted for all types of

hypothyroidism for the study, over 2,700 total cases. The cases were either identified on the first screen. In the States that do two screens listed over here, two-screen States, identified on the second screen. Or there were some cases in the one-screen States that -- on the third line down that were identified by targeted second screening.

But for the remainder of the presentation, I will focus specifically on primary hypothyroidism because direct comparisons can be made between those cases identified in one-screen versus two-screen States. And the first thing to point out that in the States that do two screens, of the cases that were reported, almost 12 percent were identified on the second screen for primary congenital hypothyroidism.

So the first question to raise is what's different between cases that were identified on this second screen in comparison to the cases that were identified on the initial screen in these two-screen States? So those are the analyses that I'm going to show first. Or in other words, what characteristics

are predictive of a case being identified on the first screen versus being identified on the second screen in two-screen States?

So these characteristics I'm showing just the significant results. And in these results, the second column from the left is the odds ratio of a particular characteristic for those cases being identified on the first screen versus being identified on the second screen.

And if the odds ratio is less than one, it means it's less likely to have been identified on the first screen compared to the second screen in relation to the referent characteristic. If it's greater than 1, like this last line here, female, it means that cases, female cases were more likely than male cases to be identified on the first screen compared to cases on the second screen.

So, again, more likely to be female than male on the first screen. Less likely to be black or Asian/Pacific Islander in comparison to white as the reference group on the first screen compared to the second screen.

Other significant characteristics had to do with birth weight. So less likely to be extremely low birth weight, less than 1,000 grams on the first screen, compared to normal birth weight. Less likely to have been transfused prior to screening for those cases identified on the first screen versus the second screen. And also more likely to have had the sample collected at greater than 24 hours and less than 24 hours in comparison to less than 24 hours. And these were more likely detected on the first screen than on the second screen.

Now when all of these significant variables were put into a multivariate model in order to assess which were the predictive variables for identifying a case on the first screen versus a second screen, it turns out only a single characteristic was significant, and so as each nonsignificant characteristic was removed, still only a single characteristic was significant.

And so, the most predictive characteristic for whether or not these cases were detected on the

first versus the second screen was race/ethnicity. That was the only thing that fell out from this analyses.

These are the odds ratios. So in comparison to white, black infants and Asian/Pacific Islander infants were less likely identified on the first screen compared to the second screen, whereas for Hispanic and infants of other ethnic groups were equally likely compared to white infants to be identified on the first versus the second screen. And these are the actual numbers of cases shown here.

Now why might there be a difference based on race/ethnicity in relation to the cases picked up on the first versus the second screen? And we hypothesized that maybe there are differences related to -- physiologically related to cases of primary congenital hypothyroidism for infants in different racial/ethnic groups.

And this appears perhaps to be the case, and let me orient you to this slide. What we began to look at was how abnormal the screening test value

was from the cutoff for screening. So for these are looking at the percent, the percent of the TSH value above the cutoff for cases identified on the first screen versus those cases identified on the second screen.

So if the cutoff value for TSH is 20 and the screening result is 40, that's 100 percent above the cutoff. If the screening value is 400, that's 1,000 percent above the cutoff. So this is the arithmetic mean for all cases down here at the bottom, and this is shown on the first line for white.

So for cases, white cases identified on the first screen, this is the percent, TSH percent above the mean, over 1,300. For the cases identified on the second screen, the TSH value above the cutoff is much less. It's about 530 percent above the cutoff.

Now it turns out that when you look at some of the racial/ethnic groups, for Hispanic, it's not significantly different from white. But when you look at black infants, the percent TSH -- this

is the arithmetic mean -- the percent TSH above the cutoff is about half of what you see in white infants on the first screen. It's a little lower, but not significant for the second screen cases.

And for Asian/Pacific Islanders, it was somewhat lower than white and Hispanic on the first screen and much lower on the second screen for the level of TSH above the cutoff.

Now we hope to do or plan to do some additional modeling to look at other characteristics to see how they're impacting this percent above the cutoff. But this is giving us some indicators that maybe there are differences from a racial and ethnic standpoint in the physiology of primary congenital hypothyroidism that could impact whether or not cases are detected on the first versus the second screen.

Now for the remainder of the hypothyroidism presentation, I wanted to focus on cases that are picked up in one-screen States here versus cases that are picked up in two-screen States. And for this, we compared cases identified

on just -- if each State did just a single screen. So the States that do one screen did just their single screen, and States that do two screens did just a single screen and not their second screen. Are there differences in the characteristics between cases picked up on that one screen and within -- between one-screen States versus two-screen States?

And for example, there are differences based on race/ethnicity. So a child is more likely to be Hispanic or to be Asian/Pacific Islander and picked up on States that do one screen and less likely to be black. So this is for cases. So cases were less likely to be black. Cases were more likely to be Hispanic or Asian/Pacific Islander. And these were the odds ratios compared to white infants.

Now there are problems with interpreting these data because this is looking at cases, and we don't have the denominator. We don't know how many Hispanic infants and Asian/Pacific Islander and black and white infants were screened in each of the States. That was not part of the initial protocol

or study. We did not request those data, and we really need to know the denominator in order to assess whether there are significant differences between cases picked by various characteristics picked up in one-screen versus two-screen States.

Now we do have a proxy for some of these characteristics. So from Vital Records, we can get the live birth information based on race/ethnicity for infants during these time periods in the States and can use that, for example, as a proxy. And we've done that to look at incidence of cases in the States overall and based on race/ethnicity.

And the first thing we notice when we look at all cases of primary congenital hypothyroidism, the rate of primary congenital hypothyroidism was higher in one-screen States than in two-screen States. More cases in relation to total births in those States.

And when we look based on race/ethnicity, it turns out that for white infants, it was also higher, but just borderline significant. The real difference is in Hispanic infants. So among

Hispanics, the rate was higher in one-screen States compared to in two-screen States.

For black infants, it was -- the rate was also higher, but it wasn't statistically significant. And for Asian/Pacific Islanders, it was actually the other way around. The rate was higher in two-screen States compared to one-screen States.

So we see differences based on race/ethnicity, and at the very end of the presentation, I'll comment on why there may be differences. But without knowing the denominators, it's really impossible to interpret these data.

So for other characteristics, we also saw differences such as differences based on sex, on infant feeding status, on birth weight, on transfusion prior to screening. But we could obtain proxies for some of these variables such -- from Vital Statistics, such as for infant sex and infant birth weight.

But for the others, in order to interpret the data fully, we'd have to go back to States and

ask for their experience with screening all infants during those periods, what the proportions of infants were in each of the categories. For example, how many were transfused and how many were not transfused prior to screening.

There were also differences based on the age of the infant at collection. They were more likely to have been collected at less than 24 hours and shorter periods of time between collection and assay in one-screen States versus two-screen States, but this may just be a systems difference between those States. So, again, we need denominators.

Now very quickly, since you're now familiar with the analyses that we did for hypothyroidism, I can breeze through the ones for CAH, or congenital adrenal hyperplasia. There were a total of 374 cases that were reported for the study for one-screen and two-screen States. But if you look at just cases that were picked up on the first screen or the second screen or a second-tier test, in the two-screen States, almost 40 percent of infants were picked up on the second screen with a

form of congenital hypothyroidism.

And again, what are the characteristics that differ between these cases picked up on the first screen versus the second screen? And only Alabama and Texas of the five two-screen States identified cases on the second screen. So the analyses were limited to those two States.

The significant variables in a univaried analyses were race/ethnicity, less likely to be Hispanic on the first screen, more likely to have had the sample collected at greater than 48 hours compared to less than 48 hours, and less likely to be classical simple virilizing or nonclassical in comparison to classical salt wasting. Less likely on the first screen than on the second screen.

When these variables were put in a multivariate model, the only variable that was significant was the type of CAH. That's the best predictor for whether or not a case is going to be picked up on the first versus the second screen, as shown here. And these are the actual numbers of the cases that were -- the types of CAH and the cases

that were picked up on the second screen shown over here to the far right. Nine cases of classical salt wasting, 23 cases classical simple virilizing, and 60 nonclassical cases picked up on the second screen.

Now one question that's been raised about the utility of second screen is are these cases that are picked up on the second screen clinically significant? And one proxy for that is did the endocrinologist treat these cases, these infants in some way with some medication? And to me, that would seem to mean that these cases are clinically significant. They underwent some treatment.

And that's shown here on the next slide. All nine or 100 percent of the classical salt wasters were treated. Over 80 percent of the classical simple virilizers, and about a third of the nonclassical cases were treated in some way. So over 50 percent total, a significant proportion of these cases did undergo a treatment.

Now this is the incidence data comparing one-screen and two-screen States for the type of

hypothyroidism. It's reassuring to see that the incidence for salt wasters was the same between one-screen and two-screen States. But again, simple virilizers and nonclassical cases were much more likely identified. The incidence rate is much higher in the two-screen States than in the one-screen States.

And when you compare the cases picked -- detected on the first screen in one-screen States with those identified on the first screen in two-screen States, the only significant characteristics had to do with the age of collection at less than 48 hours or the time from collection to assay being less than 4 days. These were more likely the case in the one-screen States than the two-screen States. Nothing else was significant. And again, this could reflect systems differences.

So one question that's been raised is what about cases that are not detected by newborn screening? Because we did ask that these cases be reported for the study, and everybody wants to know what about these "missed cases." Now this was not a

focus of the study. The ascertainment is probably incomplete, but we do have information on these cases not -- that were reported to us, not detected by newborn screening.

So for hypothyroidism, both States that do one screen as well as two screens will not detect cases using their screening algorithm, and they will not detect primary hypothyroidism cases, as well as other types, some other types of hypothyroidism. Again, understanding these are small numbers. There is incomplete ascertainment, and we can't really say anything about the characteristics of these cases that were not detected because the numbers are so small.

For CAH, also cases were not detected by the screening algorithm in one-screen and two-screen States, but all of the classical salt wasting cases that we are aware of were not detected in the one-screen States. There were none that were reported to us or reported to the labs that they were aware of that had classical salt wasting in the two-screen States during these time intervals.

So, very briefly, the summary points, what did we learn so far from the study? That among the States that we evaluated as part of the study, that in the two-screen States about 12 percent of primary congenital hypothyroidism and 38 percent of congenital adrenal hyperplasia, which includes 9 percent of all classical salt wasting cases, were detected on the second screen.

So if the two-screen States stopped performing the second screen and only performed the first screen the way that they're now performing it, we presume that these cases would not be detected because they all had normal first screening test results.

All of the primary congenital hypothyroidism and more than half of the CAH cases detected on the second screen were treated, indicating that they were clinically significant. In the two-screen States, the characteristics that were predictive of cases being detected on the first screen versus the second screen for primary hypothyroidism, the only significant predictor was

race/ethnicity where black and Asian/Pacific Islander infants were more likely detected on the second screen than the first screen compared to white infants.

Now these race/ethnicity differences are perhaps attributable to physiologic differences in how primary hypothyroidism manifests itself, and we plan additional analyses in order to evaluate this.

For CAH, the only significant predictor was the type of CAH, where the simple virilizers and the nonclassical cases were more likely detected on the second screen. Now comparing the cases from one-screen versus two-screen States, there was a significantly higher incidence of primary congenital hypothyroidism in one-screen compared to two-screen States, and this is mostly attributable to the higher incidence among Hispanics in one-screen compared to two-screen States.

Now these incidence rate differences could actually be the effect -- well, they could be the effect of different screening practices between one-screen and two-screen States, or they could be

differences in genetic or environmental factors that affect the true incidence of congenital hypothyroidism in these racial or ethnic groups.

Now this would require other types of studies to evaluate, and it's really outside the scope of this routine second screen study. And with regard to salt wasting CAH, there were statistically equivalent incidence rates between one-screen and two-screen States, but significantly higher rates for simple virilizing and nonclassical cases in two-screen States.

Now there were other characteristics that in addition to race/ethnicity that were different between the one-screen and two-screen States. But as I mentioned, we really need denominators to look at these further. These are the characteristics that we found.

But I'll point out the ones here in yellow, age of collection and time from collection to assay, may actually reflect systems differences in the screening parameters and processes in one-screen versus two-screen States.

So there are a number of limitations to this study. First, it's retrospective. So data were incomplete for some variables. The labs could only -- and the follow-up programs could only report the data they had on hand.

The final diagnoses, particularly for hypothyroidism, were not necessarily determined after adequate follow-up so that transient hypothyroidism cases could be mixed in with these primary hypothyroidism cases that we evaluated.

There were different screening algorithms between the one-screen and two-screen States, and that limited the ability to make comparisons for other types of hypothyroidism, such as secondary hypothyroidism. And the results are, of course, somewhat biased by States that contributed the largest number of cases.

But there are a number of strengths to the study. It's the only comparative study between one-screen and two-screen States. This is a much larger sample than any previous study, and those are the numbers of cases. And these come from among 4.6

million births during the time period.

There were numerous laboratory and medical variables available for analyses, and the fact that these were all individual-level data -- so not group data -- allowed for multivariate analyses in order to tease out specific associations.

So, with that, I thank you for your attention, and I would love to take questions.

CHAIRMAN BOCCHINI: Well, thank you for a very thorough presentation and very clear.

Fred?

DR. LOREY: Thanks very much. That's great. I know that was a lot of work, and there is so much information in there and a lot of interesting observations.

A couple of things I noticed, and you mentioned the denominator issue, is I think the California data is responsible for some of the things you're seeing because we're a big one-test State with 52 percent Hispanic births. And we all know that hypothyroidism is much more common among Hispanics.

We're also, I believe, the only State whose time limit for recollection is 12 hours and not 24. And I also wanted to thank you for presenting the data as they were and not making any assumptions because what we still don't have is that issue of what if this test in this case detected in this two-test State were tested in the one-test State?

Because we know that some of the States with mandatory second tests already make some assumptions or some differences in their first screen. So, for example, some of them don't follow inadequates because they know they'll get it on the second screen. So cutoffs may be different, all that kind of stuff.

And this doesn't purport to answer that question, but a lot of interesting data. But I think you do need to look at the denominators, and it also will affect the sex ratio. One thing I noticed is the sex ratio is greater among Hispanics. It's more like 3 to 1, instead of 2 to 1.

So that's going to reflect again, I think,

a bias between the California data and the other data. So those are all things that could be looked at when you have your denominator.

DR. SHAPIRA: Right. I mean, fortunately, that on the other side, so with States that do two screens, there is Texas, which has a large number of Hispanics. So the Hispanic births were fairly comparable. There were more in California than in Texas. But overall, it was fairly similar.

So what's interesting that among Hispanics, just looking at Hispanics irrespective of the numbers, is that the incidence was higher, significantly higher in the one-screen States, which is primarily California, but also includes some Wisconsin cases, than in the two-screen States, which is primarily Texas. But there are also Hispanics from some of those other States.

So the fact that the Hispanic rate of -- incidence rate of hypothyroidism was different. Again, we were using vital statistics as a proxy for that denominator. It might be different going to the State and having the information of what was

reported to them on the newborn screening card instead of what was reported on the birth certificate to Vital Statistics. There may be differences.

DR. LOREY: One other comment was I don't know if you were going to go on with this or go into more detail in the future or whatever, but one of the things -- because we have so many cases in California and because our demography is so unusual, we've done an awful lot of racial analysis broken down into much finer categories.

The Asian/Pacific Islander, lumping that category makes it meaningless really because some have much higher rates and some have much lower rates.

DR. SHAPIRA: Right.

DR. LOREY: So it really makes a difference what that subcategory is.

DR. SHAPIRA: Right. Even with this large number of cases, it was necessary to do some lumping in order to get something significant. So you're right, and I'm sure that the makeup of this

Asian/Pacific Islander group among California infants is different than among Texas infants.

So it's difficult to make that comparison, and it's not unexpected that we would see differences in the incidence rate between the one-screen and the two-screen States. What was surprising was seeing the difference in the incidence rate for Hispanic in one-screen compared to two-screen States because I would suspect that the makeup of Hispanic, although not identical, is probably somewhat similar between the one-screen States, primarily coming from California, and the two-screen States, primarily coming from Texas.

So that was a surprising result that perhaps needs further investigation.

CHAIRMAN BOCCHINI: First, Beth Tarini and then to the microphone.

DR. TARINI: Thanks, Stuart.

I have a quick question. Before one posits a race-based biology for the difference between a first and second screen State -- well, this is a comment and then a question. I think it's

important to determine the denominator because if you are less likely to be screened based on your race, you're then less likely to be identified unless -- you don't have the opportunity to be identified as a case, and therefore, you don't have the opportunity to be a case.

So if one knew, for instance, that 20 percent of the population, knowing 100 percent of newborn births were screened in State X and 20 percent were black. And then in the second screen of the total screened only 10 percent were black, then that suggests that blacks don't have -- aren't being screened a second time, suggesting there might be an access issue that's sort of driving this likelihood of blacks not being identified or Hispanics or whichever the group may be. And getting the data from the card might be helpful.

DR. SHAPIRA: Right. I mean, that's a great point, and it's unfortunate that there wasn't the foresight. We didn't think about the need for having the denominator data at the time that the protocol was developed and data was requested from

the States.

Hopefully, if we move forward on this, the State programs will see -- understand the importance of pulling those data together, realizing we don't -- it would be ridiculous to ask for individual-level data, and we wouldn't want to do, spend the effort to do multivariate analysis to see if there were interactions.

But at least to have group data for the denominator during the time interval, the proportion of for the first screen or second screen in two-screen States, or in the one-screen States, the single screen, the proportion of infants in each category that underwent screening.

DR. TARINI: But just as a follow-up, I think, in fact, the States might be compelled by the fact that if I were in a State with two screens and I knew that my black, Hispanic, or Asian population was disproportionately not getting a second screen, it would suggest to me that we have an access issue.

So on some level, the individual data may be compelling for the States apart from this

project.

CHAIRMAN BOCCHINI: At the mic?

DR. OSTRANDER: Bob Ostrander from NYMAC.

Did you look at the CAH data for Ashkenazi Jewish populations separate from other things? Because my understanding is that their nonclassical CAH rate is much higher and might provide some information about whether targeted second screening, for instance, might be valuable?

DR. SHAPIRA: That's an interesting point. Unfortunately, we don't have that information. And as I'm not aware that it's reported specifically to any State program, but it is a very interesting research question. But we can't address it.

CHAIRMAN BOCCHINI: Jeff?

DR. BOTKIN: Yes, I wonder if the study had the opportunity or has the data to look at the incidence of false positive results between the two types of State categories. And here I'm thinking about false positive in terms of parents being notified that a second or additional evaluation is necessary.

DR. SHAPIRA: And that's also an important point, but again, it wasn't a focus of the study. So we weren't provided with those data. The States should have information on false positives, but we don't have that information.

CHAIRMAN BOCCHINI: All right. If there are no further questions or comments, thank you again.

DR. SHAPIRA: Great. Thank you.

CHAIRMAN BOCCHINI: We appreciate your presentation.

Next on the agenda is Dr. Bin Chen. Dr. Chen will discuss CDC recommendations for good laboratory practices in biochemical genetic testing and newborn screening for inherited metabolic disorders.

Dr. Chen is a geneticist in the Division of Laboratory Sciences and Standards, Office of Surveillance, Epidemiology, and Laboratory Services of the CDC. Since 2002, she's been a genetics expert in CDC and led a number of projects to improve quality management for genetic testing,

including developing and enhancing regulatory oversight, initiating a sustainable process for improving the availability of quality control materials, improving quality, availability, and accessibility of genetic testing for rare diseases, providing training in quality practices for genetic testing, and developing good laboratory practices.

Dr. Chen has been a leader in international laboratory standard-setting activities, including efforts of the Clinical Laboratory Standards Institute, CLSI, and the International Organization of Standardization.

In the agenda, there is indication that there will be a vote to support this product. But given the decision by the subcommittee to not bring this to the full committee for a vote at this time, that will not occur at this meeting.

So, Dr. Chen, thank you for coming, and we look forward to your presentation.

DR. CHEN: Thank you.

Good morning. It's a great pleasure to be here and present to you, the Secretary's Advisory

Committee, the recently published CDC recommendations for good laboratory practices in biochemical genetic testing and newborn screening for heritable metabolic disorders.

Okay. So green one is forward. Okay.

Now this slide shows on the, okay, on the left the cover page of the CDC recommendations document, which was published in the CDC's Morbidity and Mortality Weekly Report, or MMWR, recommendations and reports series of publications on April 6, 2012.

And on the right is the list of contents. And as you can see, this is a quite comprehensive document covering the background information, discussing the areas needing quality improvement in biochemical genetic testing as well as newborn screening, describing the process of developing the recommendations and also providing the recommended practices that I will highlight for you in a minute.

To briefly recap the process or the long process of developing the recommendations, this project started in 2009 following the publication of

the CDC recommendations addressing good laboratory practices for molecular genetic testing for heritable diseases and conditions. Initially, a biochemical genetic testing workgroup of the Clinical Laboratory Improvement Advisory Committee, or CLIAC, was formed to provide input for CLIAC consideration regarding quality practices in biochemical genetic testing.

The workgroup consisted of experts representing both biochemical genetic testing and newborn screening, including directors of laboratories performing biochemical genetic tests as well as diagnostic tests following newborn screening, clinicians who use biochemical genetic tests or are involved in newborn screening systems, and individuals representing State newborn screening programs, newborn screening quality assurance, broad State public health programs, IVD industry, and general laboratory practice.

The workgroup reviewed the areas in laboratory, the areas of laboratory practices and issues that were identified as needing good

laboratory practice recommendations and also reviewed the comprehensive coursework prepared by CDC summarizing Federal and State requirements, accreditation standards, voluntary guidelines, and international standards that either broadly address biochemical genetic testing practice issues or specifically address issues in this area of laboratory practice.

Based on this comprehensive evaluation, the workgroup report was developed and then was reviewed by CLIAC at the February 2010 CLIAC meeting. The CLIAC adopted many of the workgroup's suggestion and also made modifications to a number of them.

CLIAC recommended that a CDC guidance document be developed and that the recommended practices apply to biochemical genetic testing as well as newborn screening, considering the commonality and connection between many laboratory procedures.

So, in recognizing that these characteristics of newborn screening and to ensure

that CDC recommendations are developed after being adequately vetted with all stakeholders, during 2010 and 2011 we collaborated with other Federal agencies and organizations to obtain additional input to complement the CLIAC recommendations.

For example, we worked with NIH to obtain advice from the Secretary's Advisory Committee on Genetics, Health, and Society. We collaborated with Dr. Puryear's office and now Dr. Copeland's office in HRSA to obtain consultation from this Secretary's Advisory Committee, and that was around the committee meeting that was held in September 2010.

We solicited input from APHL committees and at APHL and ACMG annual conferences, and we also circulated draft documents with these and other stakeholders for comment and input.

So thanks to all this input, we were able to prepare the CDC recommendations in the document. You have seen this document from the subcommittee report earlier this morning. So to recap that, the CDC document is intended to provide quality management guidance for genetic testing performed

for screening, diagnosis, and treating and monitoring of heritable metabolic disorders.

And many of the recommended practices apply generally to biochemical genetic testing and newborn screening, and where practices differ between these two areas, the recommendations are discussed separately. And you also heard that the document served to clarify clear requirements that are applicable to biochemical genetic testing and newborn screening and to provide recommendations for additional quality assurance measures.

The reason for structuring the document this way is that previously there was no official clarifications made of how clear requirements applied to biochemical genetic testing or newborn screening, well, that we were aware of. And as we know, when there is no guidance, when there is no clarifications, different laboratories may have their own and different interpretations regarding regulatory requirements.

So because of that, variations in practice may occur. So it is our intent to clarify the

minimum Federal -- the Federal minimum standards to help laboratories understand what the low bar is and from there what the recommended good laboratory practices are, and we do encourage laboratories to strive for perfection, to strive for continuous quality improvement. And this does not exclude laboratories from pursuing even higher standards recommended by any specific professional organization.

Now again, this document serves to complement the previous CDC MMWR published in 2009 providing good laboratory practice recommendations for molecular genetic testing.

This diagram illustrates how the recommended practices align with the laboratory testing process and workflow. Starting on the left, test validation or test performance establishment and verification, which is required before any new test can be introduced for patient testing, and the specific components of the pre-analytic, analytic, and post analytic phases of patient testing are addressed in the document by first clarifying

applicable clear requirements and then discussing additional recommended good laboratory practices.

The recommendations also cover personnel qualifications and competency assessment, practices to ensure confidentiality of patient information and test results, and the quality management system approach.

Now the next few slides will briefly highly some of the key recommendations in the document. In the area of test performance establishment and verification, laboratories should not only ensure adequate establishment and verification of any test analytic performance, but also document available information on clinical validity.

The recommendations cover, for example, the selection and inclusion of samples in test validation, including considerations of both positive and negative samples, considerations of representative sample types, and addressing the varying sample conditions that may occur in patients -- that may occur in patient testing.

Also clarified are the performance characteristics that need to be determined, including accuracy, procedure reference range, reportable range, analytic sensitivity and specificity, and additional performance characteristics.

Also in certain situations, if the laboratories need to use reference values provided by manufacturers or publications without having adequate samples to verify them, and these situations are not unusual when dealing with inherited metabolic disorders, which are also considered rare diseases, the laboratories should inform their clients or users of their laboratory services of this situation, ensure ongoing monitoring of the appropriateness of these values, and make adjustments when appropriate.

Truth in advertising means the claims made by any laboratory on test performance should be scientifically sound, should be scientifically valid, and are appropriate for the laboratory's patient population. And there are additional

recommendations addressing test performance establishment for newborn screening, including considerations of the specimen collection window and how it impacts the screening windows for different diseases.

The considerations of the number and storage of the samples, consideration of varying sample conditions, including samples that are not meeting the criteria for satisfactory samples, and how these samples will align with the laboratory specimen acceptance criteria.

For specimen submission and referral, laboratories should provide information and communicate with clinicians on any need for patient preparation before specimen collection. The laboratory should have written criteria for specimen acceptance. Again, that are consistent with the types and conditions of samples that were included in test validation whenever practical and feasible.

The laboratory should also determine whether samples that are not ideal -- for example, hemolyzed blood samples -- will still meet the

laboratory specimen acceptance criteria. Any specimen's deviation affecting test performance and test results should be noted on the test report. Also as a reminder, laboratories should refer patient samples only to CLIA-certified laboratories or laboratories meeting the equivalent standards.

There are specific recommendations for addressing newborn screening specimen submission and handling. For example, laboratories should inform submitters that dried blood spot specimens should be transported or mailed to the newborn screening laboratory within 24 hours after collection.

And I had submitted a previous version of this presentation with a significant typo. So if you have seen that in your briefing book, please forget that and then replace that with this one. It's 24 hours after collection, not after birth.

Also laboratories should have policies and procedures to address the time-sensitive issues of newborn screening testing -- the handling of varying infant conditions, such as pre-term, low birth weight, and illness -- and those to address whether

unsatisfactory specimens will meet the laboratory's established acceptance criteria. For unsatisfactory specimens, a second specimen should be requested.

In terms of control procedures, in general we made clarifications on the general CLIA requirements for control procedures, including performing control procedures to monitor the accuracy and precision of the entire analytic process of any test or system. In general, control procedures for biochemical genetic tests should be performed once each time patient specimens are assayed or with each batch or run of patient specimens.

Controls should be as comprehensive as possible and be selected based on the patient population, prevalence of the disease, and purpose of testing. And we also clarified acceptable control practices for time-consuming testing using single channel or single column instruments, such as amino acid analysis, rare disease testing, as well as acceptable alternative control procedures.

Test reports should provide information

that is needed for accurate understanding and interpretation by clinicians and other users of test reports and must comply with general CLIA test report requirements. The laboratory should assess the needs of users or its clients to determine the media, format, style, and language of the test reports, and to the extent possible, the terminology and nomenclature in test reports should be understandable by health professionals who are not geneticists or experts in the specific field.

And there are separate recommendations for the test report contents for biochemical genetic testing and newborn screening out of range results.

In terms of retention, overall test reports should be retained in compliance with CLIA and State requirements. However, biochemical genetic test reports indicating genotypes should be retained for a longer timeframe, at least the 21 years, to accommodate the patient testing needs.

Retention of test records must comply with CLIA and other applicable requirements. And in terms of specimens, it is good practice to retain

tested specimens after completion of patient testing for the longest possible timeframe as permitted by sample stability and integrity, technology, laboratory space, and cost considerations.

Biochemical genetic testing specimens should be retained at least after the final result reporting and, if possible, until the next proficiency testing or alternative performance assessment. The retention of newborn screening specimens must comply with applicable Federal, State, and local requirements.

Because the qualifications of laboratory personnel are critical for the quality of laboratory services, the document has specific recommendations for the qualifications and responsibilities of laboratory personnel for biochemical genetic testing and newborn screening. For example, laboratory directors must meet CLIA qualification and responsibility requirements for high complexity testing.

Technical supervisors for biochemical genetic testing should either have qualifications

equivalent to CLIA qualification requirements for clinical cytogenetics technical supervisors or have current certification in clinical biochemical genetic testing by a board approved by HHS.

Technical supervisors for public health newborn screening must meet the CLIA qualification requirements for high complexity testing, have at least 4 years of laboratory training or experience in newborn screening systems, and must also meet any additional State requirements.

Clinical consultants, general supervisors, and testing personnel must meet the respective CLIA requirements and also have relevant training or experience in the testing or laboratory services that they perform.

And so, in a nutshell, this document is intended to provide a comprehensive guide for laboratory professionals performing biochemical genetic testing to ensure the quality of the laboratory services and also highlight laboratory practices that are critical for quality improvement in newborn screening.

We also hope that this document will serve as a resource for healthcare professionals and users of laboratory services to facilitate their collaboration in newborn screening systems and also help them with effective use of biochemical genetic tests. We also hope that the recommendations might help standard-setting organizations and professional societies in developing future laboratory standards and guidelines. Also it is our hope that the recommendations will help IVD manufacturers in developing testing products that are consistent with the recommended laboratory practices.

And the recommended practices are all voluntary, and we expect that the incorporation of these recommendations in practice will improve the quality of laboratory genetic services and lead to improved health outcomes for patients and families.

So I'm going to switch gear now and talk a little bit about the continuing education activity that we provide for this document, which has been a very helpful way for us to obtain feedback on these recommendations. So last month, 107 individuals

registered for the CE activity, of which 69 completed it and earned CE credit.

The most frequently requested CE category are the generic CEU, followed by the CNE for nursing professionals, and CME for physicians.

And I should confess that these are not particularly large numbers and should only reflect a fraction of individuals who have read this document. However, we do feel that the feedback provided by these CE participants is very helpful. For example, many CE participants commented that the contents of the document was helpful, was informative, and had provided a great learning experience for them.

Some CE participants requested that more information be provided on how to explain the laboratory practices in easier terms to patients and as well as parents. Quite a number of CE participants commented that the document was long, was a lot of information to absorb, and requested that more CE credits be awarded.

And also there were very encouraging feedback to us, such as "keep up the good work."

Most CE participants either agreed or strongly agreed that the content and materials of the document had addressed a need or gap in their knowledge or skills, the activity effectively met their educational needs, and then, more importantly, if given an opportunity, they can apply the knowledge gained as a result of learning these recommendations.

And also it seems that the availability of the CE credit was a big influential factor for them to take -- to participate in this activity.

We also obtained responses in terms of changes to the CE participants' competence, skills, and practice. For example, one person commented, "The document helped me improve my understanding of quality management of newborn screening," and another person said, "After reading the materials, I'll start to collect newborn screenings on time."

And another person said, "The document reaffirmed my understanding of the quality practices required by newborn screening and assisted me with designing a performance validation protocol."

Also the CE participants planned to use these recommendations as the basis for educational materials and, to a lesser extent, laboratory policies and procedures, laboratory standards and guidelines, and public policy. They also gave us suggestions in terms of the best way, the best educational ways to increase awareness and uptake of these recommendations including wider electronic dissemination, interactive Web-based training, dissemination of hard copies of the document, and conducting educational sessions either outside or at professional conferences.

And here I have some resources. So the CDC document is available from the CDC MMWR site as well as from the Web site of our program office, and the continuing education activity is available from CDC's MMWR site.

So this is actually my favorite slide. This shows that, well, this work owes big, owes greatly to our collaborators, all the experts and our colleagues who contributed thoughts, input, feedback, talents, and expertise to this work. And

also since this is like my returning presentation to this committee, I want to thank SACHDNC and HRSA again for giving us the opportunity to present this work here.

So if there are questions, I'll try to address them.

CHAIRMAN BOCCHINI: Thank you, Dr. Chen.

That was a thorough presentation and certainly been a tremendous effort to update the recommendations and guidelines. So thank you very much.

Any questions or comments from the committee?

(No response.)

CHAIRMAN BOCCHINI: Not at the present time. All right. Well, again, thank you very much. We appreciate you coming.

Next presentation is from Joan Scott, the Executive Director of the National Coalition for Health Professional Education and Genetics. She will discuss the Prenatal Family History Project, provide data and an updated report.

As Executive Director, she leads the national effort to promote health professional education and access to information about advances in human genetics. And as a research scientist at the Berman Institute of Bioethics to Johns Hopkins University, she studies public and stakeholder attitudes about genomics.

Ms. Scott's career has focused on the application of genomic discoveries to healthcare. She is a certified genetic counselor with more than 30 years of experience in clinical genetics, genetics education, laboratory medicine, the biotechnology industry, and the ethical, legal, social, and policy implications of advances in genomics.

Thank you.

MS. SCOTT: Thank you very much. And thank you to the committee for inviting me here to present the data.

I want to emphasize that the information that you'll be seeing is the result of a collaborative effort with our key partners,

including Genetic Alliance, March of Dimes, Harvard Partners, and of course, HRSA and the funding that we received through them.

I would want to acknowledge in particular my colleague Emily Edelman. Please wave. Emily is the project director at NCHPEG who actually did the work that I'm going to be presenting and interfaced with all of our partners.

So if the committee has any questions harder than why did you name the tool the way you did, Emily will be answering those questions.

I also want to acknowledge that we had a very large and stellar advisory group that represented prominent stakeholders and a wide range of healthcare providers who play a role in women's prenatal care.

So what I'm going to do today is describe some components of the tool and some key business decisions that we made up front in the development of the tool, present implementation data from four sites, and then share with you some preliminary data around patient and provider response to the tool,

and then talk about next steps.

I want to remind the committee that this project is an outgrowth of recommendations that was identified and the needs that was identified by this committee, as well as additional individuals at HRSA and ACOG that led to the 2008 request for proposals to develop a tool to implement family history and newborn screening information into health history and to help with clinical decision-making and to educate both the provider and the patient.

The original intent was to address the life span of the woman, and we ended up -- and I'll talk a little more about scope in a minute -- but emphasizing that first prenatal visit.

So our overarching business goals that guided the development of this tool was that we wanted a tool that would help the very busy clinician to be able to utilize family health history in clinical care and that engaged the patient as part of that process and to develop clinical decision support to help guide clinical decision-making and provide patient and provider

educational materials.

We also wanted this to be available, freely available for use. We adapted the Hughes Risk App, which was developed for use in cancer centers to identify hereditary cancer, risk for hereditary cancer. And so, this is an application or sort of part of that application that is addressed for specifically the prenatal setting. And I'll talk a little more about the availability of the program at the end.

So I'm going to talk just briefly about two methodological and developmental sort of key decisions that we made up very early in the development process. And one was what is the scope and what are the conditions that we should be screening for on this tool?

We did decide that we would limit to the first prenatal visit, but even then, you could -- you know, how broadly do you throw your net? So the project group set three specific criteria for conditions that would be included on the tool. There had to be evidence that screening for the tool

resulted in some actionable items that would improve outcomes for the pregnancy, mom, or the baby. There had to be professional society support and it be considered practice of care.

So we did an extensive review of the literature of existing practice guidelines, expert opinions, et cetera. We also did a scan of what is currently included on a wide variety of prenatal intake forms. I don't think we looked at every single intake form in the United States, but we certainly looked at a lot of them.

And so, out of the initial I would say well over 100 conditions, using this criteria, we narrowed it down to these 27. And your slide, by the way, in your briefing book isn't completely accurate. If you count, there's two that are missing around intellectual disability and autism.

So let me just stop and make another point here, and these are the list of the conditions -- and I'm not going to go into them in detail -- sort of grouped by sort of major areas. One of the early recommendations from our advisory committee members,

however, is that the tool should include screening questions for conditions that would be part of a regular woman's first prenatal visit. So the woman wasn't filling out a separate tool around family history from all of the other screening questions.

So we do include screening questions on the tool around lifestyle issues, screened for abuse, maternal disease, et cetera, that would be normally part of an initial intake tool. We don't provide decision support around those. It does come out in the report, and they are flagged. But these are the conditions for which we provided clinical decision support.

So the second sort of main task then was to develop the clinical decision support around these, and the goal here was to take practice guidelines and translate those into machine-readable algorithms and then developing the appropriate messaging around that. That was done by the content experts within our project group. All of the algorithms and messaging, however, were externally reviewed by content experts either on our advisory

committee or from outside, if we needed to go beyond that.

We also did formative evaluation with both the prenatal patient and with providers. And as part of the provider formative evaluation, we included an assessment about the clinical decision support and the messaging.

So this is what an example of a consideration or a message that would get flagged by the tool, and the example here is if a woman answered that she had a family history of autism. And so, there would be two actually flags that would come out, one to consider -- and we call these considerations, not recommendations. But to consider referring for genetic counseling for autism and intellectual disability and the potential for carrier, fragile X carrier screening. Yes, fragile X screening.

The other point I want to make here, though, is that this what the considerations table looks like. But again, at the recommendation of our advisory committee early on, they felt that

exporting the report into a format that was recognizable already by the prenatal provider would improve and enhance acceptance.

So we actually adopted -- or adapted the ACOG antepartum questionnaire and prepopulated that with all of the data that we collected. Now that had mixed success in the implementation, which I'll share with you because it did generate, in some cases, a really long -- a really long report.

This is our vision of how this would get implemented into a site then. A woman comes in for her first prenatal visit. This is on a PC tablet. She would fill out all of the questionnaires, hand it back to the staff. The information gets wirely transmitted to the database, which sits on a computer there in the office, generates the risk assessment. A report is generated. The physician can review that prior to going in with the patient.

During our formative evaluation, the provider said it would be very important to have a provider interface so that if they wanted to change the information that the person gave them, they

could go back into the tool, change the information, and rerun the algorithms. And then after the visit, document their visit or print out the patient educational materials if they wanted to.

A couple of points here is that for a lot of reasons, and I'm sure you can appreciate, we did not integrate this into an electronic medical record. So it was a standalone report, but it could be scanned and then added as a part of the person's medical record.

And then the patient educational materials. So for all of those conditions that you saw, we generated lay-friendly informational tools. There was also a lot of educational messages that was incorporated in the actual screens themselves that we're going to ask you blah, blah, blah because of blah, blah, blah.

And at the very end, there was also some specifically around newborn screening, some educational messages about newborn screening.

All right. So now with that as a background, I'm going to present some implementation

and evaluation data. And again, because of the limited amount of time that we have today, a lot of this is going to be sort of at high level. But it will give you a sense of what our initial findings were.

So these are the questions that we wanted to ask in our pilot project. We wanted to know how does this actually work in clinics, and what's the implementation into a clinic? And so, we did that by an initial needs assessment, ongoing communication with the staff, and then we did some structured qualitative interviews with administrators of different parts of the projects.

We wanted to know patients' response around their acceptability of the tool, ease of use, confidence, et cetera. We did that by asking them to fill out a survey after completing the tool.

And we wanted to know from providers did using the tool impact their knowledge or confidence in using family history and their overall perceptions about the different components of the tool, the clinical decision, et cetera? And we did

this with both pre- and post surveys.

That was the initial evaluation plan. At the recommendation of our advisory committee, we did add some outcomes data, and I'll share with -- and that was done by chart audits. And that, I'll share with -- some of with you today.

So these are the four sites that we piloted. They are geographically diverse in Maine, New York, North Carolina, Indiana. Three of these are OB clinics. One was a family medicine clinic. Overall, over 600 patients were seen, and 65 providers utilized the tool.

So we -- I thought it was going to give you some demographic information. I'll get to that later.

So we assessed from the staff a lot of information about what were the key steps to actually implement this into it. And there were many in that preplanning cannot be underemphasized in having a tool that's accepted and used into the clinic.

We also looked carefully and obtained data

on the impact of clinic flow, and I'll make a couple of points here. One is that in three of these sites, this tool was an add-on to what their already patient flow and protocols were. In one site, this replaced their -- so both of those had implications as far as acceptabilities from the providers.

In all of the sites and what this little diagram, which you're not supposed to be able to really see, but what it just illustrates visually is in that flow chart that I showed you, there was adaptation and modification of the flow needed in every single -- every step along the way in order to maximize the patient's experience with it and the provider's efficiency.

Initially, there was disruption in the clinic flow that they all reported, not surprisingly. But providers did adapt as they gained experience with it. So we documented a lot of barriers and successes along the way, and certainly key to the success was having dedicated staff, recognized champions to make this happen and buy-in from the IT folk, which we did not actually

get in several of the sites. And it required some work-arounds to do that.

We also documented or asked for what changes needed to be done to the tool to implement for future use, and key among those was to develop a Spanish language version, which we did not have. It was an English-only. To be able to tailor the tools and the report to the clinic and the clinic's needs, and then to be able to integrate into electronic health record, which, of course, we would like to have the opportunity to do.

So, in summary, customization we found was critical all along the steps of the implementation, and it did require continued sort of tweaking. Customizable of the tool, particularly the providers asked for this, and then having internal support was very important.

So now let me share with you some data on the patient feedback. So we asked everybody to fill out a survey afterwards, and we got 513 responses of the 618 patients who used the tool.

This provides you with the demographic

background. I'm not going to go into a lot of detail here except to say that we had two sites, Maine and New York, which were low volume sites. And then two much higher volume sites. Across all four sites, we did see a range of ages and educational backgrounds, with Indiana being somewhat the outlier being the oldest and the most educated group.

Somewhere between 20 and 40 percent of the women that we saw, this was their first visit. English as the first language was high across all of the sites, and English, of course, was a requirement because we only had the English version of the test. And we also saw very high support across all of the -- or high comfort level with using computers across all of the sites.

This is the ethnic and race demographics breakdown. Most notably here, New York was being was -- predominantly a nonwhite patient population.

Okay. So across all sites, and there was no significant difference amongst any of the sites, patients found it very easy to use and easy to

understand. It was at a sixth grade level. And that nor were they worried about the confidentiality of their information going into this kind of tool.

The length of it was more variable across sites, although again almost 80 percent thought the length was okay. In our pilot, it took about -- where we actually sat with women while they did it and then asked some questions afterwards, it was about 20 minutes to fill out the tool.

There was a lot more variability depending on how it actually got implemented at that particular site. A high percentage, 80 percent, were as comfortable putting the information into the tool as to giving it directly to their provider. And that was those two were the preferred methods over writing a paper form or typing it into a Web site at home. And interestingly, it would be interesting to see if this shifts over time, entering the data into a cell phone or a smart phone.

So, in summary, we tested the tool across a diverse set of patients, and there was high

usability and acceptability across all of the sites, and patients were very comfortable in entering their data into this format.

All right. So now I'm going to share some data about the providers' response, which was a little more mixed, not surprisingly. So we had them fill out again both pre- and post surveys, and the data that I'm going to show you was on 25 providers where we had both the pre- and the post data.

This is the breakdown of the providers. There are 13 OBs, 8 family medicine physicians, and then 4 nurse and other categories. The volume that they used, the number of patients that they saw with this varied from about a little under half to saw it with just a small handful to over half using it from anywhere from 12. And then I'm sure these were residents who saw the 200 to 275 patients.

About half of our providers were residents and half of them were attending. So we also have that data that we can look at.

I'm going to show you the data on just the physicians because that is a little different, and

the numbers are small for the nonphysician. And there are some interesting difference between the OBs and the family practice docs.

So we had eight items on the pre- and the post that measured knowledge, and then six items that measured confidence around the use of family history and identifying individuals at risk and providing follow-up around, and we used some very common specific conditions like neural tube defects, sickle cell, CF, et cetera.

And we found that the OBs actually did very well pre- and post, and so we didn't see a significant change in their knowledge. However, the family medicine docs, there was a significant improvement in their knowledge scores.

The reverse was sort of for the confidence, and I don't have the actual intervals here on the slide. But the OBs showed significant improvement in confidence in five of the six items that we had, whereas the family practice really only documented an increase in confidence in one of the items, and that was referring for genetic

counseling.

So this is some of the data around different or we tried to measure different responses to different parts of the tool. And these are some questions, both quantitative and qualitative data that we received around their perceptions of the use of this tool in clinic.

So about half thought that having this prepopulated data form was useful in having the pedigree available. There was a lot less enthusiasm about the actual structure of the report. And again, this sort of gets back to being able, them wanting to really customize this for their setting.

Some of the positive comments that we received -- it made the process of seeing patients easier, reduces time taking family history, preformed questions allowed me to focus on more details, et cetera. However, we did get a number of negative comments that, in fact, it hindered the productivity of visits. It was difficult documenting sort of more immediate pregnancy-related issues, and they had to spend a lot of time on the

follow-up.

The interesting thing is all of the negative comments was from a clinic where this replaced their previous procedures. These are some assessments around the patient-provider engagement and the educational materials. Again, a little over half thought the patient questionnaire was very useful and the educational materials were useful.

The positive comments that we got was that it made conversation about family history easier, engaged the patient, allowed the patient to open up, helped me to give more educational info to patients, et cetera. One individual, however, said that's time I would have been using to establish my rapport with the patient.

These are some items around the actual clinical decision support part, and again, we see somewhat mixed responses. So about a little over half thought that the ethnicity-based clinical decision support was useful or the complex birth information was useful. We begin to see some falloff, though, for conditions -- again, remember,

we had a lot of screening conditions on there that were just pregnancy-related and not necessarily that we provided clinical decision support for.

So less support for that or for conditions that did not directly relate to the current pregnancy, like cancer risk.

So some of the positive comments. It was the right screening tool. We like the recommendations. On the negative side, again about the report, it was too lengthy, too much paper, it was unfamiliar. That came from the site where it replaced their previous. Hard to decide what to do with all of it.

There was some perception on one of the site there were too many referrals were being called out about the tool, and I think that deserves some follow-up.

And this is interesting, more ultrasounds were ordered. And that was because that particular site could not refer to a genetic counselor without an ultrasound order. And so, again, it just sort of shows you the amount of adaptation that needs to

occur within specific sites.

So, in summary, I think we showed that from the provider perspective, there was definitely an increase in confidence in identifying and managing risk, certainly within the OBs and there is value perceived in the patient questionnaire and in the engagement and the educational parts of this.

There was more mixed reception, though, to the workflow and the value of some parts of the clinical decision support. And again, this real need to tailor to the actual clinical setting.

So, lastly, and you do not have these slides in your briefing, I'm going to share a little bit of data around the provider behavior part of it that we added on at the end. So this is data from three sites. We're still waiting for chart audit data from the fourth site.

So it's on 522 patients that were seen and then 285 chart audits. So this slide shows five of the six performance measures that our advisory committee recommend that we use. And I'm going to share data with you on the first three. We're still

look at the data on the second two.

So it's the three-generation family history, documenting the ethnicity and the ancestral, and then providing counseling around cystic fibrosis. So just to orient you to this data, this is the first around generating the three-generation -- and we were, yes, three-generation family history. So here are the three different sites.

And let's see, did I miss a slide here? Yes, I'm sorry. So this is the three-generation family history. We were very liberal about what got included as a three-generation family history, the three different sites. So with the tool in North Carolina, there was 250 patients seen, 40 in New York, 228 in Indiana, and then these were the number of chart audits, pre-tool chart audits that we used to compare.

So the first thing you'll notice is that there's considerable variability with how well sites are doing about that issue. I know that's a shock for you all to hear that. And so, one of the sites

was doing extremely well beforehand, and they continue to do extremely well. One wasn't collecting it at all, and so they could only go up from there. And then the other one was doing sort of intermediate.

This is the data on documenting race and ethnicity of both the patient and the father of the baby. And this slide is, first of all, just showing you of the patient. And again, we see variability, although two of the three sites were already doing a good job of this, and the third site not doing so well and then showed a significant improvement.

This is on the father of the baby, which shows even more dramatic. And essentially, none of the sites were doing very little to none of obtaining information on the father of the baby.

This is the data which is even more dramatic around documenting country of origin. First of all, you see that people know this information less than in some of the -- and so, a lot of the data was not filled out when they were answering the questionnaire. But essentially

nobody, on either the patient or the father of the baby, was obtaining that, documenting that family information.

This is the data on the cystic fibrosis screening, which we actually saw that, again, variability for what was being done at the sites had a lot to do with the patient population that they were seeing. And it turns out sites were already doing a pretty good job around that, and so we didn't see much of a change, any significant change with the tool.

So, in summary, then we're obviously still going through some of this data. We did see that the tool collects more and more quality types of family histories, particularly when it comes to the father of the baby and the ancestry. The cystic fibrosis was fairly similar pre- and post, and we're continuing to look at the other areas.

We're going to be doing some additional outcomes analysis. So if there are outcomes data that you think we should particularly look for, we'd be very interested in hearing from the committee.

So, in summary, I would say that we have had a very successful pilot project here in developing a tool that met our overall business goals. We've collected a lot of the data around how to implement this kind of a tool into clinical practices, and what are some of the barriers and challenges and key areas to help for success along that.

We certainly find that within the patient, there is high satisfaction around and acceptance around using this kind of tool. There is much more variability with the provider -- for the provider information. They do see the value of the patient engagement and education. It does improve confidence. But about some of the actual use and clinic flow and clinical decision support was mixed, and I think all of that needs additional follow-up.

So what our next steps are. The tool is available for use in other settings. As I say, this is part of the now sort of a component of the Hughes Risk App. So if you go to the Hughes Risk App site, sign a ULA and user license agreement when you get

access to the software, you get the Hughes Risk App along with the prenatal tool.

We want to continue to study the impact within the prenatal population. We have gotten supplemental additional funding from HRSA to allow us to do additional outcomes data in the sites where we already have had the tool. And obviously, we'd love to be able to expand that in additional settings.

We also want to adapt this for other clinical settings, and again, we're in discussions with HRSA and the American Academy of Pediatrics to develop a pediatric version of the tool for the pediatric setting.

We think that there needs to be -- obviously, there needs to be a non-English speaking, at minimum a Spanish-speaking version of the tool. But we'd also like to see a Web-based interface and to test that out. And of course, ultimately, be able to see how this could be implemented into -- or integrated into an electronic health record.

So that's my story, and I'm sticking to

it. And if you have any questions, I'm open to Emily answering them for us.

CHAIRMAN BOCCHINI: Thank you very much for that presentation. It's certainly been nice to watch this project develop over time, and so it's good to see some of the results.

As far as the physician feedback, were you able to separate from the attendings from the residents, sort of looking at an age difference in terms of computer-based --

MS. SCOTT: Yes. We do have that data. We have not had a chance to look at it yet. So I would expect that there's going to be some differences. I would expect there will also be some differences within the patient population around the age.

But I have to say it was pretty uniformly accepted across all ages and even the use of the computer tool. So --

MS. EDELMAN: If I can add to that -- I'm Emily. Hi.

One thing we've seen pretty clearly

without doing statistical comparisons with the quantitative provider data is when we compare residents to attending, some of the concerns and criticisms that providers had about workflow and "It's taking a long time for me to get used to this." "I can't find things." "I don't like this report." There are dramatic differences between attendings and residents.

So the newer providers who aren't as invested in this particular form or even sometimes with electronic tools, the residents are more comfortable navigating the electronic tool. And so, I think that will be something that we see coming out, which is not surprising.

MS. SCOTT: Thank you, Emily.

CHAIRMAN BOCCHINI: Cathy?

MS. WICKLUND: Thanks, Joan. That was a nice presentation.

I was wondering -- and I stepped out of the room. So I apologize if I missed this. As far as the outcome data, is it possible or are you planning on following them further down that

pipeline to try to see if we are impacting any identification of people at risk --

MS. SCOTT: Yes, yes.

MS. WICKLUND: -- or behavior change or --

MS. SCOTT: If someone got identified, did they actually go for carrier testing?

MS. WICKLUND: Right. And --

MS. SCOTT: So that's part of what we're looking at to see whether or not we can do in the second round of doing a little longer. This tool was in the clinical setting for about, I'd say, 3 or 4 months in the different settings.

And then the chart pulls occurred sort of short or fairly after that. So we didn't get the long-term pregnancy outcome.

So that's one of the things we'd like to do is to go back to some of those and do a little longer term about what really happened to the patient and if the woman came back for a postnatal after delivering and maybe getting some additional information there. So we'll have to see what's possible.

CHAIRMAN BOCCHINI: All right. Jeff?

DR. BOTKIN: Yes, this is really excellent. So thanks.

I'm not quite sure how you do this. But the quality of the data that you're getting from the women as they fill out the tool. Is there any way to assess how good the quality is? And it sounded like you did get some feedback in terms of additional time that clinicians may have needed to try to clarify some of the answers.

But do you have a way of assessing the quality of the data that they were getting?

MS. SCOTT: We did some of that pre-tool. So Emily did an interview -- in our formative evaluation, interviewed some of the women, and it must have been after they used the tool?

MS. EDELMAN: Yes.

MS. SCOTT: And then compared what she got, as a genetic counselor, in comparing it with the data. So we did some of that pre-tool.

MS. EDELMAN: Yes, it was not an ideal study design just because of the limitations we had.

We had, I think, 12 women use the tool. They were not pregnant at the time they used it. We did not want to use pregnant women for our initial formative evaluation testing. So we asked women to pretend they were pregnant and think about their boyfriend or their husband's history, and they completed the tool.

And then I called them for a follow-up appointment, but without looking at those original data and then collected a genetic counselor pedigree. I don't have all the numbers off the top of my head. Things were pretty consistent. There was a couple things as a genetic counselor I missed.

I remember one thing in particular, I collected less instance of mental illness in the family. And so, that was an interesting question about are women more comfortable reporting it to a tool, or am I just not good at asking about that? Because as a cancer counselor, I never thought about that or thought about it limitedly.

And then the tool so there were a few things as a genetic counselor also collected that

the tool didn't. Rare disorders, single gene disorders in the family, things like that.

So we were comfortable based on those pilot data saying we're getting basic family structure okay. We're getting the major conditions we're interested in screening just fine. But a larger scale validation, we're very interested in doing that, but obviously, that's kind of like a randomized control trial or something that's much more extensive.

And we'd love to do that, and we've talked about it a bit. But it's just finding the right collaborators and the right support mechanism for that.

MS. SCOTT: And the interesting thing was that even in our formative evaluation where the providers were saying we really want this clinical interface so we can go back in and change things and reruns, they actually didn't use that. So we can't document how many might have been rerun because of that issue.

And I think partly that was because this

was on top of what they were already doing. And so, if there was changes, they would have made it in a different format in the tool or in their chart.

So --

CHAIRMAN BOCCHINI: Steve?

DR. MCDONOUGH: Thank you very much for your presentation.

I had a couple questions. What plans does HRSA have to share this information with the largest makers of electronic medical records in the country? And was this information sent to the hospitals when the baby was born so that pediatricians would have access to it when they reviewed the maternal record when they examined the baby?

MS. SCOTT: Regarding the second question, it depended on how the report got put into -- because they were -- since it wasn't an electronic part. So it would have been scanned as part of the record.

MS. EDELMAN: It was per the normal protocol for that OB clinic. So most of the OB clinics, yes, most of the OB clinics we were working

with or the family medicine clinics, they kind of sent over via fax or through electronic access the prenatal records for obstetric care. So it was just included in that packet of information. It wasn't highlighted or pulled out in any differential way.

We are also quite interested in thinking about the transition of the pregnant patient's pedigree and family history information to the pediatric patient. And that's something we've talked a little bit about, and we'd be interested to explore later.

MS SCOTT: Regarding the broader question about, which is a very critical one. At the same time we were putting this into clinics was the times when the first meaningful use was coming deadlines. And so, the IT people did not like even want -- you know, they just didn't want to deal with one more thing.

So for the sites that we were working with, we couldn't get that integrated into --

DR. COPELAND: And the National Coordinating Center right now has actually been

funded to develop some clinical use and clinical decision support. And they're doing that in conjunction with the EMR vendors, and this will be part of it.

CHAIRMAN BOCCHINI: Other questions or comments?

(No response.)

CHAIRMAN BOCCHINI: All right. Well, we're about 5 minutes ahead of schedule. So, so I think probably the best thing to do is we'll stop for lunch at the present time, but try and come back promptly so we can start at exactly 1:30 p.m. Or if you'd like, we come back at 1:25 p.m. And so, we can just in case -- okay, 1:25 p.m.

So we're going to start promptly at 1:25 p.m. All right. Thank you.