DEPARTMENT OF HEALTH AND HUMAN SERVICES/HEALTH

RESOURCES AND SERVICES ADMINISTRATION

Meeting of the Secretary's Advisory Committee on

Heritable Disorders in Newborns and Children

9:00 a.m.

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Renaissance M Street Hotel

1143 New Hampshire Avenue, N.W.

Washington, D.C. 20037

P R O C E E D I N G S

DR. HOWELL: Let me welcome everyone to the 21st meeting of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children.

It is extremely pleasing for us to welcome Dr. Jeff Botkin and Dr. Joseph Bocchini, who are sitting in the front row here today. They have been appointed by the Secretary to serve on the committee and have accepted this assignment. They will soon be our newest members, pending the processing of their special Government employee forms, which is something similar to being approved for the Supreme Court, but we hope it will be a little brisker.

[Laughter.]

DR. HOWELL: Dr. Botkin is a pediatrician and

a bioethicist. He is a professor of pediatrics at the University of Utah and an adjunct professor of internal medicine in the Division of Medical Ethics and an adjunct professor of human genetics.

Dr. Bocchini is a pediatrician and a pediatric infectious disease expert. He chairs the American Academy of Pediatrics Committee on Infectious

Diseases, or the Red Book Committee, and is the AAP liaison to the Secretary's Advisory Committee on Immunization Practices. And I think that experience will be particularly helpful to this committee.

Each member of the committee has received a thumb drive that contains not only the material in your briefing book, but a supplement to the books. In that thumb drive, you can find detailed information about Dr. Botkin and Dr. Bocchini, and that is under Tab 5 in your book.

Let me also note that this will be the last meeting, official meeting for Dr. Piero Rinaldo. Piero has agreed to stay on until Drs. Botkin and Bocchini were formally appointed. We obviously will miss Piero's extraordinary talent and work in this group and

on the committee. And he obviously has served very ably as chair of the Nomination and Prioritizing Workgroup. Piero, we hope, will continue to work with the committee in various advisory manners as we go forth certainly.

This is also Dr. Tom Musci's last meeting, since the American College of Obstetrics and Gynecology

has appointed a new chair of the Committee on Genetics.

And I wonder if you would comment briefly, Tom, about the new chair of the committee and who will be representing ACOG on this committee.

DR. MUSCI: Hello?

DR. HOWELL: It's on, I think.

DR. MUSCI: Yes, thank you.

Dr. Allen Hogge, who is the chair of obstetrics and gynecology at the University of Pittsburgh, will be taking over as chair. He is currently vice chair, and as of next week, he will be the new chair.

DR. HOWELL: Thank you very much.

We're looking forward to having Dr. Hogge join this committee at the next meeting.

The staff of the committee has not organized a fixed dinner menu tonight. However, we would ask that those who would be available to join members of the committee for dinner tonight to sign up at the registration desk before lunch so they'll have some idea of the number of people who will be joining us to dinner. And I hope that will be considerable.

And I have note here that Ms. Harris has some housekeeping notes.

MS. HARRIS: Sure do.

DR. HOWELL: And here is Ms. Harris with her housekeeping notes.

MS. HARRIS: Thank you, Dr. Howell.

Okay. So when exiting the general session, the restrooms are down the hallway and to the left. Altarum staff of Maureen, Jennifer, and Tiffany are at the registration desk to direct and assist attendees and answer any questions that might arise.

The committee members, organizational representatives, and presenters should stop by the registration desk. We've done a briefing book supplement. So that was everything that was added

after the briefing book was sent to you. We've got those on thumb drives, or if you want to have them upload those to your current thumb drive at the front desk, or if you want a separate thumb drive, you can pick your poison.

Continental breakfast and lunch will be provided to the committee members and presenters and

will be in the DuPont Room, which is next to the committee room.

Today, we'll have our subcommittee meetings from 2:45 p.m. to 5:15 p.m. The Education and Training and the Follow-Up and Treatment, those will be on this level. The Laboratory and Standards, they're meeting upstairs on the lobby level in the private dining room. And then there will also be an HIT Workgroup meeting. That will be in this room from 5:30 p.m. to 6:30 p.m. today.

And if any of the presenters have changed your presentations after submitting them, please save a -- let Maureen know, and she'll tell you what to do from there.

DR. HOWELL: Thank you very much, Alaina.

Our next order of business is under Tab 5 in your briefing book, and that is the minutes of the January 21st and 22nd meeting of this committee. It's a long document, more than 60 pages, and I hope that you've had a chance to look through it. They've been reviewed by me and by the staff for accuracy.

Are there comments about the minutes or

corrections in the minutes?

[No response.]

DR. HOWELL: Can we then have a vote to approve the minutes?

DR. GUTTMACHER: Move to approve.

DR. HOWELL: Second?

DR. VOCKLEY: Second.

DR. HOWELL: Those favoring?

[A chorus of ayes.]

DR. HOWELL: Any opposition?

[No response.]

DR. HOWELL: And no abstentions. So I assume that that is a unanimous decision.

Then in your book under the same tab is committee correspondence. There is correspondence from

EGAPP that is requesting comments from this committee.

So if you have any comments about that document from EGAPP, please let Michele know, and she will send a note back to the EGAPP group about the recommendation.

It's very, very nice that Secretary Sebelius has been prompt to respond to recommendations for this committee, and you will note in your book that the

Secretary has written to us concerning our recommendations on Krabbe disease, on the learning collaboratives in genetics and primary care, and resources to increase public awareness about newborn screening. And all of our recommendations to the Secretary have been approved by Secretary Sebelius.

There are letters from Ms. York concerning the committee recommendation to add SCID to the uniform panel. There also is a document about the committee report on the retention and use of residual blood spots. I think that all of you know that the draft of our document on the use and retention of dried blood spots has been posted in the Federal Register, and that will be up on the Federal Register for 60 days for public comment.

I might point out that we have already

received, and I don't believe that the committee has

that at this point, the material that just came -- that

I just got last night. We have comments from the March

of Dimes about that document, and we also have a

lengthy comment from the ACLU about the document. And

I don't know what -- but we will distribute that.

But the point is, is that we have to collect these materials for a period of 60 days, and these are among the first that have come in. And what will happen, we will go through those, make comments, and try to work on the document, and we will have a final recommendation in September of this year.

The Health Information Technology Workgroup will meet today from 5:30 p.m. to 6:30 p.m. in this room, and this meeting, as all of our meetings and subgroup meetings, are open to the public.

The other thing I would like to point out, the IOM workshop to engage the public for comments on the use and storage of residual blood spots will take place on May 24, 2010. And the scientists from the IOM who is responsible for organizing that is Adam Berger,

and Adam is here. And if you have questions about that meeting, which should be extremely popular, please touch base with Adam.

Adam, where are you? Do you want to raise your hand? Here is Adam. So if you have questions about that IOM workshop, it will be here in Washington on the 24th, et cetera.

As you know, at our last meeting, this group approved the addition of Severe Combined Immunodeficiency to the panel, and as expectations from that approval was that the Newborn Screening Translational Research Network would support some SCID pilot testing and so forth. And I would like to ask at this point if Dr. Guttmacher would be able to comment about what's happening with the residual dried blood spots?

DR. GUTTMACHER: And if we can have -- there's a PowerPoint. Guttmacher.

DR. HOWELL: Can you bring up Dr. Guttmacher's slide?

DR. GUTTMACHER: If not, I'll just act them out for you.

DR. LLOYD-PURYEAR: No. They are the ones put on --

DR. GUTTMACHER: I'll be happy to talk. Well, while we're looking for them -- looking at them is not that crucial, though it's probably better than looking at me.

This is just to let you know about a couple

of things, some of which I think many people on the committee already know about. One of them is that NICHD has negotiated a 12-month extension to a contract that we've had with Health Research, Inc., to continue operations of their novel technologies in newborn screening activity. It's a 1-year, about $1.1 million contract that was awarded last month. The PI is Ken Pass. Is Ken here?

Oh, there we go. You can read it. You can look at that instead of me now.

And basically, the idea is to permit HRI and its collaborators to look in more detail at both the evidence and the feasibility of various new technologies related to SCIDs. Okay, thanks.

And as you can see here, there are a number

of States involved in this activity, with a fair number of births involved. And there are also different technologies that are being looked at, a number of other participants in various ways, both various kinds of cash in kind, other contributions to this effort. And the purposes, of course, really are to try to figure out how best to approach the questions of

screening for SCIDs.

And this is just sort of a timeline of how we're going to be going through this. You can see that it's a fairly aggressive timeline, I think.

And then just while I have the podium, or at least the controls of the projector, I thought I'd also tell you about a couple of other current -- I wouldn't say recent, but current NICHD newborn screening-related initiatives. These are both out on the street now. So it's always good to get words out that there are some folks in the room that might be interested, and certainly, you have friends who might be interested in this, and just to let you know about both of these.

As you can see, one of them, the one on the bottom, the deadline is only a few weeks away. The one

at the top, we still have a couple of months to go.

But again, in terms of just activities in our portfolio regarding newborn screening that we wanted the committee and others to be aware of.

If you have any questions about any of these, I'd be happy to take some now, or we have other folks that can help you with it now or later if you have

questions.

DR. HOWELL: Are there any questions at this point of Dr. Guttmacher?

[No response.]

DR. HOWELL: Okay. Thank you very much, Alan.

DR. GUTTMACHER: Sure. Thanks.

DR. HOWELL: At your desk, you have a current copy of Seminars in Perinatology. That is with Brad Therrell as a guest editor, and it focuses on newborn screening. I bring it to your attention because Michele and I were asked to write a brief comment about the activities of this committee. And so, there's a brief note in there about the activities of this committee, which I commend to you.

You will also -- during the course of the meeting, you will get some copies of The Collaborator, which is produced by the National Coordinating Center for regional collaboratives. And those will be coming, and so forth.

Now, before we go and get further into the meat of this very busy program, I would like to

recognize our own Dr. Michele Lloyd-Puryear. Last week, at the Association of Public Health Laboratories meeting in Orlando, at their Genetic Testing Symposium, Michele was awarded the George Cunningham Visionary Award in Newborn Screening. This award, which is one of the higher awards of APHL, is to persons working in newborn screening that have made the greatest contributions to expanding or improving newborn screening by the public health agencies in one or more States. And this recipient must have had a very direct effect on improving the quality of life of these infants.

In the letters of nomination that went to the APHL concerning Michele, many of her activities were pointed out, but her tremendous success in involving

families and advocates in newborn screening throughout the country was pointed out, as well as her bureau's oversight of funding the American College of Medical Genetics to do the original work, and then with her continuing outstanding work of this committee.

And in the spirit of this award, Michele was not in Orlando to get this award because she was

downtown meeting with the Secretary, which I understand was a successful meeting. But Alaina Harris was there, and Alaina dutifully stepped forward and accepted Michele's award. But I would like to ask Jelili Ojodu, who is here, to please present this award to Michele at the current time. It's a very handsome award.

And Jelili, who, as many of you, is the newborn screening guru of APHL, and he is going to bring this award to Michele so she'll have something to hold her vast stack of papers down on her desk.

[Laughter.]

[Applause.]

DR. HOWELL: And APHL is quite glitzy in its award. I think you can see it here. It sits like this, and it's quite handsome. It's a tower. I think

it's a mini Washington Monument or something.

[Laughter.]

DR. HOWELL: But anyway, congratulations, Michele, for all your fine work. And we hope that this is just a prelude to many years of harder work as we go forward.

[Laughter.]

DR. HOWELL: We're going to now move ahead to our program on carrier screening. We had a report, as you remember, on the evidence about sickle cell disease carriers, and we discussed at that time that the NCAA had made very specific recommendations for sickle cell carrier screening. And in the materials that were distributed to the committee, you had copies of the extensive brochures, which are quite slick, that the NCAA has put out on this subject, et cetera.

A workgroup on screening for sickle cell was formed and is preparing a briefing paper for this review. And at this point, Dr. Frempong will present an outline of this work. And after KOF's presentation and discussion, we will have a presentation from Sara Copeland about her work with the SACGHS on the

formation of a carrier screening task force.

KOF, could we hear from you?

DR. FREMPONG: Thank you very much, Chairman.

Now can I have those slides that you had on earlier?

I am speaking on behalf of this working group of experts, and I'm really just the mouthpiece for that

group that has been working very hard to put together some recommendations and also some information about this issue that has been brewing for a number of years and sort of came to a head in the last year or so, when NCAA made its recommendation that athletes be tested for sickle cell trait.

So just to give a little background, the purpose of the briefing paper that is being put together by the workshop is to apprise the Secretary of Health of new policies and practices concerning sickle cell trait carrier screening, especially as it applies to college athletes; to discuss the impact of the athlete screening, the policies and practices and the effect they will have on the public health system; and to make some specific recommendations about appropriate

responses and actions that the Department of Health could take.

This is a list of the experts who are involved in this endeavor. It's been a very active group, meeting very frequently by phone as the whole group and as small subcommittees. And there are chairs within that list, and they are chairing different

chapters of the briefing book that's currently in development.

The topics that will be covered by the briefing book include what is known in research and clinical findings on sickle cell trait status and the health outcomes related to sickle cell trait, issues and impact of this athletic association's recommendation on the affected populations, community service providers, and public health in general. Also, sickle cell trait status, as it is now in U.S. in the screening programs around the country, mostly newborn screening, and then the recommendations that I will get to in a little bit.

As background information, the first documented deaths that were related to exercise in

people with sickle cell trait were reported in New England Journal of Medicine back in 1968. As you know, newborn screening for sickle cell disease started in the '70s, first with New York State, and various programs have different policies on reporting sickle cell trait and its follow-up.

In 1987, John Kark published the paper on

increased risk of death in military recruits training in some of the recruit centers here in the United States, and then in 1994, and now really up to all the States in this country now test for sickle cell disease and sickle cell trait as part of the newborn screening. But as I said, there are different policies for disclosing that information.

In 2007, the National Athletic Trainers Association released their consensus statement to raise awareness of sickle cell trait and provide some measures to reduce the risk of exertion or collapse as related to athletes with sickle cell trait, and at the same time, the literature was introduced, a new terminology, something called "exertional sickling" that is as yet undefined.

Last year, the National Collegiate Athletic Association recommended, as part of a settlement of a lawsuit, that its member institutions test student athletes to confirm their sickle cell trait status. And as a follow-up, Sickle Cell Disease Association of America approached CDC to convene a meeting to discuss the public health implications of sickle cell trait.

Earlier, just last month, NCAA Division I Advisory Council adopted a mandatory screening policy, and we'll hear a little more about that also.

So, in general, this year NCAA proposed that all athletes be tested for sickle cell trait, and this was defeated by their legislative council at the initial hearing. And then, just last month, this matter was brought up again. It was amended. The original proposal was amended and was then approved.

So as it stands now, the NCAA recommendation is that Division I student athletes must be tested for sickle cell trait or show proof of a prior test or sign a waiver releasing an institution from liability if they decline to be tested.

That rule will take effect in the 2010-2011

academic year, so starting in the fall. NCAA public information following the April 2010 decision was put out, and SCDAA also has prepared a response, and there's been a lot of media reaction to this new recommendation by NCAA.

So the areas that the working group is making recommendations on, is on universal safety precautions

for all athletes -- that's sort of similar to what the military had done -- issues of consent and privacy, nondiscrimination protections to be built into this NCAA recommendation and some guidelines for implementation, and then the need for research and evaluation.

So these are preliminary recommendations from the working group. The work still continues, and I'm sure that these will be refined even further. They recommend that all athletes should be taught and required to practice universal precautions when engaged in college sports without regards to their sickle cell trait status.

Screening for genetic conditions should be voluntary. Athletes should not be denied participation

in college sports because of their decision to opt out of genetic screening on the pre-participation medical evaluation. Any claims of discrimination based on an athlete's sickle cell trait status should be investigated.

The committee should be urged -- this committee should be urged to work with the Sickle Cell

Disease Association of America, the athletic associations, community-based and healthcare professional organizations to develop guidelines and educational resources about screening activities for sickle cell disease and carrier status, sickle cell trait.

Now these materials should address maintenance of privacy of medical information of the athletes, the type of tests to be used for the screening and diagnosis of sickle cell trait, and then training of athletic staff on appropriate response to emergencies at the athletic fields.

The Centers for Disease Control and Prevention should work with athletic associations and their member organizations to develop a registry of

sudden death events related to athletic performance. And the National Institutes of Health should develop research initiatives to improve understanding of why some athletes with sickle cell trait might be at increased risk for exercise-related sudden deaths.

This committee is also urged to establish an expert panel to select indicators and measures to be

used to evaluate compliance with recommendations and policies regarding sickle cell trait screening and outline a process for monitoring the compliance with those recommendations.

The next steps following these preliminary recommendations is to obtain input from professional medical associations and other key stakeholders on these preliminary recommendations. In December 2009, the Scientific and Public Health Implications of Sickle Cell Disease -- Sickle Cell Trait meeting that was convened by the CDC, a summary of it is available.

In February, at the Florida Sickle Cell Symposium and Scientific Meeting, the report on sickle cell trait, its medical implications, and issues surrounding the screening were also reviewed, and

that's going to be available through the American Journal of Hematology.

The next meeting is happening in June, and that's the NHLBI, National Heart, Lung, and Blood Institute initiative on the research agenda, and this particular conference will be held on June 3rd and 4th, and it's titled Framing the Research Agenda for Sickle

Cell Trait.

So I think that ends my presentation. Are there any questions or any omissions that I have? Members of the working group who are here can maybe fill in.

Thank you very much, Mr. Chairman.

DR. HOWELL: Thank you very much, KOF.

Are there comments or questions of KOF about the sickle cell issue?

Chris?

DR. KUS: Did the NCAA address the other divisions? They recommended Division I?

MALE SPEAKER: They just don't work hard enough in Division II.

[Laughter.]

DR. KUS: Well, that's the point. I guess that's the point.

DR. FREMPONG: Specifically, no, they did not. And even though there have been some discussions about high school level also, there hasn't been any response from the national high school athletic associations either.

So this applies to Division I, and maybe the implication is that they are the ones that are doing the most competitive, and maybe they have a longer training period. I really don't know.

DR. KUS: Another question would be in the recommendation talked about educating athletes about universal precautions. There wasn't a statement that I saw about educating coaches or the people who were actually doing, instituting the training things. Comments on that?

DR. FREMPONG: Yes, I think that was probably implied. In the recommendations from the National Athletic Trainers Association, they actually did mention, and this is part of the group that trains the athletes, they did mention these universal precautions.

So at least there's a need to somewhat enforce it and make sure that the athletes are also aware of it because some of it could be initiated by the athlete in terms of not overexerting yourself, gradual activity, when you're tired to report it and take a rest, and increase hydration.

Is there a question?

DR. HOWELL: Can you clarify for me exactly what would happen if an athlete is confirmed to have sickle cell trait? What would the NCAA recommend?

DR. FREMPONG: Well, this is where their recommendations sort of fell short. It just stops at the screening. By implication, since they say that no athlete will be denied participation, you think they will, therefore, institute some different plan for that athlete's training, but that's not stated.

And we're not sure whether those athletes will be marked in some way, will be required to have a different training program. These are not included in their recommendations at this point. So it's just a matter of knowing which athletes have sickle cell trait is as far as their recommendation goes.

DR. HOWELL: Do they have recommendations about the technology to be used for carrier screening?

DR. FREMPONG: No. But from what we understand, the different institutions are looking at different ways to do this, and most of them seem to be opting for the least expensive testing, which is the common solubility test that only tells you that you're

positive or negative and does not distinguish between sickle cell trait and any other condition where there is a fair amount of sickle hemoglobin. So disease and trait will not be distinguished by that test.

DR. HOWELL: So that test is really not the way, if you were going to screen, that's not what you would do?

DR. FREMPONG: No. In fact, that's one of the reasons why we think that there need to be specific recommendations on tests that are specific. The Sickle Cell Disease Association of America has also issued some recommendations, and I think we passed copies of those around. And they have a specific recommendation that these tests, these simple tests not be used, but that tests that define the type of hemoglobins you have

or the mutation itself be the preferred tests.

DR. HOWELL: Brad has a comment, and then we'll --

DR. THERRELL: Yes. Brad Therrell from the National Newborn Screening and Genetics Resource Center.

We've started getting inquiries from coaches

about the dates that their States mandated screening so that they want to go back to the health departments and ask for those records. They're being referred to this table on page 135 in the magazine that was just given to you, which is a listing of all the States and the date they started mandated universal newborn screening. So those questions are coming, and they're going to be coming to the health departments as well.

DR. HOWELL: Coleen, I think you had a question?

DR. BOYLE: Just a quick question. You mentioned about developing a registry of fatal events, as well as doing some research related to that. Did your workgroup consider sort of broadening that to severe, but nonfatal events. It seems like it would be

a very rare condition, very rare event. I would think that you would be able to amass a lot more information.

I don't know if you can. I don't know a lot about this. So I'm just wondering if you had given some thought to that as well?

DR. FREMPONG: Right. We haven't really defined that. But I think generally we feel that the

experts in assessing risk of rather rare events in large populations, such as the CDC and others, probably can work with NCAA to keep a record of this screening and the outcome of it. Almost all the reports of athletic injuries and deaths related to sickle cell trait are retrospective. Somebody dies. The pathologist reports seeing sickle cells in their blood, and somehow the association is established.

This will be the first opportunity to look at this going forward. The military had an opportunity to do that. So I think that the specifics of what that registry could do --

DR. BOYLE: I think it's a great idea. I'm just trying to get to more events there so you could actually advance the knowledge quicker. That's all.

DR. HOWELL: Does this group have any formal relationship with the upcoming NHLBI program on sickle cell this summer?

DR. FREMPONG: Lani, you may comment on that. I don't think we have a formal relationship. I'm sure that many of the members will be participating. I know I've been asked to give an overview, and SCDAA will

also be represented. But in terms of formal, we could inquire into it so that at least our recommendations could also be aired at that meeting.

DR. LLOYD-PURYEAR: NIH is involved. It is on the working group. NIH is on the working group that helped prepare these recommendations.

DR. HOWELL: Oh, okay. All right.

Mike?

DR. SKEELS: Just a comment from the newborn screening perspective, maybe this is more a question for Sara when she talks about what the task force is going to be doing. But I just want to raise the issue of whether the newborn period is the best time to be screening people who are going to need these records when they're 15 or 16 or 17 or 18 years old?

Because one of the major universities in our State, which has a water fowl as a mascot, has already --

[Laughter.]

DR. SKEELS: Has already contacted us to see whether we -- the newborn screening program would be able to screen their athletes for sickle cell trait,

and we're trying to figure out if that's an appropriate role for us or whether there's a way that they can get the same information at least for the athletes who were born in a State that has screening. And it's a medical records issue, really, and I don't know whether newborn screening is the answer for later in life or not.

DR. FREMPONG: Their recommendations say that if the athletes can show evidence of having been tested, most families are informed -- in this country are informed about a baby having sickle cell trait, but the record is usually not kept in any permanent form. So they may know the information, but they don't have documentation of it.

So maybe there may be a way of developing a more permanent record of it, either a letter or

something that an athlete could show, if the family kept it, to show that, in fact, the child was tested and this was the result.

DR. HOWELL: Ned?

DR. CALONGE: I think this is a significant issue, and I think a piece of paper probably isn't going to be the solution. I think the way we're

envisioning it in Colorado is that we keep all the birth certificate data forever. And so, it becomes an archiving issue, and archiving electronic information is becoming easier at the same time. So I see the only solution as tying it back to a database that's permanent like a birth certificate database.

And we're already expanding our storage capability with the anticipation we will keep newborn genetic screening information forever.

DR. FREMPONG: So in that scenario, a family could request --

DR. CALONGE: Right.

DR. FREMPONG: -- that those results be made available at the appropriate time.

DR. HOWELL: Would you comment briefly about

the military experience?

DR. FREMPONG: What John Kark had reported in 1987 was I think going back for about a period of 4 years and looking at sudden death in the military related to exercise, mostly in military recruits, and having data about those recruits in terms of the hemoglobin types, that they compared athletes -- or

recruits with sickle cell trait with African-American athletes without sickle cell trait and non-African American soldiers and found that there was an increased risk of sudden death among the recruits with sickle cell trait.

And at that time, they presumed that this was related to heat and that most of the circumstances of death suggested rhabdomyolysis as the basis for it. So then they instituted a better method, a more aggressive method of assuring hydration and monitoring the temperature and activity of the recruits. And then, in the following 10 years, on a prospective basis, they eliminated these deaths completely.

In fact, in the following 10 years, in those recruiting centers that followed it, there was no

sickle cell trait death. And overall death for all recruits related to exercise was also decreased. So that's the experience from the military, and I think it's on that basis that the recommendation is being made that since these athletic performance-related deaths seem to be similar, that maybe the same sort of precautions could reduce the risk even if the exact

cause of it is not clear.

DR. TROTTER: Rod?

DR. HOWELL: Yes?

DR. TROTTER: So I'm more than a little confused by the handout part we got, which was recommendations from the Sickle Cell Disease Association of America. And number one talks about universal precautions, and the second line is, "By implementing universal precautions, athletic programs could allow athletes to maintain their privacy of their sickle cell trait."

But if you're going to do that, why do you want to know? If it isn't changing anything you do -- the athlete is not being treated differently. They're not working out differently. If somebody collapses,

you're going to treat them. You're not going to check and see if they have sickle cell disease. You're going to treat their collapse.

It doesn't look like, from everything I read, that it makes any impact on what happens. Am I wrong? Did I miss something here?

DR. FREMPONG: Well, the chief medical

officer of SCDAA is here. Maybe she can respond? I think in general I know that the SCDAA is not in favor of this screening. So I think they are saying that if you are going to do the screening.

DR. TROTTER: Well, they're stuck with the NCAA saying that, right?

DR. FREMPONG: Yes.

DR. TROTTER: Okay. It's a conundrum.

DR. CALONGE: I was thinking about the same issue. I think where it's going to be -- we run a real chance of a lot of negative labeling with a strategy that may not translate to any benefit. That's exactly the scenario that I think we're trying to avoid in the newborn screening world. I mean, I don't actually even understand the exact risk.

So if I have a trait, what is the incidence of this? What's my actual risk of exertional sickling? And how do we put that in context with the fact that if I am labeled, I may be treated different? I may make different decisions in my life path that is based on an extremely low risk that's not going to benefit.

DR. HOWELL: We have a comment. Microphone?

DR. JORDAN: Hi. Good morning. I'm Lanetta Jordan, with the Sickle Cell Disease Association of America as its chief medical officer.

And what we know, what we've been told by the NCAA is that individuals who test positive will be treated differently on the field. They will be isolated in some way so that they will have a different practice pattern. The coaches will pay particular attention to those student athletes.

And a couple of the athletes have already been asked do you feel that you're being treated differently in any way? And one of the athletes stated, "Oh, no, everyone jokes with me, and they call me 'sickle.'" So, you know, I can only imagine.

[Laughter.]

DR. JORDAN: "Sickle, okay, it's time for you to come out on the field or go sit down." So the student athletes at this point don't realize how damaging we feel that this can certainly be down the road. But there are some differences that are already occurring, and we do have reports of those differences. So we will start to log those in and monitor them very

carefully.

DR. HOWELL: Piero?

DR. RINALDO: Well, what about after college? You know, after all, what I've read a few times is professional teams really have incredibly detailed medical records of their athletes, their investment really. And so, has anybody looked at the possibility that being branded or labeled with this trait could really lead a team not to recruit somebody? Because that would really be, I think, an even bigger issue.

DR. FREMPONG: Well, the information that has been known for years is that the rate of sickle cell trait in professional sports in the United States is the same as it is in the general population. So there has never been a question about the ability to perform

at the highest levels.

And you're very right. I just see that they may be joking about this at the college level, but recruiters either for college or for professional sports, if they know that someone has sickle cell trait, it will be very hard for me to think that they will not take that into consideration just to avoid the

liability. And for them, it's more of a liability issue.

The question of the risk of an individual athlete for sudden death or for heat-related injury is probably -- is a very small risk, but hasn't been scientifically established, and that's why maybe a registry can help. The experience has been -- and it's not only in this country. I mean, there are countries where close to a third of population have sickle cell trait. And they have -- none of them has ever reported seeing any increased harm or lack of performance of these athletes.

DR. RINALDO: So I think it goes back to what Dr. Kus said earlier. This is not about Division I issue. For one thing, it should be done from peewee

league to professional sport.

DR. KUS: I'm not recommending that.

[Laughter.]

DR. RINALDO: No. But it's really -- I think it's totally artificial that you just focus on one very small segment of all the people that could be affected. So it seems to me that the premises here need to be

revised a little bit.

DR. HOWELL: KOF, I assume that this whole thing is driven by concern about lawsuits that come -- that are against the schools. Is that correct? That must be the --

DR. FREMPONG: The discussion has been going on for some time, but the current fervor around it all stemmed from one lawsuit. A student who died, and the family sued the NCAA and the university. And as part of the settlement, NCAA was asked to address this issue. And so, a lot of the activity has been in response to the lawsuit and the question about making recommendations with no specific plan for the athletes just tells you that they just are responding to say they're doing something.

But I think it's the legal liabilities that are the main driving force and not the health part of it.

DR. HOWELL: Are there further comments? Chris?

DR. KUS: I guess I would see that doesn't this body have some response? I mean, here it seems

like we're responding to a recommendation from that preeminent medical organization, the NCAA --

[Laughter.]

DR. KUS: -- which is concerning. I mean, I think this is wrong-headed, and I think that how we respond to that is important.

DR. HOWELL: I would certainly agree.

Tom?

DR. MUSCI: Yes, just one last comment. It seems that in high-level sports there is a culture of sort of ignoring physical symptoms to push athletes to the limit, and one of the things that's really interesting about this whole discussion is it gives sort of a justification to let some individuals to take their complaint seriously while the others who may have

pain or muscle pain, to let them go on past a usual or a reasonable limit.

So it seems like this whole screening to me is backwards in that coaches, there needs to be a change in culture where physical symptomatology is taken seriously so that they can investigate whether an athlete is really having difficulty, instead of blowing

it off and pushing people to their limit.

So I think I would favor, and I heard this some time ago. I thought that and we discussed it at ACOG because it came up in our committee, just that the idea was that coaches or trainers need to just take physical symptoms seriously and not just rely on genetic information to push athletes past their reasonable limit. That just seems backwards to me.

DR. HOWELL: Are there any other comments to KOF and his committee? Any of the committee would like to speak?

I wonder if we could return his control because I'd like for you to go back, KOF, to your recommendations because we need to vote on the recommendations. If you'll give it to Dr. Frempong

there.

DR. FREMPONG: Oh, even at this preliminary level?

DR. HOWELL: Yes. Yes. You have some preliminary suggestions that I'd like the committee to look at, and so forth.

DR. FREMPONG: So this is where I started.

DR. HOWELL: You have those three recommendations, and is that all the recommendations that are your preliminary --

DR. FREMPONG: No. I'm just moving forward.

DR. HOWELL: Okay.

DR. FREMPONG: There are some that specifically apply to this committee.

DR. HOWELL: Right.

DR. RINALDO: Could you change about screening all athletes, going back to what we were talking earlier?

DR. FREMPONG: That is very broad. If you don't put it in education institutions or what level because it could go all the way down to --

DR. HOWELL: Well, this is obviously a work

in progress that this committee is going to continue to work. Their meeting is coming up. The NIH meeting will be soon, the NHLBI.

Is the committee comfortable with these preliminary recommendations to the committee? Alan?

DR. FLEISCHMAN: I'm certainly comfortable. I would suggest that you adapt the language of

"universal safe training guidelines," rather than the language of "universal precautions," since in the medical field, that has other meaning and I think will be confusing.

MALE SPEAKER: That's true. You have to practice with gloves on and a face mask.

DR. HOWELL: Fred?

DR. CHEN: Kwaku, was there much discussion about a more strongly worded negative statement against testing? Because I think there is at least some sentiment around the table in that direction.

DR. FREMPONG: Certainly, we could. We could make a stronger statement right from the start. And I think the SCDAA recommendations may be a little stronger in that respect. That you can't teach

somebody to do a bad thing well, and that's --

[Laughter.]

DR. FREMPONG: That's a feeling I have.

DR. HOWELL: KOF, you'll go down in history for that remark.

[Laughter.]

MALE SPEAKER: Take that one down. That's

good.

DR. FREMPONG: And so, maybe --

MALE SPEAKER: Why don't you lead with that statement?

DR. FREMPONG: Maybe we'll lead with that statement, or something more polite.

DR. HOWELL: I sense a considerable concern around the table about the process of screening and the value of that and so forth. But is there a general sense that the committee is on the right path? Alan has had some wording thing. Do I hear a consensus of that? We won't take a formal vote, but it looks like the committee thinks that you're on the right path, and we'll expect you to report back.

This is a very important decision, obviously,

and we're working with a group that is extremely well established in athletics and whose recommendations have a good bit of support and requirement. So we'll have to be fully aware of that fact that this is not a simple issue, and we'll have to be very thoughtful.

So we'll look forward to hearing back from you, KOF. Thank you very much to you and your

committee. It looks like you've got really great representation on the committee of all the groups, and you have a person of NHLBI on your group that, obviously, will be --

DR. FREMPONG: We'll make sure that the link is made to the meeting.

DR. HOWELL: Yes, because I think that will be a key meeting and so forth.

We're going to go ahead now and discuss -- we have Dr. Sara Copeland at the podium here. And she's going to discuss the proposed task force on carrier screening, and everybody knows Sara from HRSA.

DR. COPELAND: Good morning. Thanks for letting me present on what is likely to be an even bigger Pandora's box than just sickle cell trait

screening.

So today I'm going to review the issue, what we do know about carrier screening, current status of different carrier projects that are out there, look at our outline proposed plan of action, and then ask for your approval or disapproval of whether or not we should take this further and forward.

So first thing I want to say is most of these really cool, insightful things came from other meetings and other people. And although I don't have the citation at the bottom of this slide, they are at the bottom of the messages. So I don't -- I'm not taking credit for these wonderful insights. I just want you to know that I've picked these out of the research I did.

So key point here is that we are looking at carriers of a gene mutation, meaning that they're autosomal recessive disorders. The people are at risk to have an affected offspring. So they're not at risk for developing disease. It is due to reproductive issues that they may be at increased risk.

And this screening can be either deliberate,

i.e., we're looking to see if they are a carrier, or it can be incidental, such as what happens with newborn screening when we identify a hemoglobin trait.

So examples of possible carrier screening and issues that have been found in them. We could look for common mutations that have a known founder effect, and these are often in certain populations, such as CF,

sickle cell, or Gaucher. Or we can look for those disorders with a high mutation rate and that are widely distributed new mutations via sequencing, such as DMD, neurofibromatosis, or tuberous sclerosis. However, those are all autosomal dominant. So you would expect some of the people there to have at least symptoms.

So considerations that have been found for carrier screening is that the disorder impairs health of the affected offspring, and you need to have a high frequency of carriers in the screened population in order for it to be useful. You need to have valid screening methods that are available and cost effective, which is always a key.

You need to have options once you have identified these carriers because once you've

identified the carriers, you need to know then what impact that will have down the line. You need to be able to make sure that there is consent, that the knowledge of benefit and harm for carrier testing is known and anxiety addressed, which is always difficult to quantify and to deal with.

You need to make sure that privacy is

protected, and stigmatization is minimized. The sickle cell trait example is a wonderful one of these. And then you need to have the professional resources, which is a growing issue in the field of genetics anyway.

So looking at this from the various perspectives, because we can't just look at it from one side, there is the public health impact. Are we going to be able to decrease the burden of disease? Looking at it from the medical genetics-clinical practice point of view, A, do they have the time and the resources to do this? B, can they get reimbursed for it? And C, what is this going to do to their clinical practice?

We need to look at what the current screening programs are out there and how is what we propose going to impact the current system. And then we need to look

at what we're doing with carrier detection as part of newborn screening. And at this point in time, generally, this is an incidental finding. We're not looking to find carriers.

So there have been two big meetings that I was able to identify and find the proceedings from. The first was in 2006. It was the Genetic Carrier

Screening: Moving Population Genetics from Theory to Practice. And then there was another one held by HRSA in 2008, Population-Based Carrier Screening for Single Gene Disorders: Lessons Learned and New Opportunities, as well as numerous, numerous, numerous presentations at national meetings.

So when thinking about this, we need to think about the who, what, why, when, and how. So who to screen? Do we do this population wide, or do we just do it in high-risk populations, such as Ashkenazi Jewish population? Or do we do targeted screening if there is any indication from the history?

And then how do we screen? Do we just get a family history and look and see, okay, you're from this ethnic background and you have a second cousin with

this disorder? Do we do genetic testing for sequencing? Do we do targeted mutations? Do we do it on the blood spot? Or do we maybe look for downstream markers that indicate a carrier status?

Another big issue is when do we screen? Do we do this in the newborn timeframe? And I think it's been pointed out that keeping the information with you

is a difficult issue. Do we do it in childhood at the time of other mandatory testing, such as lead and hemoglobin levels? Do we do it at age 18, when technically that's the age of consent? Do we do it when people are planning to be pregnant or when they're already pregnant?

And then what is the purpose of the screening? Is it to inform reproductive choices? Should we only do it if the carrier status has health impact, such as urea cycle defects for ornithine transcarbamylase deficiency, and pregnancy outcomes, SC trait, Fabry, and when there is no other interventions that can avoid the problems or problems that affect only those who are carriers? Do we do it with certain disorders? Are there other reasons for doing this kind

of screening?

And then re-screening is a big issue, as we've noted with sickle cell trait. Will this information stay with them so that they actually know it for informing their reproductive choices? Who is responsible for this counseling? When should the counseling be done, and who should be targeted for re-

screening?

Direct-to-consumer testing is here. I think you can now buy it at your local CVS pharmacy.

FEMALE SPEAKER: Walgreens.

DR. COPELAND: Walgreens. I'm sorry. Wrong drug --

[Crosstalk.]

DR. COPELAND: Oh, they stopped it last night. Wonderful. But unfortunately, that's not the only place where you can get it.

However, my main concern, coming at this as a pediatric geneticist, is who's making sure that the testing is done according to AAP guidelines? Are we testing these kids for disorders that they may not want to know about?

Who's responsible for this counseling? I don't care what they say, you can't get adequate counseling on the Internet at this point in time. And what is "adequate counseling?" I don't think that those standards have been established yet. And then who's responsible for keeping the information for later when they're considering reproductive choices and then

discussing it again? Information changes. People change.

So we do have some previous experience to draw on. These are publications -- CF prenatal screening, the California experience. Prior to newborn screening introduction, less than 50 percent of OBs offered the CF panel mutations to their patients, and less than 17 percent of couples were offered prior to the universal newborn screening for CF. This has improved.

The panel to screen for is growing, and you need to know what to screen for based on ethnic background as we learn more and more about mutations. And then you always have to deal with what do you do when your prenatal and newborn screening results are

discrepant.

The best example of population screening in a targeted population is the Ashkenazi Jewish experience. In 1973, they started testing for Tay Sachs disease, started with enzyme, moved to DNA in 1990. In '08, they had a recommended panel of 9 disorders, but possible to do mutation analysis for 16 disorders with

the known founder mutation. The Ashkenazi Jewish experience is unique in that it's a community-based effort, and it is not based in the medical field.

We have some other experiences that are not so auspicious. There is the sickle cell disease Air Force policy that we've discussed previously and the stigma being related to that, to say nothing of the current NCAA policy. And there is the publication below that talking about reduced maternal bonding, discrimination, and stigmatization for sickle cell trait identified.

So what do we get out of the previous meetings? Because my goal is not to reinvent the wheel. So the 2008 meeting in Rockville, some of the endpoints were what to screen for and when to screen

and developing a criteria. So their top three considerations should be carrier frequency, disease burden, and the cost of screening.

And you need to know, what you screen for depends on why you're screening. So what actions can be taken, and when should this occur?

How should we balance the screening interests

of individuals, communities, and societies? The first is to engage the relevant communities, which is why the Ashkenazi Jewish population has such a robust screening program, and they have managed to be so successful.

Identifying the rightful gatekeeper is challenging. We have a hard enough time with that right now with newborn screening for disorders that affect the children that we're screening, and maybe we need to look at other screening models to consider, such as cholesterol or blood pressure screening or obesity screening. When you come in for your routine health check, which I'm sure everybody goes to annually, maybe we can talk about it at that time.

Or else maybe we can use other models. Just bypass individual interests and do population

screening, such as with immunizations and seatbelt laws. I think there is a wee bit of controversy related to that.

Should we be targeting these to certain subpopulations? And then how do you identify which subpopulations? And so, there's a balancing act that needs to be done. So targeting issues, who do you

target your screening to? Or if you're not targeting your screening, then how do you target your counseling in the endpoints? So do it on the back end where you customize your counseling related to the risk that you can identify from the history.

The consensus was that the community should drive what is offered. We need to engage the relevant populations. But defining this is very difficult. Is it ethnicity, self-identity, or scientific markers? And maybe it's through point of service -- newborn, prenatal, age 18? In high school in Jerusalem, they have a screening panel where everybody does a cheek swab. And subpopulations should be targeted only if population characteristics can justify it.

And then there is consent. So this is not

just a simple consent because you have multiple complex tests, or you could potentially. And describing what it means to be a carrier can be problematic when you're dealing, for instance, with X-linked disorders. Are we going to start screening for mitochondrial disorders? So who's a carrier, and who's not?

Getting that point across when, as

clinicians, we can't get the meaning straight can be a bit difficult as well, and there is a lot of levels of uncertainty about the tests. Genotype-phenotype is a wonderful concept. However, it's not proven to be all that easy to come up with, and you just multiply these, the more complex the test and the number of tests that you offer.

And then we need data. We need to be able to measure what we're doing. So pre- and post testing education, how do we measure that? Maybe we should do some surveys to make sure that tests are being appropriately offered. Who's opting in, and who's opting out?

The cost per net health benefit measurements, what kind of qualitative measures of choice are there,

et cetera? The evaluations of genetics competency of health professionals, which we all know is a struggle since the genetic levels keep increasing exponentially, and primary care physicians have enough on their plate at this point in time. And then population-based studies for other conditions, and are we going to do community-based research?

The other meeting was in '06, and it was the Genetic Carrier Screening: Moving Population Genetics from Theory to Practice. They came to the conclusion that we need standardization of criteria for how we're going to select these tests. We need to understand the burden and natural history of each condition, inheritance, carrier frequency, and genotype-phenotype correlations, which could be argued that we still have problems with that with the newborn screening disorders.

Fundamental questions about the performance of tests and how to follow up must be considered. And reading these results can be a trial for a clinical geneticist. So lab report and lab reporting are also another big issue.

They thought that in light of the success of CF carrier screening, a similar model could be adopted for SMA -- spinal muscular atrophy -- carrier screening in the future. They looked at the Jewish population and thought that maybe they need to expand the carrier screening in that population beyond that population and look for models of earlier preconception or childhood

screening should be undertaken and funded. But again, it's getting to the grassroots and getting to the community-based organizations.

They had suggestions to improve care for newborn screening tests that are incidental findings in carrier status. So for sickle cell trait, the results must become part of all students' health records. The mandatory nature of newborn screening can put certain populations at a disadvantage, and they noted the Latino population. So counseling is very important, and education in a broad sense is a cornerstone.

Case law analyses have been very good at protecting against genetic discrimination, but we're still not really sure what kind of duty to disclose we have. And it's very important to seek input from both

professionals and community members. Bottom line is deciding which conditions should be added and when is difficult at best.

So here is my outline. I have been not very proactive at this point in time. I've done a literature review. I'm waiting for the sickle cell trait group to finish their preliminary

recommendations, using that as the kernel from which to build this task force on. I would like to get your feedback and -- about this proposal today, and then I'm going to present to the other Secretary's Advisory Committee in June.

I have a list of interested people who would like to be on this task force, and if I haven't contact you and you want to be on the task force, feel free to give me your name. You probably will end up working, though. And we're going to have our first core group meeting, which will probably be via telephone, and then we'll develop writing groups based on very broad topic areas.

So what do I know? Some work has been done previously, and some populations have been very, very

successful. There is no model for true population-based carrier screening, and there are many issues and probably no right answers to all of them.

Thank you. And this is just so you don't have to come up with -- this is what I'm asking for, but it doesn't need to be done right now.

DR. HOWELL: Thank you very much, Sara.

The last fall meeting at the National Institutes of Health that was convened by three institutes, including NICHD, had a meeting on carrier screening for spinal muscular atrophy. And one of the comments that came out of that meeting was the fact that there was no active group at a national level looking at carrier screening, and a request was made to this group to consider that. And certainly, it's within our purview and our bylaws and so forth.

I met with -- in view of the fact that this is a very broad issue, I had met earlier with the Secretary's Advisory Committee on Genetics, Health, and Society, and they were very interested in this and wrote back that they would like to participate in a joint working group. And this is the group that Sara

was speaking about today that would come up with some issues.

It's been very interesting. This was a very successful meeting at the NIH last year talking about spinal muscular atrophy. It has been very interesting as the group that convened that meeting has been working aggressively to do a report of the meeting, and

there are folks that are very enthusiastic about screening and some that thinks it shouldn't be done. And so, it's interesting to try to come up with a report of the meeting and the perception of that group. But I think that at this point in time, it is moving along.

So I think that's the background against which this is done. And obviously, I think that this group is very much aware of the very old Tay Sachs carrier screening program that's been extremely effective in identifying carrier Tay Sachs disease such that we rarely see infants in the Ashkenazi community who have Tay Sachs disease at this point.

So that's -- if you look at one potential outcome, that's the other. And then, obviously, the

other extensive experience has been in cystic fibrosis.

And again, those have been always offered, and they've been families -- have been parents who have chosen if that's what they would like to do. But they basically have been offered, and they have also been rather than a public health program, like we have in newborn screening, it's been a selective group that's been

identified and so forth.

But I wonder if there are comments for Sara as she moves along with this working group to address some of these issues. It seems we have several. We'll start with Alan, and then we'll go to then Mike.

DR. FLEISCHMAN: Sara, this was a really terrific tour de force here of all of the issues. Two thoughts. One, I had the opportunity to learn at the conference that Rod mentioned on spinal muscular atrophy, and I think it's extremely important to separate out the potential for carrier screening and newborn screening from the general issue of carrier screening at other times, like in preconception or prenatal care.

And I think that the more that we can

separate that and, in fact, keep clear the

distinctions, the better off we'll be in this work.

And I would ask a question -- and by the way, I would

volunteer to be on that group. And I'm sorry I'm

saying that publicly.

[Laughter.]

DR. FLEISCHMAN: But I would ask a question.

Could you tell us a little more about the practices in newborn screening when incidental findings of carrier status occur? What actually is happening these days with that practice?

DR. COPELAND: It depends on where you're born, and it depends on the State. Our Genetics Services Branch has funded several newborn screening and hemoglobinopathy newborn screening consortia. And those, we're working on improving the counseling with the community-based organizations. But at this point in time, there is no universal responsibility, and that's just on the hemoglobinopathy traits.

For cystic fibrosis, it's another issue entirely, and whether or not genetic counseling is ever done outside of the brief -- outside of the brief

counseling they get in the cystic fibrosis clinic when they're confirmed to be a carrier is a different issue entirely. So there is not a lot of uniformity around it, and it's something that needs to be improved markedly.

DR. HOWELL: I think that there -- obviously, as Sara points out, there are tremendous variation in,

number one, whether or not persons are advised of their carrier state. And obviously, if advised, what happens to it? I think if you've seen one State, you've seen one State, frankly, et cetera. Brad?

Before we go to Mike, let's ask Brad because he had looked at this particular question.

DR. THERRELL: Right. And actually, at a national level, we discussed hemoglobinopathy screening results a number of years ago and had parents come to the meeting and so on. And the general consensus at the meeting was that those carrier results should be reported out by newborn screening programs, and they are.

All the programs report back, but they report back to the physician or the hospital. Now what

happens after that is the question.

The other thing is that 2 years ago or 3 years ago, the Texas legislature introduced a law to require sickle trait screening as part of the Texas program. It failed, but the department went ahead anyway and implemented it as part of the rules. So Texas is the only program that I'm aware of that

mandates sickle carrier screening as part of their newborn screening program, and they've been doing that for a couple of years.

It didn't really change anything in the program except that now they inform the parents of those children by letter that they've been detected, and they should seek counseling.

DR. HOWELL: Thank you very much.

Mike, you were the next in the queue here.

DR. SKEELS: Just I don't think that -- am I turned on here? Maybe not. The little light is green. Okay, thanks.

I don't think your committee's work is complicated enough. So I want to throw in a couple of other ideas.

DR. COPELAND: Oh, good.

[Laughter.]

DR. SKEELS: First of all, this relates to what both Alan and Brad just said, but those of us who are operating newborn screening programs do so at the direction of State legislators, and they tell us what we're authorized to do and what we're not. And right

now, if you look at the laws, they almost all talk about disease and disorders. And if you have an ancillary finding of a carrier, then, of course, you can report is and you should, and so on and so forth.

But it would take a fundamental change in the laws of probably 50 States for us to be authorized to explicitly look for asymptomatic carrier status. So that's not a trivial issue, and it's something that I hope your task force will at least survey, at least look and see how many State laws are inclusive enough to allow us to do this intentionally rather than incidentally, as you said.

And then here's something that's totally out of left field, but now that I know that this is going to be a collaborative effort that goes beyond just the

mandate of this committee, I hope someone will look at the Clinical Laboratory Improvement Amendments, which are used to license or actually certify laboratories in the United States, to see whether the definition of a clinical laboratory under CLIA is broad enough to cover the direct consumer testing that's being done and other things.

Because if you look at that statute, it's all about diagnosis, treatment, and assessment of health of individuals, and I don't think that just doing, looking for specific sequences or just for your information you're a carrier probably meets that definition. And that's a really big deal for medical laboratory practice.

DR. COPELAND: Gee, that's -- sure, we'll do that.

DR. HOWELL: Becky?

DR. BUCKLEY: Is this on?

DR. HOWELL: Yes, I think so. Could you get a little closer?

DR. BUCKLEY: In the beginning, you mentioned carrier detection for autosomal defects. Are you not

going to include X-linked defects?

DR. COPELAND: I was going through examples of possible forms of carrier screening. But if we're doing carrier screening, there's no reason why we wouldn't do X-linked.

DR. BUCKLEY: Okay. Because in immune disorders, many of them are X-linked. In fact, they're

far more common than the autosomal recessive, and some of these are subtle in the offspring. So I think it's certainly important to include those as well.

DR. COPELAND: Yes. The X-linked disorders add a whole other spectrum to the disorders, but definitely something to consider.

DR. HOWELL: It makes the follow-up so intriguing and so forth, particularly in very large North Carolina families.

[Laughter.]

DR. HOWELL: Piero?

DR. RINALDO: Sara, I agree with some comments made already that, clearly, the newborn screening world and the individual testing should really split very early in this process because I

cannot see how you could have a single set of recommendations. I'm wondering, though, at what point you will start talking about how you do it. Because in your presentation, carrier screening is presented as somewhat uniform approach at the analytical level.

But are you going for $1,000 genome? Are you going for panels of mutations? Are you going for exome

sequencing? The granularity of how it could be done and the cost and the residual risk vary quite dramatically. So that, to me, is an equally important question among the ones you included. So I think it should really be added to that list about the mean of doing it.

DR. COPELAND: Exactly. And I think it gets to also just who you're testing as well. Because if you're looking at a specific ethnic population, and you know there's a founder effect, then you may just do single mutation. But in other cases, it may be very different. And I think that's a whole working writing group.

DR. HOWELL: Sara, have you considered the possibility of adding some of the groups that are for-

profit that are offering wide-scale carrier screenings using chip technologies?

DR. COPELAND: Adding?

DR. HOWELL: To your working group?

DR. COPELAND: That is a very good idea.

DR. HOWELL: It might be very interesting.

Obviously, these folks are in a brave new world, and

certainly, they have passionate opinions about the value of their technology and carrier detection. And I realize that's a little bit outside of what we usually do. But the point is it seems to me it would be appropriate to at least think about this and consider the possibility at least in having these folks come and present to the committee about their position, and of course, they're using chip technology, as Piero has alluded to.

Chris?

DR. KUS: Sara, in your review, did you find guidelines as to what to do when you detect a carrier state from a newborn screening program?

DR. COPELAND: Oh, no.

DR. KUS: Okay. Just -- yes.

DR. HOWELL: Jerry?

DR. VOCKLEY: Not that we spend a lot of time worrying about reality on this committee, but we've had a hard enough time coming to grips with the cost of adding tests to the newborn screen, where we're unequivocally identifying diseases where at least we hope we have some impact on treatment and outcome. And

so, I'm a little worried that this ends up diverting attention, if not resources, from an area where there is potential for relatively immediate impact on outcome to something that's very much broader.

Now I think we have to recognize that this is an issue that's going to present itself. You know, I'm not saying we can ignore it. But I also want to be very careful about how we put any sort of findings or recommendations out there because I do worry it could distract from newborn screening and end up being somewhat detrimental in the short run.

DR. HOWELL: Denise, you had a comment about that?

DR. DOUGHERTY: Yes, I think it's related because what I didn't see in the concerns that came out

from those meetings was this concern about evidence base and how in the world you would do systematic evidence reviews here. But I did see it come up in the informed consent slide that you showed, that there is -- there's a lot of uncertainty here.

So I'm sure it will come up when you test for SCIDs together, and it may actually help with these

private purveyors of tests to really be clear to include as part of your plan having a plan for looking at the evidence base for doing the screening.

DR. RINALDO: One more comment. Sara, it just occurred to me, though, that there is one aspect of newborn screening where every day we are screening and detecting carriers, and that is this issue of in maternal cases and how it's growing to a point of at least almost a dozen of the conditions in the ACMG panel now of known newborn screening results stem from a primary defect in the mother. So you are reporting a carrier.

So I think it's also something somewhat to explore about giving some thoughts and guidelines about how to deal with that. Because my impression is that

the way these cases are dealt with vary quite a bit from State to State.

DR. HOWELL: Ned?

DR. CALONGE: At some point, you're going to have to face this. Maybe you've already figured that out, and maybe I shouldn't even open my mouth. But there is this really tough challenge of defining

termination as a health outcome, and I will tell you, experientially, it was more difficult under the last administration. And so, there are issues that I think the committee is really going to have to wrestle with in terms of what is a very important part of the decision process in why you do carrier screening and the other screenings you've talked about and how you're going to describe that particular endpoint as a health outcome will be a challenge.

I'd like to tell you I have the answer, but I don't. And I just think you're going to have to recognize that as you talked about the costs and the health benefits and those issues, you're going to have to wrestle with that definition.

DR. COPELAND: Definitely.

DR. HOWELL: Coleen?

DR. BOYLE: I was going to just follow up on that comment, as well as the comment that Rod made in his introduction, the fact that the Secretary's Advisory Committee on Genetics -- and I can never remember the name of it.

[Laughter.]

DR. BOYLE: Is actually obviously also dealing with these types of issues, and I guess in your recommendation, I was a little surprised that it was this committee that's taking on this issue versus a sort of a workshop that really straddles both of the committees since what you're tackling clearly goes well beyond newborn screening.

DR. COPELAND: My slide for that presentation will have SACGHS to convene.

DR. HOWELL: But it will clearly be a joint effort between the two committees.

DR. BOYLE: I think that's totally appropriate then. Thanks.

DR. COPELAND: Yes.

DR. HOWELL: KOF, you had a comment?

DR. FREMPONG: I just wanted to say that, I mean, for now decades, of course, getting results of your sickle status as a part of newborn screening has been in existence, and different States report them differently. There has always been implication, I think, in trying to get to the families to inform them about that information is either we use that

information for reproductive planning, for themselves as parents to get screened and to see whether they're at risk for producing a child with sickle cell disease.

In this country, unlike not a few other countries, there is no plan to prevent sickle cell disease as a public health policy. But as we know, some European Mediterranean countries -- probably most notably Cyprus is probably the most "efficient," and now also I think Italy -- aggressively want to reduce the number of babies born with severe beta-thalassemia. And so, their carrier screening is not mandatory, per se, but is almost required of people who are getting married.

Now in both places, and more especially so in Italy, they actually tried pre-pregnancy counseling to

see whether -- or premarital counseling to see whether people will make choices in terms of partners for marriage and eventual childbearing, and that failed. Their prevention programs only worked when they introduced prenatal diagnosis and offer for termination of affected pregnancies. That's where their so-called success in reducing the number of births actually has

been seen.

We just recently heard about the experience in Bahrain as related to sickle cell disease, where, again, they claim it's not mandatory, but, in fact, now it's expected that all young people who are seeking their parental, family approval for marriage actually get screened or show evidence of screening or they have been screened before, that that's taken into consideration in their counseling.

So I don't know. When people suggest carrier screening, certainly as related to sickle cell disease, I think there's a feeling that this information is useful for reproductive planning, even though nobody has really carefully looked to see whether it ever really gets used for that purpose. But I think by

implication, even those who are involved in nondirective counseling are surprised when somebody who is counseled, a family that is counseled goes ahead and they have a child with sickle cell disease.

It's almost as if something failed. So, by implication, the idea is that you would take that into consideration, and you will prevent the birth of

children without stating so.

DR. HOWELL: Mike?

DR. WATSON: I think KOF has captured the clinical intervention piece of this nicely, and it's important to keep in mind. So I would encourage you, I think, to not just talk about this list of conditions. Piero mentioned technologies, but I think the critical thing is the markers by which one detects those conditions and the predictive capability around those in many of the diseases in a lot of screening programs are miserable.

And that's the backend side of what that clinical intervention step really is, is that if we're making very poor predictions, then it's going to be a disaster. So I would highlight the markers that relate

to those conditions that are going to be screened.

DR. HOWELL: Are there further comments?

Sara, could you go back to your charge slide?

DR. COPELAND: My charge slide.

DR. HOWELL: Comment from the microphone

while you were getting to the charge.

MS. FOX: Michelle Fox --

DR. HOWELL: Can you pull that microphone down so that it will be closer to you? Thank you.

MS. FOX: Sure. Michelle Fox from the National Society of Genetic Counselors.

I so appreciate how complicated this all is, but if we look at the experience of screening for cystic fibrosis, now the recommendation from ACOG that couples should be apprised of this and screened and we bring it up in our genetic counseling sessions. And when couples understand that it is part of newborn screening, as it is in many States, they are very comfortable with that and not wanting to go forward with carrier screening.

And so, how complicated this is where we say we're going to separate it out, but we are facing the

fact that it is merging together.

DR. HOWELL: This is the charge to this workgroup, and can we have any comments about that as they proceed? Sara has already talked about that. Would you agree with that in general? It's a rather general charge, et cetera, and I think that the comment that Michelle made is that if you have a condition for

which there is an extremely effective newborn identification and treatment, obviously, the interest in carrier screening will diminish, I would assume, considerably.

Alan?

DR. FLEISCHMAN: Well, I'll defer to Coleen.

DR. BOYLE: I was just going to make the recommendation that we change it to -- that this would be sort of co-managed or co-chaired by this advisory committee and the SACGHS.

DR. HOWELL: We would certainly anticipate that. But let's make that specific.

DR. BOYLE: Okay.

DR. HOWELL: Okay. Certainly, it's anticipated it would be a joint committee, and I think

that having a co-chair would be a very good idea.

Any further comments? Mike?

DR. WATSON: Just one last comment. As much as we'd like to separate newborn screening from carrier screening, newborn screening is the ultimate carrier screening test. It identifies two carrier parents. So it doesn't separate out all that easily, and I think

there is plenty of evidence in the incidence of cystic fibrosis around the country that suggests that newborn screening has been used in that way.

DR. HOWELL: Mike?

DR. SKEELS: I don't know if this is helpful or harmful, but I'm still stuck on the word "disorder" because just for the CFTR protein, there are, what, 1,300 or 1,400 different known variants, right? So is every one of those a carrier/disorder?

I mean, where I'm going with this is we're rapidly going to get to the point where we quit talking about disorders and we quit talking about carriers for disorders, and we're just going to talk about gene sequences. We're just going to talk about letters, right? And what's holding us back is we don't have the

clinical correlation to be able to do that.

So I guess I'm just asking sort of a scope question here. Is this task force going to deal only with carrier status, meaning it's one of maybe several mutations, which when both copies are present leads to a disorder? I saw your definition on the first slide. I mean, is that the narrowness of this? And if so, I

think that's great. But I'm just worried that we don't know what "disorder" means.

DR. HOWELL: Would you have a different word?

DR. SKEELS: Well, I don't know. If you use "variant," that's probably too broad. I'm not really sure. I'm just trying to understand because this could go cosmic on you really fast.

DR. COPELAND: Well, one thing I really want to make clear is we're not going to establish a panel that we think should be screened for.

DR. SKEELS: Yes, I'm thinking much more broadly than that.

DR. COPELAND: Right. And so, just maybe criteria for looking at what disorders might be introduced to a panel, much like what this group has

done for evidence review.

DR. SKEELS: Criteria for what a disorder is

--

DR. COPELAND: I'm sorry. I'm coming at this from the medical terminology, and that's how we use it in genetics. It could be gene sequence. I wouldn't use "variant" because there are a lot of variants of

uncertain significance, and benign variants.

So variant is different as well, and I think we're looking at disorders, carriers for disorders, known gene mutations that cause impact on outcomes of health. So carriers have one copy of a known deleterious mutation would be, but I don't know how to put that in a slide.

DR. RINALDO: Can you call them clinically validated or clinically significant variants?

DR. SKEELS: Yes, that's good.

DR. HOWELL: Our newest member has wisdom at the microphone. Jeff?

DR. BOTKIN: Jeff Botkin from the University of Utah.

This has been a very helpful discussion,

certainly for me. But I guess I want to comment on the stunningly broad charge that this slide illustrates.

[Laughter.]

DR. COPELAND: How do you think I felt?

DR. BOTKIN: And I guess part of my comment would be or the point of my comment would be to say that this discussion and in the briefing book really

illustrates some large gaps in the literature with respect to carrier screening. In particular, how it is that clinicians respond to this information, how they convey it to their families that they're involved with, and then how people respond to the information.

And having looked at this issue a couple of years ago, it seemed to me that there was a significant absence of literature on how people actually use this information in reproductive decisions or whether they use it. So one of the outcomes for the working group might well be to focus on or articulate the significant gaps in research that would be necessary to fill in order to make carrier screening, in order to have a foundation for making recommendations about different types of carrier screening.

DR. HOWELL: Thank you, Jeff.

There are persons here from the Secretary's Advisory Committee on Genetics, Health, and Society. I wonder if anybody here would like to comment?

I knew Cathy would have a word to say.

DR. FOMOUS: Cathy Fomous from the Secretary's Advisory Committee on Genetics, Health, and

Society, from the staff. If you have specific questions, I'd be happy to respond.

But I will say, as Rod mentioned, that the committee has expressed enormous interest at its February meeting in this topic area. They're waiting for the presentation in June to make a formal decision on whether to go along with the proposal and have this joint task force. But there was enormous interest in the topic area.

DR. HOWELL: This was the morning of the great Washington snow, and everybody stayed and attended. So that was impressive.

Thank you, Cathy, very much.

We had two other folks who were listed as public commenters in the carriers thing, and the first

we had was Andrea Williams from the Children's Sickle Cell Foundation. Andrea, are you here? Here she comes.

MS. WILLIAMS: Good morning.

One of the comments that I have for Sara is that the targeting ethnically, I don't know where I would fit in because I have about five different ethnic

backgrounds. So that might be something that might get a little hairy.

But to the chair and members of the committee, I'm grateful for another opportunity to address you with my comments today. We have heard a lot about sickle cell trait carriers and athletics, and as we continue to discuss the recommendations within the scope of the committee, I offer that we keep a bigger picture in mind with regard to sickle cell trait carriers.

This committee has made great strides with regard to the newborn screening program. Your commitment to maintaining balance and focus is observed as you work with the subcommittees to bring about the best possible recommendations. It is with that same

tenacity and strength that we need you to address the overarching issues with regard to sickle cell trait.

There are a growing number of teens and young adults who have been identified as sickle cell trait carriers via the newborn screening program who may not know their sickle cell trait status despite the work of quality short-term follow-up programs. I work with

such a program from the University of Pittsburgh Medical Center and Children's Hospital of Pittsburgh. I work with these families, and I hear their concerns over the phone when I'm talking with them and doing the follow-up and asking them, "What will you do with this information?"

Their concerns are, "How will I remember? What do I do with it for all these years until my child is a teenager?" So I gently remind them to put it in their baby book, try to keep it with their immunizations, and try to give Children's Hospital a call if they remember and they can't quite remember what the result was.

It seems a logical -- some of these newborn screening follow-up programs just lack the resources to

get back to the families and to revisit them at the time that they would need this information most. It seems a logical next step for the committee to consider adding sickle cell trait as a secondary condition under sickle cell disease and to establish a comprehensive long-term follow-up program initiative or initiatives supported with resources from various organizations

that would address the overall needs of the child with sickle cell trait that have been identified previously by the newborn screening program.

This program would address the overall needs of the child and include information on general health, athletic, and genetic information to be offered to the parent at birth and to the teen as they transition into adulthood. It is my hope as a mother of four, two children with the sickle cell trait and one with sickle cell disease, that you will take the necessary steps to ensure that this information gets to those persons who need it most when they need it most. This can be another example of how the newborn screening program can work to universally save lives.

Respectfully submitted. Thank you.

DR. HOWELL: Thank you very much, Andrea.

Now we also had Maria Levine from the March of Dimes that had signed up in the public comment. Is she here? Well, apparently not at the current time. Maybe she will reappear later, and we can hear from her.

We are running ahead of schedule, which is

always a great problem to have. So what we're going to do is we're going to break now, and we'll return in about 20 minutes and stay ahead of the game. That will put us at just a little after 10:30 a.m.

Thank you very much.

[Break.]

DR. HOWELL: Professor Botkin and Professor Steele, if you will find a seat? Excellent.

A number of folks have had difficulty in hearing in the back of the room. It's a sizable room. So can I encourage everybody, the microphones are quite good, but please speak very closely in the microphone.

We're now -- the next session we have a lot of information to share. And we're going to hear a

variety of activities that are in health information exchange within the newborn screening. We're going to hear from the co-chairs of our Health Information Technology Workgroup, which is Dr. Alan Zuckerman and Ms. Sharon Terry.

And as you remember, the committee recommended the formation of a specific health

information technology workgroup that would coordinate the committee's activities in this key area. And today, Alan and Sharon are going to present the draft charge for this workgroup for the committee's approval and also discuss some proposed activities.

Alan, are you going first?

DR. ZUCKERMAN: Yes.

DR. HOWELL: Okay. Alan Zuckerman is going to lead off, and then Sharon will come in. And they co-chair this Health Information Technology Workgroup.

DR. ZUCKERMAN: First of all, we want to thank the advisory committee for giving us this opportunity to make information technology a regular part of your activities. What we're going to do this morning, the group is now in formation. We've actually

met twice to work on this presentation. I want to share with you some of our charge goals and our membership, clarify any confusion about the relationship of the workgroup to the existing subcommittees, and then Sharon is going to give you some highlights of external events we think have created some exciting immediate opportunities to deploy

information technology in newborn screening.

We also feel that the time is right to move forward with a recommendation on monitoring the implementation at the States of HL7 lab messaging. And we've pulled together a series of additional projects that we'd like your input on as we choose what our first projects will be.

The charge that's been proposed is to advise the advisory committee and its subcommittees on opportunities to use health information technology, systems, and standards to facilitate the exchange and use of newborn screening information.

And our goals are to bring forward recommendations and reports and best practices for implementing systems and standards in newborn screening

that the advisory committee can deliberate on and, if approved, distribute to appropriate agencies and programs, such as the groups you will be hearing about during this session, but in addition to that, to the State newborn screening programs and work through the Association of Public Health Laboratories.

We also want to ensure that the products

coming forward from this committee and its subcommittees and workgroups, including special projects such as those on quality measures, are in line with current information technology standards that are being defined by the Secretary.

We also hope to bring forward recommendations on the monitoring of the adoption and implementation of those standards and their application to newborn screening. Because having standards sit on paper does nothing if they're not out in use, and we need to understand both that they are being used but also begin to address some of the barriers to adoption of standards.

We will be meeting in conjunction with the advisory committee three times a year and doing most of

our work by phone. We will schedule our meetings, the first of which is tonight at 5:30 p.m., so it doesn't conflict with the other subcommittees so we can participate fully in their activities.

The membership that's been proposed includes liaison representatives from each of the three subcommittees, as well as our chairs and staff. We've

recruited a significant number of Federal partners, including different groups within CDC and exciting participation from CMS and AHRQ. But our biggest focus is on our State and professional society partners, and so we've identified a number of individuals working in State programs, as well as in other societies.

It's of interest to note that the American Academy of Pediatrics has just formed a child health informatics center. Its first medical director, Chris Lehmann, will be on our call tonight, and he's also been named to an HIT advisory committee at NQF. We also hope to involve some of the educators and counselors in this.

And we've also identified some information technology experts, including representatives from the

major vendors in this field, and we feel it's important that we partner with the vendors and obtain their input, as well as working with our partners in the State laboratories. And we also hope to involve the National Institute of Standards and Technology in our work.

Again, our goal is to help the existing

subcommittees implement their work and not to try to duplicate or compete with them on identifying content, but to primarily advise on methods and implementation. We've already had conversations with the leadership in each of those groups and identified a few areas of information technology needs that fit with what they're currently doing, and there will, of course, be ongoing needs to develop new vocabulary and coding guidance as new tests are introduced and as we begin to examine the difference between initial screening, confirmatory testing, and the types of things such as carrier screening that might be done on different populations at different times.

Now I want to give Sharon opportunity to clue you in on some other events that are happening in the

Federal landscape.

MS. TERRY: Great. Thanks, Alan.

And I'm going to go through these very quickly because we really want to leave time for conversation, discussion at the end.

A number of things are happening, of course, in the overall environment around this, around us. For

example, the growth in HL7 laboratory result message supported by EHR certification criteria is converging on common standards in the use of LOINC codes.

CMS is going to develop quality measure standards -- quality measures for newborn screening for use in 2013, meaningful use around EHR regulations. CMS and AHRQ are already developing a model EHR format for children under CHIP-RA. The Nationwide Health Information Network, including Project CONNECT and CONNECT Direct and funding for various State HIEs, should also include newborn screening.

And the ARRA/HITECH Act, et cetera, has increased attention to public health informatics and immunizations. So attention to children and vulnerable populations should absolutely be included there.

So all these activities are happening. They're roaring ahead. We're really concerned that newborn screening stay integrated as it moves forward and that we're ready to give guidance to these projects.

DR. ZUCKERMAN: And one of the important ongoing roles of the workgroup will be to pay attention

to the HIT Standards Committee and the HIT Policy Committee that are advising the Office of National Coordinator and the Secretary. And we will have representation within the workgroup from both of these groups, and this will give us an opportunity to give this committee updates on other standards that are being set.

What we would like to introduce now is a proposal that you consider a recommendation today on introducing the monitoring of the implementation of HL7 lab result messages as one of our first activities. We would like you to endorse the concept of monitoring the State use and compliance with the existing HRSA/NLM-developed guidelines for coding, terminology, and electronic messaging in newborn screening.

The reason we bring it forward now is that the HL7 lab result messages for incorporating results into EHR will become part of the meaningful use certification, and this is the way to get newborn screening results into lifetime electronic health records. We also want people to appreciate that the existing guidance is not set in stone, and we want

States to come forward, request changes and additions, to be sure that the standards will accommodate their needs.

We also would like you to ask us to come back in September with additional detailed proposal for what we should begin collecting in January to see what the States are doing or planning to do. And we think that informing the States of the activities of other States will be very important, which is why we want to see this happen.

Just to give you a few examples of what we hope to bring forward at your next meeting, we'd like to report much of this data by percentages of hospitals or providers, as well as live births, to look at the use of LOINC codes, look at the reporting of

quantitative results, and hopefully move towards some uniform datasets on clinical data collected when newborn screening is ordered.

And one of the reasons to do such things now, if you think back on your sickle cell discussion, the way to get sickle cell results permanently connected to a birth certificate would be to have HL7 messages. But

if the State labs aren't producing them, then the birth certificate can record that newborn screening is done, but 10, 15, 20 years from now, we won't be able to go back into that type of database to get information out.

The same way that we hope that these will become part of individual personal health records and of electronic health records in both hospitals, ambulatory settings, and contribute to building medical homes for children identified through newborn screening.

Well, that's the first of our proposed projects. In addition, we'd like you to consider charging us with expanding the coding and terminology to include screening for new conditions, such as the lysosomal disorders and SCIDs and for the confirmatory

testing, which now will be including genetic testing and which will often be done on specimens other than dried blood spots. There is a lot of work in progress on initiating confirmed case reports to trigger long-term follow-up, and we'd like to have some input to messaging formats and coding standards there.

We know that quality measures are beginning

to go forward for newborn screening, and we'd like to participate in a process that will make these accessible. And we need to move quickly because the regulations that will go into effect in 2013 will be formulated in the next 6 to 12 months most likely.

We also would like to consider integration of newborn screening data with birth certificates, both in terms of linkage that the screening was done, but potentially the linkage of the data that was collected.

At the recent APHL symposium on newborn screening, one of the main concerns of the States is that after the initial screening, they're not hearing back from providers about the results of confirmatory testing on hearing, metabolic testing, and other things. So they're unable to give accurate statements

of what the significance of those initial screens were, and we'd like to begin exploring mechanisms for using information technology to improve the collection of data on follow-up.

There are a series of other projects that we're considering that have come out of our discussions with the subgroups. We're listing them here on the

slide and would again like to see if any of them are of pressing interest at the committee.

But what we need most of all from you today is input and affirmation of our charge and goals and our approach to building the membership. Final roster will be ready soon for circulation.

In response to these external events in technology that have created opportunities, we'd like you to charge us to move forward with the recommendation on monitoring the adoption and implementation of HL7 messages at the States, and we'd like to get some input on some of the other proposed activities for the upcoming year that we've set before you.

Thank you.

DR. HOWELL: Thank you very much, Alan and Sharon.

Are there questions or comments for our presenters?

Tom?

DR. MUSCI: Yes. One thing that occurs to me is that I didn't see anywhere on that list of

participants someone from the prenatal care provider perspective. The reason I bring that up is I realize this has to do with screening results, but in fact, patients often come back for their postpartum visit, and the prenatal care provider has no idea that there was a positive screen.

And that's for one thing. And secondly, it's a perfect opportunity to begin the discussion about identification of the carriers. We talked about carrier screening earlier. So I don't know if there's a way to think about that in terms of this particular workgroup, closing the loop and bringing the prenatal care provider back into it, essentially is where it started. Supposedly the discussion about newborn screening should begin in the prenatal visit prior to

delivery.

And it's always a problem when after the delivery, the obstetrician's job sort of ends, but then the patient really thinks about their obstetrician or their prenatal care provider as their medical home. So I think somehow linking that back would be a very useful, overall high-level service.

DR. ZUCKERMAN: I totally agree with you on that, and this is something we do want to address. In fact, some of us are already engaged in these activities. At Integrating the Healthcare Enterprise, there are activities going on jointly to look at the ACOG ante partum records, and labor and delivery records, newborn discharge summaries, their postpartum summaries. And there is a perinatal workflow that's being developed, will be going out for public comment soon. And we certainly can and should consider providing feedback.

Hopefully, these confirmed case reports and some of the standard newborn screening reports could be circulated to a broader range of providers. And we will definitely take that into account, and we will

also come back to you with suggestions on a member to participate in the workgroup.

Thank you.

DR. HOWELL: Alan, do you have the support to do what you have recommended as far as getting the work done?

DR. ZUCKERMAN: Well, I think a lot of work

will take place in other venues and will be dependent on others. The development of quality measures is underway elsewhere. A lot has been invested in different projects, but I think we'll have a better idea in September, once we begin looking at some of the projects and see how much of the work we need to do, how much our role will be to pull together work and standards that are under development to come back here for dissemination and approval.

So, at least at this point, I don't think we need additional resources.

DR. HOWELL: So you think that there probably is enough to at least get the thing going. Is that correct?

DR. ZUCKERMAN: Yes.

DR. HOWELL: Sharon doesn't seem to be quite as confident.

MS. TERRY: I think this is another full-time job on top of our full-time jobs. I think that's the right answer. I also think that to get started is fine, and then we really should think about a bidirectionality here. There is an opportunity for

newborn screening to be recognized for the excellent public health system that it is and to be integrated into these absolutely wonderful things that are coming out of the Office of the National Coordinator, et cetera.

And on the other hand, it's the perfect test for a lot of the things that the nation is trying to do because it is so well organized, compared to other systems at least. So I think we're going to want to say what is the opportunity, and how do we want to rise to the occasion? And I suspect we're going to find that we're going to need resources to do that.

DR. HOWELL: Well, I would assume, however, with your auspicious position in this whole system that you can help steer resources this way. Is that

correct?

MS. TERRY: I will do my best.

DR. HOWELL: Good. We don't want to put you on the spot, but we'll expect you to do that.

DR. ZUCKERMAN: And one of the people who will advise us will be Lee Stevens, representing the Office of National Coordinator, who's working with

States and their health information exchange and other funding. And again, the main request we get from States is funding to implement technology, and we're very eager to help facilitate that, identify sources, and we will, hopefully, in September be able to come back with an initial look at the HL7 lab messaging, the kind of resources that would be needed to roll it out in the community, as well as what we might need to continue supporting that effort.

DR. HOWELL: Mike, does the National Coordinating Center have any role in trying to get information back to the States as far as confirmatory diagnostic studies that Alan mentioned that -- because the State labs commonly don't know what happens to the patient. Is there a way of that? What?

DR. WATSON: Yes. That's what I get to talk about next.

DR. HOWELL: Okay. We'll wait to hear from you.

Chris, you have words?

DR. KUS: Just do you have any comments about how you might monitor the HL7 messaging, or is that too

early where you want the workforce to look at that?

DR. ZUCKERMAN: Well, no. In terms of how, we are already collecting data through the National Newborn Screening Information System, through other surveys. HRSA has a number of grantees and projects we hope will expand. And NIST may also play an interesting role in that as they begin to develop conformance testing tools for all laboratory work. So we think engaging the State public health labs, other labs that are doing the newborn screening work is very important.

But we also feel this can't be an annual survey. We need to monitor more frequently than annually, and we need to get some substantive detail on not only are people doing it, but are they doing it

right, and are people using it? Is it getting the results to the necessary providers, including, of course, the prenatal providers, as well as the health departments.

DR. HOWELL: Further comments or questions of Alan?

Oh, Nancy?

DR. GREEN: Hi. Nancy Green from Columbia.

So I'm certainly impressed with the work that you've done, Alan, and I want to give you a little taste from the ground of the meaningful use issue. So New York State -- this gets back to the carrier screening results and the link to medical records.

So New York State communicates the newborn screening results to our hospitals electronically. Those go into the electronic medical record -- not, unfortunately, the prenatal or perinatal, but newborn record. And as part of our HRSA-funded project, we have surveyed a couple hundred primary care providers about whether they actually check the newborn screening results from when they're looking at these newborns in clinic.

And this is a couple of different hospitals, a couple of primary care, family practice, and pediatrics, and the answer is no. They don't. You're not shocked, right? That fewer than 30 percent routinely check the newborn screening results, even in a newborn clinic follow-up setting.

So when you think about meaningful use, I

don't have a solution for that other than some sort of yet another annoying pop-up. But please keep that in mind.

DR. ZUCKERMAN: Yes, I'm very familiar with that issue still being out in primary care practice, needing to follow that. Some of the proposed standards will involve documentation in the record that these results have been checked and that any appropriate follow-up has been initiated, and this is part of a general issue in follow-up in labs that JCAHO and other groups are looking at.

And again, one of our concerns is the role of the hospitals because newborn screening results often come back to the hospital after discharge, and we would like to see progress in that area of an obligation on

those who order the tests to follow up on them. But the key to making meaningful use work is to document that things not only have happened, but have been reviewed and to need to report back on a practice-level basis that newborn screening results have been examined within 30 days is one of the proposed standards.

DR. LLOYD-PURYEAR: Chris and Coleen and I

and others just had a meeting with National Center for Quality Assurance, and this speaks to what Nancy just said. They also surveyed medical records, and ordinary pediatricians, it was around 30 percent. The QuIIN network, however, was it 70 percent, 90 percent?

Seventy percent, yes, between 70 and 90 percent. So the attention to newborn screening results is not impressive.

DR. GELESKE: If I could just say, Michele, on that, there is a QuIIN project now, a joint project with the AAP and ACMG to try to implement some tools and get that out there, and that's likely to lead to an EQIPP module. EQIPP is a quality improvement program that the AAP sponsors for members to receive their maintenance of certification.

So as that gets out there, everyone is going to have to every 7 years re-up for their certification. So, hopefully, that will get some dissemination that way.

DR. HOWELL: Thank you.

Roger, you had a comment?

DR. EATON: Alan, I was trying to look

quickly at the membership list. Is there somebody on there who has a particular perspective of compliance with privacy regulations on the committee?

DR. ZUCKERMAN: We actually don't have an individual identified yet, but that is one of our concerns, and I think --

DR. EATON: It might be a good idea at least to consider that because these are two parallel efforts that sometimes collide. And to have somebody -- you know, if this is a workgroup of this committee, to have somebody with that perspective on the committee just to remind of that perspective, it might be a good idea just to consider that.

DR. ZUCKERMAN: Yes, we now have a national privacy officer, and one of the issues that States

often talk to us about when getting hospitals to report back are misperceptions about privacy and role of HIPAA. So we do want to include that in some of our activities. Again, I haven't heard much about specific activities. But certainly, almost everything will engage privacy.

MS. TERRY: And Roger, I'm on the HIT

standards group, and I'm also -- this is Sharon. And I'm also on the privacy and security workgroup for the HIT standards group. We spend a lot of time working on that. I have a senior counsel who is, in fact, here. Ann Waldo, who is a privacy expert. So we'll begin fusing all of that in as well.

DR. HOWELL: The committee needs to look at the charge to your group. Can you back up, and let's look at the charge? And I'm not suggesting that we vote on this -- there we are. But is the group comfortable with the charge to this committee? It's a fairly broad charge and so forth, and you've heard what they're doing. Is the group comfortable? Can we nod yes and so forth? I don't want to go through a vote. Just nod yes.

It looks like the group is quite comfortable with that, or else they're nodding asleep. But anyway --

[Laughter.]

DR. HOWELL: Thank you very much. And so, we'll expect you back in September with some early results from your work and so forth. Thank you very

much, Sharon and Alan.

DR. ZUCKERMAN: Okay. Does that constitute endorsement for coming forward with a report on the HL7 monitoring?

DR. HOWELL: Yes. That constitutes -- I mean, there were much nodding around the table. I think that constitutes.

MS. TERRY: This specific thing is important, too, that we get the charge to go ahead with the HL7 as our first project.

DR. HOWELL: Yes. Yes, I think that that's implicit to move ahead with the HL7 as your first project.

MS. TERRY: Great. Thank you.

DR. HOWELL: Thank you very much, and so

forth.

We are now going to hear from Dr. Mike Watson, who is going to present some work from the National Coordinating Center and the Newborn Screening Translational Research Network and how they've worked to standardize datasets for long-term follow-up.

And also, at the break, you had two brochures

put at your place from the National Collaborating Center, properly called the NCC Collaborator.

Mike?

DR. WATSON: And thank you, Rod.

Well, I've spoken about this project before. And as I think everybody knows, it is a contract that has certain obligations attached to it. So we're actually quite well into this -- at least I was into the right slide set for a minute.

Ah, it went backwards. Okay. So, yes, many of the activities I'm going to talk about are activities that have been going on, actually, for a year to 2 to 3 years under two different Federal agencies. It was obviously, actually, from the point where we proposed a uniform panel for newborn screening

that our evidence bases around genetic disease in general were miserable and that we really needed to organize our efforts to bring patient information together to better understand the genetic diseases that may or may not be candidates for newborn screening.

And I think some of that is evidenced in the recent request for proposals that came out of NICHD for

studies to really take advantage of some of the resources being developed to better understand the natural and clinical history. I hate natural history. I'll go with clinical history because nothing is natural once a doctor gets his hands on it. It's all a clinical history after that point.

So we're very much interested in facilitating the development of the clinical histories of these diseases. And it's an enormous problem because the vast majority of things that are candidates or are in newborn screening are very rare diseases with even rarer, ultra rare subtypes, be they mutation subtypes or other ways of classifying subsets of patients within individual diseases.

There is also significant population genetic

variation in the diseases themselves, in the locus itself, in the heterogeneity, in the ways people can muck up a gene, and then the genetic backgrounds on which those genes are acting all contributed to additional variation, which requires really that we pull this stuff together at a national and even an international level to acquire enough patients to be

well informed about what these diseases and subtypes of these diseases actually do mean. And to be able to pull that off, data and data systems and their compatibility are the fundamental key issue we have to face.

Now, as I said, to Federal agencies have been engaged in this activity for a while now. HRSA funded the National Coordinating Center for the Regional Genetics and Newborn Screening Collaboratives. The collaboratives themselves have been doing priority projects since 2007 to really begin to look at acquiring long-term follow-up information on patients, both information at the point of diagnosis and information on treatment and follow-up over time of the patients who are identified in the newborn screening

programs.

One project was engaged by the New England regional collaborative through the Massachusetts newborn screening program. That's very much a State-based model and at its focus has been obviously then conditions already part of newborn screening. Region 4 has been -- through Sue Berry has been involved in a

project that's using diagnosis of management at the provider side of the equation to pull this information together into databases, into data warehouses that hold identifiable, deidentified, and anonymous data as appropriate to the particular data type.

The Southeast regional collaborative has also been looking at dietary interventions and following patients that are identified and placed on dietary interventions and monitoring their progress and follow-up.

More recently, the NICHD has funded the Newborn Screening Translational Research Network for which we have been given the contract as the coordinating center. Its focus is on the development of resources and an infrastructure to support long-term

research and development related to newborn screening

and not just conditions in newborn screening, but

conditions that are candidates for newborn screening to

both facilitate our knowledge of those things that are

part of newborn screening, but also to have an adequate

evidence base when public health has to make decisions

about conditions and whether they are appropriate for

inclusion and addition into newborn screening programs.

And that's why the candidate conditions become a very important part of this project. The major area of focus, at least as relates to long-term follow-up of the Translational Research Network is to develop resources and an infrastructure to support long-term research and development. We have already established a newborn screening laboratory network that is rather loosely defined right now. It's defined as a workgroup.

But I think as one begins to look at the enormously variable conditions that are part of newborn screening, you can see that different States become involved as networks in some groups of conditions. Different clinical provider groups become involved at

different points. So we have clinical centers, networks, and committees, but as individual diseases come in and partner with us to use our resources, we end up with very different practice groups in some of the areas in which we're involved.

Obviously, informatics strongly underlies the infrastructure that we're developing, much of which

we're developing is modeled around the NCI's cancer biomedical informatics grid and sort of the ideal that that presents, but not something that we are ready to build from the top down, as NCI did. It only cost them I think around $200 million at this point.

We're building from the bottom up in a very modular way with that ideal in mind, but looking at how we develop the specific infrastructure around things like LSD screening or a particular disease that's already part of newborn screening and what the tools are that are really needed to support that kind of activity. And we have related legal, statistical, clinical trials activity, and ethical guidance within our Translational Research Network workgroups.

Now, as I said, the regional collaboratives

have been focused on the conditions of newborn screening. Right now, we're beginning to segue over to working with the individual States to determine the type and level of detail of information that we collect at the point of care of a physician and a patient in diagnosis and follow-up, and what aspects of that information and what level of that information needs to

be provided back to States so that they actually have an understanding at some level of the outcome of a patient who is identified in their program, which can inform them as an evaluation tool.

There is a subset of conditions in newborn screening, organic acidurias, where speed is really critical, and moving people through the system to diagnosis, intervention is very much more important than it might be in other areas. So there are some sort of sentinel areas that can be very informative about the efficiency of a program and its ability to move a patient through the system. Others where it's less important as a sort of speed issue, but very important for understanding the diseases.

And so, we have a workgroup that Amy Brower

has been working with in the individual States and will be meeting, I believe, in the next couple of months to start looking at the kind of data we're collecting, which I'll give you more information on shortly. But how that information can be translated into something useful for the State programs. And we're expanding this to all of the regional collaboratives to the

extent that they wish to become involved.

The Newborn Screening Translational Research Network itself is focused on the infrastructure that supports the conditions already in newborn screening and our ability to bring that data together centrally, but also becomes much more centrally active around some of the pilot studies. We don't expect that to be a long-term situation where we're, more or less, driving the coordination of activity. But as RFAs and other grants, as Alan talked about earlier, come out, opportunities to partner with us to use our infrastructure and resources should become the predominant mechanism by which the NBSTRN is used.

But because we have to do pilots to test the systems we're building, we're much more aggressively

and actively involved in some of the pilot studies that are developing around the country.

This gets a mind of its own every now and then. Okay. So we've established a standing committee for the NBSTRN. There are now 12 workgroups functioning on different aspects of the development of the Translational Research Network. We're building and

testing its infrastructure. We have a Web site that I'll show you towards the end and its Web address. IT infrastructure options and designs are under consideration and actually become a bit variable from condition to condition and the partnerships you develop in working around a particular condition. There are ones where the CTSAs, the Clinical and Translational Science Award Network is much more actively involved. They are also developing some of their own infrastructure and tools.

Others where the regional collaboratives in metabolic disease have been really taking the lead, where we have a lot of activity already. We have a policy workgroup looking at a lot of the issues that we're facing, both in the development of electronic

medical records and the privacy issues associated with the information on patients and how that's brought together and protected.

And then we're about to engage in some coordination of the SCID and the lysosomal storage disease pilots. The LSD group will be meeting, I believe, around the end of June to start hammering out

some of the protocols by which we'll be involved in those pilot studies.

We've put a lot of effort into beginning to define the clinical information that's useful, and what we've found was that there was obviously a lot of interest in many Federal agencies in this information and somewhat independent and divergent at times activities toward building the infrastructure by which this information is collected. So as sort of a self-fulfilling prophecy exercise, we went -- we have identified about 88 data points now that one acquires at the point of care that could be very informative to the outcomes and assessments of patients.

And what we found was that some agencies were interested in surveillance from an epi perspective,

other in the public health system itself, others in patient care, and NIH, obviously, interested in new knowledge generation. We did an exercise of really surveying all these disparate groups to find out where they felt that any individual data point fell within these four groups. Surprisingly, almost all of the data points were of interest to everybody, which we

hoped argued that working together to collaborate on the development of a system was the preferred way to approach this particular infrastructure development project.

So, as I said, 88 data elements have been developed. They've been placed into 24 categories of data, including demographic information about patients, socioeconomic status, family history, prenatal history, newborn screening information, emergency management -- all things that are acquired in the traditional patient-physician process of providing care. And because that is the point at which so much of this data develops, we place a lot of interest and effort in identifying tools that facilitate our ability to bring data up from that particular point.

If you have to go into going back into files and bringing data into databases secondarily, you begin to get a lot of drop-off of patients in order to get as many as possible involved. Obviously through consented processes for so many of these types of studies, getting people into the similar kinds of data systems and evolving that point of care tool is critical.

Our committees have been very active. We have probably nine States now who have representatives to our various committees. There are 16 individuals representing various of the State newborn screening programs involved in our different committees, and more are being engaged every day.

This group met -- I was out of the country last Thursday and Friday while the clinical centers group was meeting to take all of this dataset material to the next level. What we found was that as we looked at the data for each individual condition, that about 80 percent of all data points were in common among all the diseases of newborn screening, things like demographics, socioeconomic status, have you been to the hospital recently, all were in common across all

conditions.

But about 20 percent of the dataset points are disease specific. They could be enzymology that's specific to a disease, molecular information, other kinds of biochemical analyte testing that might be very specific to a condition. And those are the ones that we have in pretty good form already for the metabolic

diseases and have workgroups in hemoglobinopathies and endocrinopathies now working on bringing those conditions up to the same level.

Fortunately, these give us a good starting point for the pilots that we're about to engage in on LSDs and SCID because we have this sort of uniform set of information now that we can build on for the disease-specific components of those conditions because those fundamentally become the protocol by which one will be following these patients. They define the critical data points or the minimum dataset. They also define many other less critical points that are part of the information acquired at the point of care.

And these have been meetings of 45 to 50 people each time out. So we've gotten a number of

additional data elements recommended by others who have been participating in these activities.

So on the emerging side, I've alluded to the fact that we're engaging now on the pilots. The Severe Combined Immunodeficiency disorders, I think, is a bit more straightforward. I don't have huge concerns about that's rolling out into newborn screening programs.

It's relatively straightforward, a highly sensitive assay.

The lysosomal storage disorders didn't give me that same warm, fuzzy feeling. Of the five that are about to roll into newborn screening, two are somewhat concerning -- Fabry and Gaucher -- in a significant proportion of adult onset patients that will be identified in those newborn screening programs. So we thought it very important that we have a controlled and organized system into which these pilots are functioning so all programs that are participating get feedback from other States and other programs about what's going on so that we can collaborate and share that information and minimize problems that might occur.

We're also supporting the developing of new technologies for their use of newborn screening. This is another set of projects and one that Alan Guttmacher described earlier around new technology development. We've been working with the Mayo Clinic, where Dieter Matern has been looking at a couple of competing technologies that could be used in newborn screening

for lysosomal disorders, recently have partnered them with Applied Liquid Logic that has a microfluidic system that Illinois apparently is considering using as its screening tool.

We wanted to bring it together so that all these technologies were being compared against one another in a much more uniform way to identify that which is most appropriate and applicable to newborn screening for this group of disorders.

Our next steps are at the meeting that will take place in June -- at least on the LSD side, we're setting up the SCID meetings now -- will be to go to those disease-specific aspects of those LSDs that will constitute the valuable information for understanding outcome and for really acquiring that clinical history

information about these disorders.

Tied to this whole dataset activity is having

defined all of these datasets, we are now in the

position of beginning to do the language

standardization in LOINC and SNOMED and other systems

that allows these to then be at least data that's very

compatible around which HL7 will then facilitate

communication across systems.

We're certainly looking at some difficult areas. Enzymology is typically done on substrates that are handmade, sort of typical laboratory-developed tests, and how we develop the standards and the reference ranges around which we compare laboratory results is going to be a little bit different than I think has been the case of most areas of laboratory medicine.

We'll be looking at where data is being held. There is certainly a lot of activity at the individual State level, with the States interested in holding as primary holders of follow-up data information about the patients that have been identified in newborn screening.

But given our interest in this candidate condition issue around newborn screening, we think that a hybrid model of where that data is held primarily or shared from a primary source is probably a likely outcome. No State will probably ever have adequate information to inform clinical history individually. So figuring out how to pull this together from

obviously data that's very important at the State level into something that can be aggregated nationally and internationally would be increasingly important.

The Web site for the NBSTRN, this is its homepage. You can find it at www.nbstrn.org.

And on that, I'll say thank you. Both of these projects, they're obviously independently funded, but they're doing very similar kinds of things, which is my nightmare when it comes to auditing. But I think we've worked our way through that, and we're grateful for the funding that has recognized this fairly important area for both genetics and newborn screening to be moved forward.

Thank you.

DR. HOWELL: Thank you very much, Mike.

Are there questions of Mike about the coordinating center and the Translational Research Network?

DR. WATSON: So Coleen has one.

DR. HOWELL: Coleen has a question.

DR. BOYLE: Just, actually two. One quick question is I guess I'm looking at your slide, and this

is not the quick question. This is the longer question. The pilot studies. Are they sort of virtual pilot studies, or are you actually going to have data as part of that?

DR. WATSON: No. We're actually engaging experts in the diseases to develop the datasets that are appropriate for each of the conditions, which fundamentally define a protocol of data that will be collected around that disorder.

DR. BOYLE: Right. So are you going to be collecting information on newly screened, for example, for SCID.

DR. WATSON: That is our ultimate goal. We have to have the tools in place to do it, obviously. Once we define the datasets and the protocols, we're in

a position centrally to bring the data into the databases as needed if we don't have the distributed tools that allow it to be captured at the point of care.

DR. BOYLE: I understand that. I was just trying to define what the pilot study was.

DR. WATSON: Yes?

MS. TERRY: Oh, I was just going to -- I just want to clarify that the SCID study is a separate contract that's funded by the NICHD that Ken Pass is the PI on and that NBSTRN is helping to coordinate the data collection and the management. They're helping to find the subjects and bring them all together. That's how it's working on that project.

DR. BOYLE: You're developing the infrastructure, but there's not really any data that's being inputted yet.

DR. WATSON: Well, the regional collaboratives are very actively collecting data. Region 4 has vast amounts of data now on conditions in newborn screening. I wouldn't be at all surprised if as a lysosomal storage disorder pilot evolves, that

those groups that already have data systems in place for capturing that diagnosis and follow-up information that they won't integrate into the tools they've already developed.

We're partnered in that process with the Lysosomal Disease Network that is another NIH-funded, Office of Rare Disease funded activity of a large

number of individuals interested in research and management in the clinical care of LSD patients.

DR. BOYLE: Okay. My quick question was once you start to enroll children, families into this network, will there be a consent process?

DR. WATSON: This is central. This is local. This, I expect, will function as all of our long-term follow-up projects have. At the point of diagnosis when a patient identified as screen positive newborn screening goes to a provider who is going to be the one directly collecting the information on diagnosis and follow-up, they will be offered the opportunity to have that data captured and brought into these datasets with information about the obvious protections that have to be put into place around what is identifiable to that

provider that's in those databases, what is deidentified to others participating in that particular disorder, and what is anonymized but might be used for surveillance and other types of activities.

DR. HOWELL: Jeff?

DR. BOTKIN: I think it's hard to overstate how important this is and exciting. I guess my

question sort of follows up on Coleen's to a certain extent in that I'm uncertain about how the clinical nodes of the network are going to work. It sounds like, at this point, most of the research aspect involves data collection and observational research about outcomes for various conditions.

But I think, as you had stated with one of your first points, that the real strength of the network down the road is going to be the ability to standardize investigational interventions for the kids and compare interventions across the network, very much like the children's oncology group sort of format.

Health departments really aren't research organizations. And so, how do you see the clinical nodes working down the road to be able to do that

comparative effectiveness type of research, and are these academic medical centers? Is the CTSA network going to be involved with this down the road?

DR. WATSON: I expect so. I think certainly on the metabolic disease side, those patients typically end up in the academic medical center environment, as do many of the patients with something like SCID. You

move into congenital hypothyroidism, you know, you don't need a geneticist for that one. And other hemoglobinopathies are, many of these conditions are in the primary care environment more than they are in the specialist environment.

We're talking to the AAP about how to engage the PROS network -- they're Pediatric Research in the Office Setting group -- into bringing data together on patients that are more likely to be really taken care of on the front lines of primary care. I think one of the premises we went into this project with was that to have that imprimatur of research placed on newborn screening and State programs had the potential for limiting the potential participation of as many people as possible in newborn screening.

We didn't want people running off worried that research was being done on them. So we've started with what I'll say is a bias, which is that much of the research will be secondary. After a screen positive is found, they move into the diagnosis and follow-up side of newborn screening programs. And it's at that stage where they'll be engaged in the potential to either be

recontacted should opportunities for clinical trials of new therapeutics develop around a condition they might be diagnosed with or around the collection of their clinical information to inform improvement in care and in understanding of these diseases.

DR. HOWELL: Becky? Can you get closer?

DR. BUCKLEY: With regard to the SCID pilot, are you involving the Primary Immune Deficiency Treatment Consortium? Do you want to tell us about it?

DR. WATSON: Yes, I do. This is full-blown chaos, frankly. We started with Krabbe disease in New York. The North American Pediatric Transplantation Network has been very actively involved in the follow-up meetings and outcome meetings around Krabbe disease. But it's going to be the same people in SCID as well,

to some extent.

So, yes, we're beginning to talk to them. It's now coordinating these disparate activities that arose independently. Krabbe, because New York was screening for it and needed to be tracking long-term follow-up. The other four just LSDs because several States, Illinois and Missouri, have mandated that they

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be added to their programs.

So as each of these shoes drop, you find something else that you're trying to coordinate into a collaborative activity to ensure that we get the most information we can out of this exercise and protect patients as well as possible as we do this work.

DR. BUCKLEY: Well, the reason I asked about the PIDTC consortium is that their goals are similar to the ones that you list on your slide, and this group is hoping to identify all SCIDs that are born in the United States, be able to follow-up and find out what happens to them.

DR. WATSON: Yes. No, the one thing that is guaranteed in this is that one of the most interesting scientific or clinical translational questions of the

day is what the human genome means. And we're engaging it around newborn screening, which brings lots of other groups who weren't so shortsighted as to not see that as the clear next step in understanding what the human genome sequence around the genes involved in their disease actually means to phenotype.

So they're popping up all over the place. We

engage them, and we try to work towards collaboration with them as we go so that we aren't going in different directions, but trying to build systems that are compatible.

I think one of the major rate limiting steps and why we have such a miserable evidence base today is that you cannot build these IT and informatics system for every one of the 5,000 or so rare genetic diseases that are out there. So to build a central structure that allows people to take advantage of the infrastructure is really what that cancer cooperative study group model did.

And I think we want to -- we're trying to make sure that we're talking to everybody else involved. Whether they choose to collaborate or not is

another question, but we're certainly making them aware of our interest, the tools we're developing and the tools they're developing, and how we can ensure their compatibility over time.

DR. HOWELL: Mike, thank you very much. I think that by all means continue to talk with Mike. But obviously, there will be a tremendous amount of

networking because the identified patients will historically move into the networks they have been in the past.

Thank you very much.

Under the Newborn Screening Saves Lives Act, which governs the oversight of this committee, HRSA has established a Newborn Screening Clearinghouse. This act indicates that this clearinghouse will maintain current data and quality indicators to measure performance of newborn screening, such as false positive rates and other quality indicators as determined by the advisory committee under Section 1111.

This section indicates the various quality indicators that the committee is expected to report on.

As you recall, the bill has very specific requirements for this committee to do, and we're to report on long-term case management outcome; minimum standards and related policies and procedures used by State newborn screening programs; standardization of case definitions and names of disorders for which newborn screening tests are performed; quality assurance, oversight, and

evaluation of State newborn screening programs; identification of the causes of and the public health impacts of, the risk factors in heritable disorders; coordination of surveillance activities, including standardization of data collection and reporting, harmonization of laboratory definitions of heritable disorders and testing results, and confirmatory testing and verification of positive results. A small, little menu that we'll be reporting on.

With these requirements in mind, the HRSA staff has begun assessment of the current National Newborn Screening Information System housed at the Newborn Screening and Genetic Resource Center. And next, Sharon will continue her forte at the podium, and she'll be joined by Amy Brower, who will report on the

results of two assessment activities.

The first is the Assessment of Newborn Screening Programs Data Information System and a report from the Newborn Screening Clearinghouse meeting, Information and Data Collection for Newborn Screening: A National Approach.

Sharon?

MS. TERRY: Great. So I'll go first, and then Amy can go second.

I'm going to report on a meeting that we had last week in Orlando as part of the American Public Health -- Association of Public Health Labs, APHL. Sorry. I'm with Mike, newly back from Paris yesterday on what came out to be a 15-hour flight.

I want to point out that I am speaking as the PI of the National Newborn Screening Clearinghouse. We convened a meeting with HRSA to talk about data issues that are indicated in the act, as Rod just mentioned.

And so, the agenda for this meeting was set by HRSA, APHL, NLM and others, and Genetic Alliance over several months prior to the meeting. It was a special meeting of the Association of Public Health

Laboratories. It was on May 6th in Orlando. It was the afternoon of the final day. Remarkably, we had about 130 people present, mostly APHL members, although a couple of other people did join us, about 13 others. And the APHL members, of course, were from the State newborn screening programs and the regional collaboratives.

I convened this meeting with HRSA and did it as an exercise in understanding what do we need to know from the stakeholders, and this is one group of stakeholders around data for the newborn screening system overall in a very broad way. So the goals were to begin what will be at least a year long and perhaps longer to determine by HRSA process of collecting information for HRSA on the needs of a data system for the nation.

Our goals were to listen and understand the various States' models around data and systems in projects, the needs of the State programs, the needs of the other stakeholders, the easy solutions that already exist that we should be implementing either in newborn screening or in other technology solutions, and the

difficult interfaces between health information technology, health information exchange, and other efforts, describe to the APHL members that were there some of the external activities in data collection, storage, and use, and to report back to this committee.

Essentially, what we did for the afternoon was do a series of very brief presentations. The

Newborn Screening Clearinghouse was presented, although, again, this is not an activity within the Newborn Screening Clearinghouse. The data portion will not be within it. The NNSIS was presented by Brad Therrell and Walter from Natus. Sorry, I'm really not -- Mike told me that by now I would not be talking very well.

And then we moved on to the survey that you'll see from Amy today the results of, and then also a series of presentations from the States and/or vendors around model projects in the States. And now what I'm going to show you instead of any kind of recap of those kinds of presentations is essentially what happened during this meeting in terms of hearing from the stakeholders.

So, essentially, this was a town meeting. Alaina Harris was there from HRSA, and she and I listened to the people in that meeting, and they gave us results. This is a word cloud that we created during the meeting that evolved over the course of the meeting. The word clouds allow you to see what kinds of terms were being used over and over. It's hardly a

scientific method, but it just gives you a flavor of the kinds of things that emerge as important things during the meeting.

So, first, I'm going to show you a series of concerns, and then I'm going to give you some recommendations. Concerns, and again, these are not -- I've not distilled these perfectly. We've not brought them back to the planning committee. There wasn't time. And we do need to do all that. We will be putting out a very official report in the sense of distilling everything. But this, again, is a draft report to give you a flavor of what happened.

Are the indicators collected today by NNSIS suitable for the emergence of HIT? There is no consensus on the definition of disease or out of range,

preference by some States to default to "as defined by" and usually a local specialist. If there are common definitions, concerns about who makes the decision to set those standards.

Shouldn't the coding and terminology guide be made mandatory? Shouldn't it be made voluntary? So we have certainly divergent opinions galore, as you can

imagine.

Will standards drive today's program activities for the sake of the standards or some sense that maybe the standards are becoming the standard and not the actual clinical activities? How will the States be compared if the data is collected? And it already is, and how are they already compared?

The newborn screening system is split between or amongst HRSA and CDC with little coordination was a concern. Not only does each State decide what it wants to measure and how, but sometimes one individual within the State decides, and that was one individual within a State expressing concern that she is or he is the one.

And then, a quote, "We are moving in one direction, putting money into special projects, and for

example, HL7, but will we have to start all over when national policies change again?" So a sense of are we just being jerked around, and there will be new things coming down the pike again?

Will State newborn screening programs be required to report to, and then you can fill in the blank, many systems, multiple times, over and over?

One person described it as will we have to have multiple hoses coming from our program into multiple systems? Will those systems not talk to each other? Will there be multiple ways that information is looked at? Will it dice and slice things so that we're saying one thing with the data here and another thing with the data here? Lots of concern around that.

Concern that the State newborn screening programs can't expand the newborn screening program workload beyond their capacity and that many of them feel beyond capacity already, and there is not resources to do this. And finally, concern that we not make this a shame-on-you data collection system.

So, again, there were many more concerns, and those may be not the most critical ones. They were

certainly the ones we kind of heard over and over and were important, I think.

There was also some concerns about Amy's survey, and I thought Amy was going before me. So I was going to put these up because I don't think these are reflected in Amy's notes. But essentially, the concern from the State not so much about the survey

itself, but why weren't the States engaged more in taking the survey, and Amy will be giving you those results, trying to understand how do we get the data out of the States to actually drive our decisions with real data.

So the recommendations that, again, came up throughout this meeting. It would be useful to have reports organized by, and you can pick again, States, diseases, screens so that these comparisons can be made. It's true that some of this already exists in NNSIS, and Brad talked about that. But that in some cases, States don't know how to do that, or they want canned reports for it.

There were suggestions that you simply push State program data to a collection center without

onerous manual labor. Again, vendors were present who talked about that's already possible. We've seen hearing screening in the U.S. accelerate because vendors have been involved in a really dynamic and innovative way, and maybe the newborn screening system needs that as well.

And compare what States are already tracking

for with their own needs with the data track by NNSIS, again harmonizing if I'm tracking for this, shouldn't I also be reporting here and not having two separate systems or more than two? Ask other stakeholders besides the State programs how are they using data so that the data is collected that is meaningful and that leads to, for example, meaningful use, et cetera.

Understand the importance of standardization, that there is a forum that's needed to allow the State programs to discuss, for example, units of measurement, seasonal variations, again some kind of enhancing the data in context.

Give State newborn screening programs guidances and definition. There was some concern that there's a lot being asked, but that the national level

policymakers aren't asking clearly enough, nor giving guidelines and mandates more specifically.

Gather all data, available data now to elucidate cutoffs, definitions, standards, problems. And it's better to have all this come from real data and not ideal systems. So once we see the data, see how messy data is, then what would emerge as problems,

issues, et cetera. We all have sort of a sense of that, but there was a request there, really, to say what if we did start to collect this now and understand, let the data talk, essentially.

Encourage the vendors to work with one another and the States that don't use the vendors, but create their own programs and HIT infrastructure to create customizable programs with interoperability and a standards basis. So a real desire to save some money here and not create 51 separate programs that then operate in many different ways.

ARRA and HITECH funding has happened for infectious diseases, and that there is already interoperability, interaction with HIEs in some States. Why aren't we seeing that kind of ARRA funding for

newborn screening? So, and that might be to Rod's point about that I should be advocating for money.

And then learn from the infectious disease systems world overall that there, in fact, are some good public health pieces there that could be applied.

My meta comments, and these are mine. I didn't have time to harmonize them with Alaina, though

she didn't protest greatly that I put these up here, that there is familiar stresses here that State programs serving State needs and a national agenda always have stress. And I think we should not think that this is unusual, but, in fact, figure out ways to alleviate that stress and actually use other systems that, in fact, already deal with that stress.

That there's a tsunami of HIT infrastructure changes, needs, et cetera, that are not being felt yet at the State level on one hand and certainly are being felt on the other hand. But I think that's only going to increase. That resources need to be carefully evaluated and capitalized on. There is not unlimited funds, but in some cases, there is not enough funds. In other cases, maybe there could be better

reorientation.

Care coordination is most critical to States, and it's complex across many systems. And we touched upon that several times here this morning already. And that families, essentially babies, need the best. And so, if we keep that focus, what happens when we ask that?

And then, so these are some, a few slides of things that this committee might consider. They are in no hierarchical order. They don't belong necessarily to just data collection. But I wanted to give you everything that I heard that I think maybe you should think about.

Positioning the newborn screening system as prime example of HIT for the nation; recommending mandatory use of coding and terminology, the guide; examining inefficiencies in the disparate national system. Some of that is a lack of coordination from the Federal agencies. Other places, it's because these health information technology systems don't talk to each other. Highlighting exemplary programs in this disparate national system and propagating those

programs outward.

Enabling interstate cooperation, collaboration. Instead of competition, figuring out what are the incentives to have that happen. Stronger and clearer national mandates. Incentivizing the vendors and the State systems to create technologies that enable HIE that is platform agnostic, but

interoperable, and I could explain that more if we need to go into that.

Establishing more of the elements needed for standardization and rolling those out. Utilizing the capability of the current system to automatically deliver data now.

And that is all.

DR. HOWELL: Thank you very much, Sharon.

Are there questions or comments of Sharon? Obviously, newborn screening is certainly a place to start with electronic records, as obviously every person born in the country is in the system, and it's the first medical record, really, the physical examination. So it's a great place to start.

Jane, you had a comment?

DR. GETCHELL: I have so many comments.

[Laughter.]

DR. GETCHELL: I mean, I am trying to understand the whole relationship of all these disparate information technology networks and systems. In my ideal world, I think you said it right. A record would begin at birth. It would go into what I'm

envisioning as the health information exchange.

Our newborn screening lab data would ultimately end there. The physicians' notes, observations would end there. We could query this health information exchange for whatever information was needed. I don't know if that's -- is that where we're headed?

DR. HOWELL: Sharon?

DR. GETCHELL: Like interstate could access that HIE, even though, as I understand it, it is a State-owned thing? I just would like to know where we're going with all this, and I'm kind of confused right now.

MS. TERRY: Yes. And so, I think a lot of people are confused, Jane. So I don't think that's

unusual. I think there is a vision for this, and I think some of it's coming out of the Office of the National Coordinator. Certainly, Michele has been leading some of it for HRSA. There is individuals at CDC that have been working on it. Clem McDonald at NLM has been working on it.

And so, the vision is beginning. There are

simple, tiny pieces of this like the HL7 messaging that our workgroup wanted to take on because they are absolutely critical to the rest. There is a lot of problems, though, and that is that there is a lot of disparate systems already.

It's less confusing in newborn screening than it is in a lot of other medical informatics kinds of places. So I think this is still a really good place to start.

I think one of the things this committee could do is say exactly what you just said in the sense of understanding Michele, ONC, NLM, et cetera's vision, which has been a really collaborative one with a lot of input, and say to the nation and to the Secretary, we really need to have that first piece of health

information exchange happen this way with this kind of rollout with the integration of these systems, whether they be hospitals, care providers, et cetera. I think it's going to take strong leadership, and I think that's the kind of thing that this committee can certainly articulate.

DR. HOWELL: Well, I think that's something

that many people feel would be a very worthwhile goal is to have that as the first, starting from electronic record and have -- it obviously begins at the State, but have it available throughout the country. We have a variety of comments down here.

MS. TERRY: And just before you go that, but one of the remarkable things, again, sitting on the HIT Standards Committee, and they didn't even have newborn screening on their radar screen at all when they were rolling out what meaningful use meant, et cetera. So I brought that to them, and they still were like looking kind of puzzled, saying wouldn't it be better to do this at the hospice care end or palliative care end or not understanding, I don't think, that this is a really ripe system because it's been a kind of quiet system in

the sense that it operates under the radar, and people don't pay a lot of attention to it.

So I think that the rest of the world doesn't understand what we understand here, and we need to articulate that more clearly.

DR. HOWELL: Jerry?

DR. VOCKLEY: I'm not a newborn screener, nor

do I play one on TV. But I come at this from the level of the care providers, and so I'm worried about what I would call a trickle-down effect, except that I think it's going to be more like a tsunami.

And that is that, you know, you're asking Sharon if she's got money to do what she needs to do, and she's asking States if they have money to do what they need to do. And in the end, we have all of this new data collection requirements, and they hit the care providers. We have to keep in mind that there is no built-in capacity in most medical offices, in most inborn error clinics, in most genetics departments to be able to provide time to enter this kind of data.

So I think we just have to really be very careful as we promulgate these recommendations. And

hopefully build these systems, which are unquestionably going to be very helpful if we can actually collect the data. So there are going to have to be foot soldiers in this process, not just the infrastructure.

MS. TERRY: And there is some incentive money going to each physician singly, which is quite remarkable, from the Federal system to roll out EMR.

So there will be something there.

I think you're also right, though. But I think if we look at, again, the future as in 5, 10 years from now, and things like I think Mike mentioned Liquid Logic with their iPhone-size bedside newborn screening device that takes the drop of blood from the heel of the baby, does the analysis, and this gets beamed to the electronic medical record instantly. So the recordkeeping is so much less.

I know that there's a big, big leap between there and there. I mean, I had the experience of going to a Kaiser doctor, even though I'm in the Blue Cross Blue Shield, and the trouble that he had putting the stuff in the electronic record and never looking at me because he couldn't really type --

[Laughter.]

MS. TERRY: -- was significant. And I get that there's going to be lag time there, but I hope that we figure out some ways to make that easier for you.

DR. VOCKLEY: Yes, and it's not just saying how are we going to get the record information from the

bedside to the computer, which is critical. But there is the process that's involved in that because you've got to capture the intellectual input at the level of the care centers that go into the follow-up on what you're doing. So it's not just a drop of blood, and it's not just a lab result. It's ultimately if we don't know what's happened to that child, all of that information is useless.

And that's where I think we're in trouble at this point because there may be some incentives to go to -- move to an EMR, but that doesn't hit most of where a lot of this is going to occur, which is at our care centers because most of them are already involved in electric medical record. And if there's money that's going to them anyway, it's to the institution.

There is a dam on the end of that trickle that blocks it from getting to the care providers.

DR. HOWELL: Tracy wants to comment about that briefly.

DR. TROTTER: Just a slight addendum. Most primary care people are not involved with electronic medical record. It's no more than 20 percent of

private offices. So we've got a long ways to go just to get that involved before we put any data in.

DR. HOWELL: Clem McDonald is here, and he has the answers to all the questions you might ask.

[Laughter.]

DR. MCDONALD: Well, I wanted to really respond to the first question about where we're going. And I think the honest answer is that there's not enough fixed in stone in terms of systems that are working and successful that we can predict one way or the other. But I think that the idea of the interchanges would be almost the perfect one because it would be so efficient and easy to do. But there are only three or four of them that are really running full blast.

The NHIN CONNECT project is a promising other thing that could help either the HIEs or in point-to-point communication with some software. But a key thing in all of this, I think we really ought to be desperately careful not to create hundreds of little systems within a doctor's office. It just won't happen. It won't work.

We have to develop systems that people can embed in and the interface is the interface of their system, not the interface of the other system. So I think the questions is a very good one to keep our eyes on sort of some coherence in where we're going, and I want to -- I always -- I loved Sharon's presentation. Just these word pictures and everything. So thank you, Sharon. You nicely summarized a lot of difficult things.

DR. HOWELL: Rebecca?

DR. BUCKLEY: Yes. The other thing that I would like to add to the difficulties that Jerry has already outlined is this issue of informed consent and HIPAA and local IRBs. Because if you're going to have informed consent for the clinical information to go

into this, then you're going to have to have local IRBs or institutional IRBs approving all of this.

MS. TERRY: And we completely agree with that, and we think it's going to put a pressure on the system. And in fact, we have a project with the American Society of Human Genetics and PRIM&R to look exactly at that kind of question with the onslaught of

health information technology and what will happen.

And the other interesting pilot project is one in Michigan with the Michigan Biotrust and a company called Private Access that we've been working with quite a lot to actually ask what if we do this consent, but it's dynamic. It's portable. It's electronic. You're able to carry it with you, and you can change your mind as you go through a system over time. And consenting parents first and then children when they're age of assent or consent.

DR. HOWELL: Well, Sharon, I think that it's clear that there are many, many roadblocks in this effort and so forth. But I still think that the idea of trying to focus on newborn screening as the first entry point and as a prime suspect for electronic

medical records and so forth nationally is a wonderful place, and I think we ought to push that.

MS. TERRY: And I would say again to you and to the committee that your -- some strong statement of leadership around that would make a real difference because I think the rest of the nation's health information technology structures are not paying

attention to newborn screening as much as they need to.

DR. HOWELL: As we move along, perhaps you can help us form some commentary that would speak to that.

MS. TERRY: Sure.

DR. HOWELL: Because I would enthusiastically support that.

We better move. We're getting close to lunch. So we need to stay on schedule at this point and so forth.

But we have Dr. Amy Brower, who is going to talk about her survey of the State newborn screening program. And of course, Amy comes from the National Coordinating Center for the regional collaboratives.

Amy?

DR. BROWER: I like this mike. This is cool.

DR. HOWELL: Yes, that's right.

DR. BROWER: Yes, hi. I know. It's great.

Later tonight, right?

So, hi, everybody. I'm going to take you

back into the weeds a little bit. As Sharon and

everybody said previously, health information

technology is poised to impact all of our lives, and what we wanted to do was take a little break and talk to the key stakeholders in the State newborn screening programs and hear what they've been doing for over two decades.

So for two decades, information about newborn screening programs has been collected, and it's primarily been through the NNSIS. So we did a little survey on the NNSIS. This is just a reminder of what the NNSIS was or is and the data elements that are part of that. This was provided this morning by Dr. Brad Therrell, who is in the audience. So we just wanted to remind the committee members of sort of the scope of what the current NNSIS is.

So it's a listing of program contacts,

laboratory, and follow-up. Every State has two contacts in general, and those are included in the database, and then there is different information related to newborn screening that's collected in this online database.

This is more about the data elements that are included in the NNSIS, which is online, and you can

look at later at your leisure. We have a lot of data to get through. So I just wanted to provide this as a reminder of the scope of the current NNSIS.

So what we wanted to do with the survey was to plan for the future expansion of this type of national information system. This was drafted, the survey, by a team of many stakeholders from HRSA, NICHD, Genetic Alliance, NNS, GRC, CDC, APHL, ACMG representatives from both of the coordinating centers, and selected newborn screening programs. So we really wanted to create a broad survey and assess what they think today about the information systems.

These are current users of the NNSIS that we queried. Two in general from each State and territory. Some of the States use commercial laboratories. So

for those States that do, the questionnaires went to the commercial laboratory. Some States use the same follow-up coordinator. So, in general, with the denominator, you'll see that it's less than two per State. The timing, we just completed this between April and May.

So, in general, the survey was emailed out to

87 individuals. Each State was represented. We received responses from 64 individuals, representing about almost two-thirds of the States. Fifty percent of the 74 percent that responded provided contact information. So that's what Sharon said we could tell that there were about 18 States at least in the States that identified themselves that responded to the survey.

You can see from the bar graph that the majority of respondents either work in newborn screening, in the laboratory, or in the short-term follow-up. We have short-term follow-up defined as the confirmation of the diagnosis and/or the initiation of treatment.

So each of these slides in the upper left-

hand is going to give you a response rate so you can orient yourself with each slide as I go through them. And then the upper right, with the title is what -- the question we were asking. So, in general, first we wanted to see who they communicate screening results to from the laboratory. About 80 percent of the respondents said they communicate those newborn

screening results to the primary care physician. Only about 8 percent communicate all results, whether they're abnormal or normal, to parents.

We wanted to understand the tools that they use to communicate the screening results. You can see that the response rate was 92 percent, and the majority either use a phone or a fax to communicate those screening results.

We also wanted to understand how they communicate the confirmatory diagnosis or who they communicate it to. You can see that about half of them communicated to the primary care doctor and about another half communicated to the specialist or subspecialist.

We wanted to understand the tools that they

use to communicate that confirmatory diagnosis. Again, most of them use phone and fax. But we think because of the urgency of communicating that diagnosis, they also are now using emails. So we're seeing more electronic use of information sharing when the results are critical.

This is NNSIS data entry and frequency. We

heard from about three-quarters of the respondents for this question. Almost all of them use the NNSIS, and we were interested in how often they use that. The majority of respondents said they use NNSIS as time permits, but about a third of them said they use NNSIS or access it to enter data on a daily basis.

These were the respondents from the individuals of 4 percent that said they don't use NNSIS and why they don't use it. And you can see the majority it's related to --

[Microphone feedback.]

DR. BROWER: -- either short staffing or --

[Laughter.]

DR. BROWER: -- short-term follow-up data.

We also wanted to look at how much time each

program spent entering data into NNSIS because this gets at resources. This is an unfunded recommendation that the States participate in this registry. So about a third of the States reported that they use this on a monthly basis, less than 10 hours. So you can see the different response rates for time spent on NNSIS.

We also wanted to -- this was feedback from

our meeting last week, as Sharon said, in the town hall. One of the States asked us to start to do a cost estimate based on the number of hours that they spend. And what we found was that if we think the folks that enter the data into NNSIS in general make $30 an hour -- that was just a rough estimate -- you can see that 10 percent don't enter at all. Another 10 percent spend about $60 a month, or $720 annually, entering data. About 50 percent of programs and respondents spend about $30, or $360, but another 30 percent spend $300 a month, or $3,600 a year. So that's just beginning to look at the cost burden of entering data in a national database.

We wanted to understand not only do they enter data into NNSIS, but do they use the Web site?

Because the Web site has many analytical tools and summaries and canned reports that programs could use for either program development, quality improvement, or other types of information. We heard that about 50 percent of the respondents access the Web site monthly. You can see that the response rate is down here, and that's because not everybody accesses the Web site for

that type of information.

We wanted to understand how they're utilizing the NNSIS information. A key factor in any successful effort is to understand what your stakeholders want. So we wanted to understand for these programs, both the laboratory and the follow-up personnel, what types of information were important to them. And this is what they reported. That about 84 percent were interested in the number of diagnosed cases, 71 percent in the amount of the NBS fee, and you can see the different responses below that.

We wanted to understand how they're currently using the data that's in NNSIS, whether it's for program evaluation or development, whether it's to generate daily or other periodic reports describing the

efforts in their laboratories or other efforts. We found that the majority of programs use it for internal comparisons across the board, one time stamp to another time stamp. And they also use it for external. So looking how their State is doing, whether it's the number of disorders screened or the number of cases identified can vary in one State to another.

This was just a blanket question whether or not they found that the NNSIS information was useful, and you can see that the majority do think the information is useful, and only about 12 percent said it was not useful.

These are the types of program databases that each of the entities use. As Dr. McDonald said, we don't want to create a different EMR in every PCP's office. We also wanted to understand from the newborn screening programs whether they each have their own homegrown data system and whether or not the NNSIS is another layer on top of their own data system. So that would get at the burden of entering data twice.

What we understood was that 76 percent, so the majority of programs, do have their own database

that they use as a primary database in entering case definitions and newborn screening results.

We wanted to ask about NNSIS expansion, and these are just some of the data elements that the individuals highlighted that they would like to see in future expansions of this type of data collection, whether it's including maternal data, the ability to

edit individual cases. When I looked at the individual responses, it really got at expansion of analytical capability. So the ability to ask questions about their own data and their laboratories and their follow-up and the ability to compare outcomes across programs across time and to overlay that with national standards. So national case definitions, national definitions on the analytical results from the laboratories.

We wanted to also ask about their future program needs. So looking at their individual newborn screening programs, what types of things were they hearing from their IT groups or their other strategic groups in their departments? They all wanted to participate in long-term follow-up on outcome

measurements. They wanted to be able to link their newborn screening results with vital records. They wanted to have real-time linkage. So they wanted to be able to assess their cases in a real-time basis day to day.

They wanted the ability to do automatic downloads and uploads. They wanted to start to embrace

the HL7 data exchange, and they wanted to be able to do electronic communication with providers. And that was across the board, whether they're subspecialists or primary care.

We also took the opportunity, since we were doing the survey, to talk a little bit about case definitions. As Dr. Watson said, we're working on a uniform or minimal dataset across all disease areas for newborn screened disorders. And we wanted to understand what laboratories do today for case definition.

We found, on the left-hand side, that the majority let their specialists and subspecialists clinically diagnose these cases. So, in the laboratories and in the long-term follow-up programs,

they don't have their own case definition. They look to the primary care provider or the subspecialist to diagnose that case.

On the right-hand side, we talked about true positives, and we found that the majority of the programs do have their own algorithm to identify true positive cases analytically in the laboratory.

We wanted to understand whether or not there was the ability in the laboratories to confirm demographic information, and this gets back into the linkage of newborn screening with vital records. So do you have the mother's name right, the date of birth right, the sex right? We found that about 50 percent of the programs don't have the ability to confirm their demographic information.

We asked whether programs do long-term follow-up in a coordinated way. We found that about 40 percent said no. About 37 percent said yes on some conditions. Only 17 percent said yes on all conditions, and I think this is in line with the surveys that Dr. Hoff completed in 2006 through 2008 in saying that long-term follow-up was not a focus yet of

the newborn screening programs. But now that we have the definition of the components of long-term follow-up from the Secretary's advisory committee, we think that efforts related to long-term follow-up will increase.

We also wanted to understand whether or not the programs were able to confirm that they didn't miss any cases so that every baby born in their State

actually had screening. We found that about 48 percent of programs were able to do that confirmation, and about 45 percent said they weren't able to. It was interesting that about 8 percent said that they didn't know whether or not they could do that or not.

We wanted to also know, as you know, that several States require or mandate a second screen. We wanted to understand whether or not those screens, the first screen and the second screen, could be linked together.

One hundred percent of States that do a second screen all had linkage between the first screen and the second screen, and we wanted to understand how they did that. So you can see that the majority used some method that's developed in their own laboratory.

Forty-six percent use the mother's name, 39 percent use numerical linkage, and 22 percent use the bar code.

We wanted to also take the opportunity to understand about the linkage between newborn screening and newborn hearing data. We found that about 54 percent of programs said that they do have linkage between the newborn screening program and the newborn

hearing results. And this shows how they're connected to each other. So the majority are connected electronically. Others have many methods.

One of the other methods is they're down the hall. So they just walk down the hall and talk to them about each individual case, and then you can see the other methods. So we are beginning to see linkages in the States between vital records, newborn hearing, newborn screening. So that is really evolving at the State level.

We wanted to take advantage of having this group of stakeholders and talk to them about information technology as a whole and the whole expansion of HIT and understand what they feel is the barrier for expanding HIT within their own program. We

saw that about all of the answers relate to resources, either funding or staffing.

A few of the programs called out access to the data, and that was primarily the follow-up groups not having access to the screening results to be able to link positive screening results with outcomes as the children grow up. And then you can just see the list

of the answers provided.

We found that this was interesting, I thought, that about 52 percent did not have concerns about information sharing, but almost 44 percent did. And if you looked at the response rate for the -- or the individual reasons that people were concerned about sharing information in the Internet, on the Web, it was all related to privacy.

So they all said if privacy concerns and data sharing concerns could be addressed, then we have no problem entering data. So that they all called out HIPAA concerns and just in general data on the Internet being freely accessible.

We asked whether they have concerns about expanding a program like the NNSIS into other areas,

and 60 percent said that they did have some concerns. But again, all of those concerns related to privacy issues and how the data was going to be shared on the Web, not questioning the value of actually collecting this data.

So we just wanted to open it up for discussion and feedback on the survey, on the results,

and the use of the survey results. What we've heard so far from the State programs is that they would like to expand this beyond the laboratory and follow-up personnel to the State genetic coordinators and to other people involved in HIT within the State so that we can get a broader understanding of information needs for each State and on expanded efforts.

Thank you.

DR. HOWELL: Thank you very much, Amy.

Are there questions or comments for Dr. Brower?

[No response.]

DR. HOWELL: That was a very comprehensive report, Amy.

I hear no questions or comments. So thank

you very much. It's lunch time. We will return promptly at 1:45 p.m. And certainly, you'll want to be on time because we've been waiting for a very long time about this report on the second screen.

What? 1:45 p.m., yes. Oh, I said 1:15 p.m., 1:45 p.m. You'll have plenty of time. 1:15 p.m. is the time we will return.

[Break.]

DR. HOWELL: We're going to now proceed with our report on the second screen study. And we're now going to hear from Mr. Jelili -- Chris?

We're going to now hear from Mr. Jelili Ojodu, and Jelili is the manager of the Newborn Screening and Genetics Program at the APHL. He has been responsible for providing guidance and direction for this program within the institution.

Twenty-two-point-four percent of the newborns in the United States receive the presumed benefit of a routine second screen. Literature and some State practices suggest that cases of congenital hypothyroidism and adrenal hyperplasia that are missed on the initial screen cases are detected on the routine

second screen.

However, most newborn programs do not support the operation of a routine second screen. And as you remember, this second screen study was proposed by the Laboratory Standards and Procedures Committee. APHL was the data coordinating center for the study, and Mr. Ojodu will describe the study to date.

And I think that he's backed up by his fine colleague to his right, Dr. Harry Hannon, who has been involved in the second screen study for a long time.

Jelili?

MR. OJODU: Thank you, Dr. Howell.

Good afternoon, everyone.

As Dr. Howell mentioned, I have Dr. Hannon here as a tag team partner. We're going to quickly go through these slides, and hopefully, we'll have some interaction for some questions afterwards.

I'm Jelili with APHL and the manager of newborn screening and genetics there.

So just a little bit about the background of this. As Dr. Howell mentioned, 4 years ago -- and I'm looking around the room here, you should have actually

the protocol for this study in front of you. It should have been passed out. So if you do not have that, you should get a copy of that.

But about 4 years ago, we discussed in the laboratory subcommittee the proposal to figure out something, a project that would be important as it relates to laboratory harmonization. This was right

after the ACMG came out with the core panel of disorders, and I think it was Dr. Hannon that said I think the next big thing would be to figure out harmonization of States that do one or two screens. And I think right after that, there was consensus among the group of folks in the room that that was major.

For decades now, States have been either screening babies either 24 to 48 hours primarily in about 75 percent of the States, and then about 22 percent of the States do two screens. When I say two screens, two mandated screens. One 24 to 48 hours, and then the next screen about 8 to 14 days after birth. And so, that's where this project arose in the laboratory subcommittee, and we took it upon ourselves at APHL to be the data coordinator, and I'll talk a

little bit about that later.

The protocol that should be in front of you show the scientific literature in reference to the case for doing two screens or one screen. And there have been many published articles, dating back to 1985, La Frankie, et al., Doyle in 1995 from the Washington program, and also in 2006 about the case for doing two

screens for endocrine disorders, primarily CH and CAH.

And as I said, one of the main things that came out of this meeting that we had 4 years ago was the need to figure out an evidence base to prove or to justify or to figure out the research question on the validity of doing a second screen.

And so, just a little bit about the project timeline here. We can't believe that it's been 4 years, but it has been 4 years that we met in D.C., December 4th through the 6th, and we had participants from all of the States that currently and still currently do two screens.

We had additional -- additionally, we had three States that collects over 85 percent of second screen on their population, and then we had 3 control

States -- California, Massachusetts, and Wisconsin.

Representatives came from laboratories, the State

public health labs, follow-up programs,

endocrinologists, docs, parent advocacy groups, of

course members from this committee, and private lab.

And right after that meeting, we got unanimous support

from the stakeholders, which was everyone around the

table and from the States that performed the two screens and the control States that we should proceed with this project.

It was split into two, and the protocol that is being passed around would reflect that. That the study, we were going to have two parts of the study, a retrospective part, which is going back 5 years and then was 2002 or 2003 through 2007, and a prospective study. And we were going to work with the main question that we left on the table after that meeting in December of 2006 is how we're going to work with the States to get IRB approval because even though all of the data that we were collecting were anonymous, we still needed to go through every State's IRB, being that we were not able to get CDC's -- APHL was the lead

on this, and we weren't able to get a CDC IRB approval for the States to then use it for their approval. So that's how we proceeded.

So the study hypothesis, as you can imagine, for us then was to figure out if additional cases of CH and CAH are captured by the practice of a routine second screen algorithm. And the questions that we

wanted to address include, among other things, if there are any biomedical or laboratory-based practices that cause nondetected cases on the first screening, and how effective is detecting treatable cases and preventing negative outcomes?

And also, a little bit about the post analytical and analytical steps that were taken with the first screening. I think Rinaldo's paper in 2006 talks a little bit about the need or the process of if, in fact, it's necessary to have a second screen if you have the right process in place for analytical and post analytical steps.

And of course, a big thing now where the public health dollars stretch so thin, the cost effectiveness of doing a second screen. You can

imagine for the largest States out there that do one screen right now, for them to add another screen to their panel would almost mean that they're doubling their cost. So this is going to be important, and we knew that right from the get-go. And we knew the fact that whatever we came out with from this study would have some repercussions on how States move on with

their newborn screening panels.

And then the study question, of course, then would be how -- the best way to answer and evaluate these laboratory and medical results collected on the second screen. So we started off with a laboratory form. If you look on your protocols, page 9 through 11 has this information in hand, and this is the laboratory information, and this is the general content of the laboratory data for each analyte and screen that was collected.

For each newborn that was picked up on a first or a second screen, each one of these variables were collected, and you can see how detailed that is. We changed or converted what you have on pages 9 through 11 into an electronic database, which we stored

on our Web site at APHL, which is secure and is only accessible by the States that are participating in the second screen study. So they are the only ones who are able to get into the Web site and put in the data, anonymized data. Sorry, my phone is buzzing there.

And so, these are the variables. Dr. Hannon had put in this teaser slide here from the Newborn

Screening Quality Assurance Program, and it just shows the cutoff values for 2008 as reported to CDC for T4, TSH, and 17-OHP. And as you can see there, there are different -- there are differences in the number of cutoffs that we have there.

The two States at the bottom there are the control States, Massachusetts and Wisconsin, and let's see here, Washington does not do T4 but does TSH. So these are the kinds of things that we expected to see and we expect to see in the database as we collect the data.

As we collect the laboratory information, it was also very important to make sure that we collected the medical information, and these are some of the variables that we were collecting -- hypothyroidism

type, neonatal history, CAH type. You will be able to find these questions on I think pages 14 through 16 of the protocol that's in your possession there.

For a State to enter one of these babies into the system that was positive for either CH on a first screen or a second screen takes approximately about 45 minutes to about 60 minutes to enter each patient into

the system. And so, as you can imagine, it took quite an enormous effort on the part of the States that were putting the information into the system to actually make sure that all that information is in there.

This is with the reduction in the number of folks that worked in newborn screening, and I'll probably get into that later as we talk about the IRB issues that occurred during this whole process.

This slide shows briefly the States that currently do two screens. And as you can see there, it's amazing if you look from all the way from Oregon and comes down to New Mexico and Washington State, then it comes all the way down to Texas, and then it seems like there's nothing else. And the only outlier there you can see is I think Delaware.

I'm not sure what the deal -- well, actually, I do know what the deal is. Delaware used to outsource their newborn screening tests to Oregon, and when they brought it back in-house in 1999, as Jane informed me, they just continued the process of doing two screens as the case in Oregon.

And so, the States in light green are the

recommended States that currently do about, as I said, 85 to 90 percent or currently get 85 to 90 percent on a second screen. That's Washington, Alabama, and the State of Maryland. The control States are in blue there. We have Wisconsin and the State of Massachusetts, and we're currently working on California to get IRB approval at this point.

So this is where we are, and Dr. Howell has mentioned over the years where are we with this project? And quite frankly, the IRB issues has been something that I'm hoping that this committee can give us some guidance on not only for our project, but for projects that will be had in the future.

We had to get our protocol through every one of the States' IRB for this retrospective study. Now

let's just put aside the prospective study. The retrospective study on itemized data 5 years, information that's already collected, we went through every State's IRB to get this done. And in some cases, it took a little bit longer than expected. In some case, you should all have a one-pager from -- an email correspondence that I received from the State of

Colorado. And in there, they expressed their best wishes for us to go ahead with this program, but they were not able to participate on this study.

And quite frankly, it's understandable when you have a State that has 70,000 births a year and only one follow-up coordinator. It's almost impossible for that person to be the person that's going to enter data in the system, and we're talking about, as I said, about an hour for each patient that they enter.

And even with some funding from CDC to actually help out, assist these States, we came up with the idea of providing about $50 for every hour that States put in the data. And it did help some States, quite frankly. They were able to bring in somebody to put in the data. But Colorado said they weren't able

to do that, and so we will try to work with them to see if they can be part of the study. But as you can see here, we've gotten IRB approvals from Alabama, Delaware, Maryland, Oregon, Texas, Utah, and Wisconsin, one of the control States.

Just talking about the numbers, and these numbers specifically relate to births or approximate

births in the year of 2008. And so, those are the numbers at least that we will capture for the retrospective study.

And Harry is going to talk about this a little bit later, but we calculated that at this point, we will have about approximately 70 percent of all of the babies that would have received a second screen from those States that do two screens, and at this point, we probably -- well, I think we've made a decision to move ahead, that denominator of 70 percent will have to do as we continue to analyze this data.

Maybe one of these other States that haven't gotten their IRB approval will be able to do so in the near future, but we're going to move ahead with that.

I think this is where I transition over to

Harry.

DR. HANNON: So as Jelili was talking about, our issues and challenges with IRBs, which have beaten us to death for about 3 years, about the only thing I can say about it is we have been persistent and diligent about trying to get them, as you can see, across the schedule from getting the first one in until

2009, getting the last one in and rejection from Colorado.

So what we decided was that, as he was saying was that we'd look at what we have and see what we can do with that. And so, I just pull this out to give you some idea, a feel for what we actually have in the database, although the database is not clean. And we found out that some of the States failed to enter either the first screen or the medical or whatever.

And Stuart Shapira, who is helping us from CDC, would go into the database and look and see how it was going and what was in there and what was missing. So we've had to go back to some of the States, Texas, even Oregon and others, to put in the missing information, and that what's what we're studying right

now.

We're trying to clean up the 67 percent to make sure we have the total representative database to start making, get the working group who's -- the designated working group who's supposed to evaluate the data and pull it together and see what we've got. So as you can see there, we had roughly a million newborns

in 2008. I just picked one year as an example, and that was the 22.3 percent based on 2008.

Now, as we look at this, we have a little bit of a sliding scale. And it goes from 2003 to 2008. We're asking for 5 years, which means that there is probably a 3- to 4-year overlap within the group. But there may be some that are 2008, and some that are 2003 in terms of the database.

But we have about 15.3 percent of the 2008 births in the dataset when it's cleaned up, which is about 67 percent of what we could obtain if we had all those routine that do second screens in the database. If you multiply the number of births per State that receives a second screen that we have IRB clearance for, that gives us about 3.5 million births in our

database to evaluate for the CH and CAH second screen aspect.

So what I did because Rodney was wanting to see some data, and of course, we've had to make all this up. So --

[Laughter.]

DR. HANNON: I figured that I would find some

data for Rodney, and this data, although you may laugh about it, serves a second aspect. This is a QA aspect. Okay, when we look at the database and we look what's in the Newborn Screening Resource Center in terms of reporting cases, that will give us a little idea of how accurate or complete the data that's in the database is.

So we'll use that as a QA reference point, but what I'm going to show you is actually what is in the Newborn Screening Resource Center database on captured cases and those -- by total captured cases and confirmed and those that were captured by a routine second screen. And then I'm going to show you those that were captured by we'll just call it "targeted" by the two control States, okay, for each of these

methods.

And this is going to be our QA thing. We'll look at it in terms of the number of cases that are entered into the database as a crosscheck, and so we start dealing with the States. Once we feel that we have all the data in, we'll start looking at parameters to judge the quality of what we have.

One thing, and if you see Texas here, Texas had to have their own little bar graph on the side because if we put them on the scale, everybody else would be flat. So Texas allowed us to get 67 percent because they had 424,000, okay? So without that, we'd still be down about 15 or 20. But Texas scale is different. These are the total cases for CH that was -- this is the total number of cases that were found by year, starting with 2003.

So you see some of these go 6 years, and so these are the total cases. The interesting thing is that these things vary a good bit from year to year, and this spikes, which was interesting in the database. Go to the next slide.

Okay. These are the confirmed second

screens. These are babies that were picked up as cases and confirmed by the second screen. They're captured by the second screen.

DR. LLOYD-PURYEAR: Are they the same babies that --

DR. HANNON: It's the same babies by year, okay?

DR. LLOYD-PURYEAR: But the first one?

DR. HANNON: The first one is total, which includes those detected on the second screen. That's total cases confirmed in a year, and each bar represented a year by State, okay? Back up.

Okay. This is the total number of cases, which includes those picked up in the second screen. This is for Wisconsin that doesn't do a second screen. This would be 2003, '04, '05, '06. '07, '08. So that in 2004, they had this spike. And that's true across the board, and this is the total number of cases detected by State across time.

Okay, so that's the total number of cases we have to work with. Wisconsin is the control State. These States we all have, except for Wisconsin, we have

IRBs for, okay? And we're collecting that data in the database. That's the total number of cases. Next slide.

Okay. These are the cases that were picked up by the second screen, presumably -- this is coming from the Newborn Screening and Genetics Resource Center database -- presumably are different from those that

were picked up in the first screen. And the presumption is that they were not detected in the first screen. They were negative, okay? So these are the ones that were determined in the second screen.

If you look at Alabama, I'll show you something about Alabama's data, which again raises some issues about what data is in this database that we're going to pick up. But you can see Maryland has about the same number of births as Wisconsin and Massachusetts. Now these are cases picked up on the second screen. These are, these two control States, I'm going to call them a targeted screen. They might differ from that in targeted screen.

But these include those babies which were a borderline abnormal. Actually, there are about four

parameters. There are babies that had a borderline abnormal for any analyte in the screening panel. They are rescreened or a second sample is obtained, and they're rescreened for everything, okay?

Then the next category would be those babies which had a questionable specimen, an unsaid or is questionable quality, and they've got to repeat for

those. The third category is the NICU babies, low birth weight preemies, and then the fourth category would be those babies which the physician receiving a negative report for some reason decided they wanted a repeat, and they collected the second sample and sent it in.

Now I talked with Gary about those parameters. That's where I got them, and I talked with Roger about his. And they're essentially about the same. But you can see this is by a targeted process in Wisconsin, very similar number of births, very similar pattern in terms of cases detected. One being by every baby screened, the other being by a selected population.

This is usually somewhere between about 8 and

12 percent of the total population. So this might be about 8,000 babies that showed up here in the targeted second screen that are picked up. Next slide.

These blanks here are either they reported none or they reported nothing, okay? So it was -- we had no confirmatory aspect when they were there whether it was blank because they had none, or they had a zero

and they didn't report any. Although it says in the database that they are the number zero should indicate they detected none and the blank should indicate they reported none, but I was too uncertain to draw that conclusion. But you see the white bar, no data reported? That could be that they reported zero also.

But if you look at Delaware for CAH, these are the number of confirmed cases on the first screen, okay? Which includes those that we captured on the second screen. This is total number of cases. This is Alabama for CH. It's amazing how they tend to vary from year to year in terms of numbers.

And this is Wisconsin, which is our only control that we have IRB on. And again, there is a similarity not so much here to Maryland for CH and

Wisconsin as it was for CH. Next slide.

Okay. These are those babies that were picked up in the second screen for CAH, but not in the first screen, and again, the Massachusetts I put on here is the control, although we don't have the IRB. Wisconsin had essentially no, had no babies picked up on the second screen, their targeted process for CAH.

Massachusetts has this one in the middle here. So there's a lot of difference between what's detected for CAH and CH, and that could be a prevalence aspect also.

And Texas didn't report data for 2 of these years also. But here's Delaware, they had 1 in 6 years for CAH, this screening. Maryland had 1 per year in 3 years, and you can see that there's not a lot of CH. And there's Alabama. We'll come back to that issue.

This looks like a lot of babies for a second screen compared to those, and there are much less in Texas, even though this is 30 at the top. Next slide.

You've got a pool --

DR. LLOYD-PURYEAR: Those slides differ from what we have in our briefing book.

DR. HANNON: That's correct.

DR. LLOYD-PURYEAR: Okay.

DR. HANNON: Do you want to know why?

[Laughter.]

DR. HANNON: We corrected it because the person making the slides for me pulled the same set of bar graphs over onto another title for CAH, and I didn't realize it until I was looking at it on the

plane coming up here, and I said, gosh, these look remarkably similar. Then as I got to compare them side by side, I said it's the same data for the CH and CAH on the second screen. So I corrected them before you corrected me.

DR. LLOYD-PURYEAR: I just wanted to make sure the committee knew that.

DR. HANNON: We have handouts with the corrected data, okay?

I pulled one of them just to put them side by side to show you some of the data issues we're dealing with from the resource center, and I'll give you another tidbit of information. And also as I was looking at the data on CH, and now these include all cases, like for CH that's simple realized, salt

wasting, and nonclassical. They're all added together. For CH, it's only the primary hypothyroid. I didn't add secondary.

Now a couple of States who list transient hypothyroid, and they have like -- each of them have 20 or 25, which is remarkable because I don't know how they got the transient data information because

somewhere they had to be confirmed as transient, and they only have like three or four cases, okay? But they've got 25 transients. Just two States out of the whole population. So it gives me some concern when I'm looking at this as a QA component of my data.

And then you look at Alabama. I put these side by side. Just use CH as an example because you all get bored with all this data. This is really not our database, but comes from the resource center. So I'll put the primary and second screen together for some States, and so you could see, just for hypothyroid, you can see here's Delaware on the total cases confirmed, and here is the two cases for 6 years of screening all the specimens a second time. Here is Maryland. That's the second screen. There's Oregon.

Here is Alabama.

It's remarkable that second screen picks up as many as the first screen. So, obviously, the data entry is wrong. They put total cases in both places. To some extent, but they're not totally accurate about that because you can see it's not exact profiles. So as I'm pulling this data out, the old philosophy is if

you've got one tainted piece, you need to worry about the rest of the meat also.

So that gives me some concern about pulling all this data, but we will use this as a crosscheck on our data that's entered into the system. And next slide.

So our next steps are we want to get this thing over. I've been beat to death long enough. I want to live to see it completed. We want to complete data collection for all the States where the IRBs approve. That means right now we have that 67 percent. We want to clean that database up and make sure everything is entered in there and then take the total number of cases in both categories and compare it to what's in the resource center's Web site to see how

those look, not believing either one is absolutely

correct, okay?

And then we want to seek completion of

pending IRBs and gather data into the electronic files.

That is, those States that haven't cleared the IRB

that are working on it and pending, we will bring them

in at a later time down the road as we are trying to

work on what we're doing, and we'll keep that separate. And at some point down the road, if we get those, we'll add them into the database and increase the 67 percent.

And we want to designate this workgroup, which Stuart Shapira would be involved from CDC. He's the medical person who was at Texas before he came to CDC. And others will include like Roger from Massachusetts, some of those who don't do a second screen, as well as some who do a second screen.

Now this is an enormous database now. They won't know from what State the data is coming as they begin to analyze it. So we wanted to avoid any finger pointing of anyone in this process and just look at the total data aspect in terms of interpretation of the

hypothesis, which the second screen truly picks up cases that others would miss.

And we will report back to each of the participant States first. We want those who shared the data, did the work to have some idea of what's coming out of the study before it goes to the screening community. So they will get a first pass at what we

have and an opportunity to criticize before we put it together in a package for the screening community. And obviously, at the end, we'd like to submit the data and conclusions for publication in a peer-reviewed journal.

So that's where we are, Rodney. Unfortunately, I don't have the answer.

DR. HOWELL: Harry, my next question. What timeline would you put on your next step?

DR. HANNON: Well, presently -- presently, the data -- we have interacted with each of those States that have missing information. We've given them funds. They are now entering the rest of the data. Stuart Shapira will go back through the database and see if we're missing anything from anybody as we try to accumulate this.

Timeline is as good a guess as mine. I would hope within the year we would have it completed and the outcomes done. But we've got to get all the data, make sure it's clean, designate a working group to look at all the data, and compile it and develop some conclusions from it. I'd love to have it by the end of the year, but I'd love to have had this study over in

2007.

[Laughter.]

DR. HANNON: So that's the best answer I can give you.

DR. HOWELL: We have a number of questions around the table. We have Mike and then this Mike.

DR. SKEELS: Oh, thank you.

First, I want to congratulate you on getting this far with this. I know that it's been difficult to pull it from the States. So I want to commend you. Good job. And I also want to say that I mean, I appreciate Colorado's problems with staffing and not being able to participate, but if there's anything that could be done to lower that threshold to encourage participation not just by Colorado, but by others, that

would be terrific.

And you were talking about flattening things.

I'll just point out that if you mash Colorado flat,

it's actually bigger than Texas. So you may have to

have a different scale.

[Laughter.]

DR. SKEELS: But now my question, I'm looking

at the U.S. map, and the States with routine second screening, and you did distinguish -- you used the word "routine," which is great. But in a lot of those other States that are not colored on the map, there is a requirement for second samples when there's early discharge. In some States, that means 24 hours. Other States, that means 48 hours. So the actual number of babies in the United States that are receiving second samples I believe is quite a bit more than the 22 percent.

So my question is, A, am I right about that? And B, do you have any data around it?

DR. HANNON: Somewhat, I tried to capture that by looking at the control States, Massachusetts and Wisconsin.

DR. SKEELS: Right.

DR. HANNON: Those are all those picked up and identified as cases on the second screen for a variety of reasons that a second sample was collected. I gave you the primary four, and the preemies and NICUs capture about 80 to 90 percent of those that are second samples collected for and screened. Those are

the cases that were picked up on those, and that references about 10 percent to 12 percent of the State's births. So they're routinely hitting about 10 to 12.

The 24 to 48 is not as big a problem. I mean, the 24 or less than 24 is not as big a problem now as it was historically. So that would have to be examined in that period also, but at this point, we only have the database of what's going in. And we just have the control States. We don't have an IRB from California. So our control population is rather small.

I wanted to indicate that by that target process they're picking up similar case profile patterns as to those that are doing a routine second.

DR. SKEELS: I think you need to be a little

bit more rigorous in your analysis. I think you need to convert, for example, the Wisconsin and Maryland data to -- you need to do statistics before you draw an inference about whether, in fact, the targeted screening is just as good as universal screening.

MR. OJODU: We plan to do that.

DR. HOWELL: Mike, you had a question and a

comment?

DR. HANNON: I just did the profile. So similar.

DR. WATSON: Yes, I have a specific, and then one or two general questions. The variability in the cutoffs had no relationship to the detection in the second screen?

DR. HANNON: I pulled that slide, and that's data reported to CDC in 2008. Unfortunately, we are not into analysis of the database, so we don't know what that contributes. But that was given as an example of the types of information that are being pulled from each of the States for each of the screening algorithms that they're using so that we would have that information. It's one of the list of

parameters. There is about 20 different parameters collected, that being one.

But I wanted to show you just the variability of this in those right there and even inclusive in the control State. So it goes -- now whether that contributes or not, that will be the workgroup's analysis aspect when they look at those variables.

DR. HOWELL: Some of the variation in cutoffs were really quite extraordinary. I mean, they were not trivial. There was 15 to 80 or something like that in one of the slides.

DR. HANNON: Yes, as I told Jelili when we were getting ready for this presentation, it is what it is. We can't change it.

DR. HOWELL: Yes. Right. But it's varying.

Jane?

DR. GETCHELL: Well, kind of related to the cutoff question. We get pressure fairly regularly to eliminate our routine or mandated second screen. And in these times of economic difficulties, you can understand why we get that pressure. I have always said, well, let's wait and see what this study shows --

[Laughter.]

DR. GETCHELL: -- in response to that pressure. So take all the time you want, Harry.

DR. HOWELL: Well, you know the reason I have bugged Harry mercilessly is that it's perfectly clear that everybody ought to have a second screen or nobody, depending on what the data are.

DR. GETCHELL: Well, and then I wanted to make the other comment when it comes to the cutoffs particularly. Programs are set up to either do it or not do it, and you can't just turn it off. I mean, it takes time to validate a whole new process. Just anticipating what may come out of that, I think we need to think about what recommendations go along with the data when it's presented.

DR. HANNON: Well, obviously, we made it a point to say that you get to see it before anyone else does. As a participant, we'll let you see it, and we'll discuss what comes up on it from there before it goes any further.

DR. WATSON: So that was my specific question.

DR. HANNON: What was it?

DR. WATSON: My generic question is more prospective. It's obviously a broken system out there if you can't get data back easily. Do you see -- I mean, are there things about the data systems in those States where you were able to get data more readily than others, and can you think about that in the

context of these data systems that are being built for collecting really laboratory information?

DR. HANNON: I don't think it's the difficulty of getting the data that much. It's, one, getting past the IRB and, two, finding the time and resources to enter the data.

Jelili and I just -- we were trying to finish up Alabama, and we found out they had not -- the medical data on the cases had not been entered into the system, okay? So we talked with the lady from Alabama, and USA is one and UAB are the two hospitals that are involved in the medical aspect. And USA had theirs and ready to enter, but UAB got into issues. They needed the hospital-specific IRB, and then because UAB is asking for it, USA, University of South Alabama backed

off on theirs because what's wrong here? Because University of Alabama at Birmingham wants an IRB.

Anyway, we talked to the physician at the UAB, and she was all in support of a second screen. She thought it was the best thing since newborns, I guess. And she wanted to know where are the examples of IRB. So since we sent her some examples down, even

though Alabama already had a specific IRB for the State, now we get into a hospital-specific IRB, okay?

So now we have to help her get through that system to get her IRB, and she is working on it, and we just received, I think, that they have cleared the IRB. So I mean, those are just the type of things we run into. Every time we think we have something clear, we cross another bridge, we hit another barrier. It's just been banging your head against the wall for 4 years.

DR. HOWELL: Important study. Brad has a comment?

DR. THERRELL: Yes, a couple of comments. One, on the cutoff issue, what Harry showed you was cutoffs reported to CDC, right, in your PT program.

And States that do two screens generally have two different sets of cutoffs, if not more, and so they report one of those to CDC.

The other thing is it's not necessarily a cutoff that was determined for the analytical procedure. It's a cutoff for the system. So, in some States, they may have decided to follow up on 0.5

percent, whatever that cutoff is, as opposed to determining it analytically like you can do with mass spec. Because this isn't a mass spec procedure. This is a much broader type of procedure.

Secondly, the problem is not really getting the data back so much as it is definitions. So even in those States that are in the study, they don't agree on the definition of a classical CAH, for instance, or a salt-wasting CAH, or those sorts of things. So that's a bigger issue that has to be determined in your analytical process.

MR. OJODU: I completely agree. In fact, I think after the core panel of disorders was put together several years ago, one of well, several things that were supposed to follow up after that was to be

some kind of case definitions for all of the disorders on there and figuring out how we can harmonize that. I think certainly that's something that would help us in moving forward.

Mike, just going back to your question. As Harry said, resources, we didn't figure in resources for this project at the beginning of it. We got

everyone to buy in, and everyone was happy with the protocol. And then they went back to their individual States, and it was just -- it was a different. It was a different animal.

There were some States that were able to get the data in almost immediately afterwards. And for all of those States and the people that have been putting information into the system, thank you. We're almost there, but --

DR. WATSON: Was it all paper files?

MR. OJODU: Say that again.

DR. WATSON: Was it all paper files?

MR. OJODU: No, it's electronic. So everything you see there is turned into an electronic database that's saved onto APHL. So they just log in -

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DR. WATSON: It was paper files that they had to extract the information from?

MR. OJODU: No. They actually go -- everything there has been transposed into an electronic file. And so -- oh, yes. So they are pulling, especially the medical data from the medical chart.

So the laboratory, say, for example, I'm going to use Oregon, for example. Luckily, they had a consultant in Judi Tuerck, who works both the lab and the follow-up. But in some States, you had somebody enter all the laboratory variable data information, and then you had another person in the follow-up, maybe a nurse or a doc. In the case of Delaware, it was Lou Bartoshesky. He entered all of that information. And so, it makes it difficult to just enter all of that information at the same time. So it just depends.

DR. HOWELL: Piero?

DR. RINALDO: I second what many others have said, that really you had to endure quite a process to get through it, and so I encourage you to keep doing it. However, I think -- well, my questions are a

different level. One is I think it probably, at the end of the day, for congenital hypothyroidism, the evidence will show that, indeed, there is benefit.

With CH, though, it's more complicated because there is another variable that, for whatever reason, is not included here. And that, in fact, in looking at the map, at least seven States use a second-

tier test. And I'm a little concerned about the fact that as you add California as a control, then your control group will be diverse. There will be two States with no second-tier test and a State who does have it. So that's really my retrospect, as this has been evolving over the last several years, if this has been sort of reconsidered.

The other question is if I look at your first slide, so this is strictly about sensitivity. And so, there is no really concern about specificity in terms of what happened in terms of false positives and what's the impact of a second test.

And you know, you can start thinking about what happened if you have first normal, second abnormal, I doubt it will stop there. So it might

become third, fourth, and fifth. So there are huge, obviously, issues related to all this. So, and I understand that perfection is the enemy of good, and so you might never get off the ground.

But I'm really concerned about the fact that in at least eight States, the second-tier test is the standard of care, and it seems to work quite well.

DR. HANNON: I am a strong supporter of the second-tier tests. Our data collection ends at the year 2008. My best collection is probably you in California that are doing it in 2008. Maybe one other. I mean, New York was there for a while. We send out PT challenges to all the States that are doing second tier. So our database ends at either 2007 or 2008 when there is not very much second tier going on in our control States especially, as well as the other States.

DR. RINALDO: So the concern is that there is a risk that clearly needs to be sort of evaluated very carefully that the conclusion reflects an outdated practice.

DR. HANNON: I fully understand. We're moving to more and more second-tier testing. I mean to

second-tier confirmation to reduce the number of false positives that go out to improve our specificity of testing, and I'm strongly supportive of that.

Your other question had to do, what was it?

DR. RINALDO: Specificity.

DR. HANNON: Yes, we're not looking -- our hypothesis was do we pick up more cases? We weren't

concerned about the rate of false positives, of their reduction by a second screen, which a second screen could be a total QA process, which helps eliminate that as well. But it's a tough question, and there is any time you take one State, you're only dealing with one State. And once you move to try to incorporate that in the thoughts and issues and parameters of other States, you're in another State and it's a new environment.

DR. HOWELL: Dr. Botkin?

DR. BOTKIN: I wonder for the IRBs that are expressing concern about the project, are they expressing concerns over human subject protection issues, or are they addressing problems with the administrative support cost, program support?

MR. OJODU: Both. All of the above. I mean,

when we have to get an IRB approval from a hospital

when the State has already approved it, at that level

of years of working on this, it just becomes very

difficult. But, yes, there is no money, of course.

There are less people putting the data into the system,

and it just makes it difficult for people to actually

say they're going to participate on this study even

though it's beneficial.

DR. BOTKIN: And I guess just a quick comment. It's not clear to me that the hospitals in this context are engaged in research if the data is coming out of the health department. So I'm not exactly clear why the hospital IRB has jurisdiction here. And then secondly, for the human subject protection issues, what are their concerns?

DR. HANNON: We didn't investigate what the concerns were. We investigated how we could help them get over the hump and get the data. We would come down, let's hit the road, get what we need to get, and provide them what they need. So I didn't investigate, and we didn't ask why.

Their concern apparently had to do with fear

of reporting the data and so forth and release, even

though the State had an IRB already. We had to give up

on the first, the prospective study, which we wanted to

do in a better fashion and do QA control of the data as

we collected it because we couldn't get anybody to

consider a prospective study. I think did Delaware

give us a -- we just had one.

Delaware gave us a prospective IRB clearance as well, but that's the only one we got, and we only had 13,000 babies. So we just canned that one and concentrated on the 5-year retrospective study. So I don't -- I can't answer your question.

DR. BOTKIN: Yes, and I would just say I think it may be a broader problem that if IRBs perceive their authority to be protecting the programs against potential embarrassing information, as opposed to protecting the welfare of the babies who are part of those programs.

DR. HANNON: Could be. We only had one out of -- you consider there's got to be a lot of hospitals involved in this study, and we only had that one.

DR. CALONGE: So, Harry, I was intrigued by

the targeted testing for congenital hypothyroidism and was wondering, it sounded to me like you said those were based on near-normal or near-abnormal values rather than other clinical data. I was just wondering do you think a State might have the data capability, a State that does a second screen have the data capability to see, to look retrospectively about

whether or not that targeted approach would capture almost all the cases of a universal second screen. Do you get my concept?

So you looked at the numbers and said, boy, that looks pretty similar, and so the question is what is the additional value of universal versus targeted? And not that that should be your study, but in a State that was interested in trying to capture that, do you think the data exists to do that?

DR. HANNON: Remember, the word "targeted" was my word, not theirs, okay? They have an algorithm by which they selected those States that do a single screen, by which those samples are selected to go into a second screen or request a second specimen for testing. So I just lumped them as sort of a targeted

versus routine of all.

So, obviously, you know, there is economic issues about testing everything. But I have told Mike before, it's a great QA program, but it's an expensive QA program.

But we do happen to know of one delayed diagnosis that occurred in a State that does a routine

second screen because they didn't capture all the babies in the second specimen, and therefore, it was normal on the first. The second screen they found never got. So it showed up as a case in the physician's office, and they came back. It was still -- the first specimen was still normal. So there are issues regardless when you get down to that part.

DR. HOWELL: Harry and Jelili, let me thank you very much for this presentation, and we'll look forward to your returning with final data in the near future.

[Laughter.]

DR. HOWELL: Thank you. That's a lot of work, and we appreciate it. It's an important study, though. Thank you very much.

We're going to now go to the Newborn Screening Contingency Plan. Alison Johnson is Deputy Director of CDC's National Center --

DR. BOYLE: I'm actually doing it for Alison.

FEMALE SPEAKER: Yes, Alison had an unexpected --

DR. HOWELL: Oh, who is going to present?

DR. BOYLE: Coleen.

DR. HOWELL: Oh, Coleen. We're going to have you speaking as Alison Johnson, and we all know Coleen. So here you go.

DR. BOYLE: Okay. Thank you very much.

And Alison had an unexpected meeting with the Director of CDC. So, unfortunately, she couldn't be here. And for those of you who have been with the committee for a while, Susan McClure from CDC's Division of Laboratory Services actually was here a little over a year ago to talk about the national contingency plan. So this is an update and also to tell you that the plan is finalized and I guess here for your approval.

Just to give you a little bit of background,

the plan was mandated by the Newborn Screening Saves Lives Act, and the act itself -- the act itself, as you can see from this slide, had eight objectives. And we used these objectives as the basis of the plan.

At this point, the plan doesn't include newborn hearing screening. The EHDI system decided they would look at the framework that was developed for

blood spot screening and change it to fit their system.

Just a little background on contingency planning, for those of you who may not have much involvement in emergency preparedness and response, Alison actually listed two very appropriate national contingency plans that are currently active. One is on the National Oil and Hazardous Substances Pollution Contingency Plan --

[Laughter.]

DR. BOYLE: -- and the National Marine Sanctuaries Contingency Plan. So I don't think I need to explain any more.

DR. HOWELL: It doesn't appear that either of those is working.

[Laughter.]

DR. BOYLE: So, anyway, Congress directed CDC to develop this plan in consultation with HRSA and State health departments. Usually contingency plans are an agency directive. So that would have been HHS developing the plan. When CDC went to Congress to ask why it was delegated to CDC, we were told that CDC has robust planning and response capabilities and a direct

relationship with State health departments. So that's why were charged with this.

What is a contingency plan? This slide has a definition for you, and as you can see, this isn't a plan that you use in an everyday situation. Obviously, again, reminding you of the Gulf situation. It's a plan you use when things go wrong. A contingency plan doesn't include every step you need. It's essentially the basics for what to do in an emergency situation.

Actually, in developing the plan itself, we pulled together many partners, including many of you in the room. And I have to say the plan was developed in collaboration between my division, and really Alison Johnson was the primary person there, and the major effort by Eric Sampson, Harry Hannon, and Susan McClure

in the Division of Laboratory Sciences.

And these are the groups that were pulled together. We also engaged HHS's hospital preparedness program. So, in addition to all the State partners and others represented on this slide, we did involve HHS-level operatives as well.

The plan itself is not a strategic plan.

It's an operational plan. So it's really detailed and focused, and it describes the how, the who, the when, and where for disaster planning.

Susan did talk to you about the workshop that we held in September of 2008 where the participants included the Federal partners, State public health programs, State emergency preparedness programs, and clinicians. And really, these are the subject matter experts that helped us in developing. We also used the expertise within the context of CDC, both in terms of emergency response planning and contingency planning.

This is just a slide showing that we've framed the objectives based on those eight mandates that Congress gave to us, and it really included the whole scope of newborn screening from the collection

and transport of specimens to the education of families about newborn screening and follow-up.

This is a timeline. Obviously, the law was enacted several years ago. We are at the point where the plan has been vetted, and it's been approved and signed off by HRSA. And it's actually -- I think we actually have this right here. So the plan was

circulated. We had a final draft in May -- actually, in August of '09. And then we began the plan into clearance, and unfortunately, from a CDC perspective, things got a little lost because of H1N1. We tend to use that as an excuse for many things, but I actually think it was a good excuse this time.

So now we're at the point where we're coming to the committee for your endorsement, and then the plan would go to Dr. Frieden for final signoff. And then the next steps for the plan was to post it on the CDC Web site, to share it with the appropriate partners, to add language to CDC's public health -- we actually provide in CDC's Office of Preparedness and Emergency Response, we're going to add language to actually have this as a requirement as part of State

emergency preparedness planning so that it's sort of an enforcement, a potential enforcement piece.

And obviously, we need to continue to work and follow up, obviously. A plan is a plan, and it needs to be acted upon, not necessarily in an emergency situation, but exercise need to be developed around it and then strengthened through that.

So questions? That was a quick run-through.

DR. HOWELL: So your plan is essentially done at this point in time?

DR. BOYLE: That's correct.

DR. HOWELL: And it's currently under review of the CDC, and it's been reviewed by HRSA?

DR. BOYLE: And I do want to point out, Rod, there was I guess the plan that you have access to has one additional objective that was added, and that has been taken out. So the plan reflects the eight objectives that Congress charged us with.

DR. HOWELL: Mike?

DR. WATSON: Yes. Having been involved in part of this process, I think it's important to appreciate two distinctions in all of this. One is

that a contingency plan is dependent upon something being prepared upon which -- through which they can act in the contingency plan. And there was quite a dearth of preparedness that could become part of a contingency plan.

So when you look at this contingency plan, you'll see a lot of things that you'll wonder why it's

not there, and it's because there is not an existing system into which one can engage a contingency plan. So I would think of it as sort of two separate problems, and it took us a good day and a half to get past what we thought we should be prepared for to what we actually have on which we could organize a contingency plan.

DR. BOYLE: Yes? And if I can't answer -- go ahead.

DR. GETCHELL: Did I understand you correctly that contingency planning for newborn screening will now become a performance measure perhaps under the PHEP grants?

DR. BOYLE: Well, that's the discussion that is ongoing.

DR. GETCHELL: I think that's a great idea.

DR. BOYLE: Oh, well, good. Well, that's --

[Laughter.]

DR. BOYLE: I'm just reading what Alison said. I'll convey that to her.

To me, that's sort of how you'd make this happen. So --

DR. GETCHELL: And the reason I say that is because I don't know that emergency preparedness fully appreciates the --

DR. BOYLE: Yes. I agree. I agree, and that's the conversation we're having. So, actually, I think if they hear it from others other than internally, I think that would be a good thing.

DR. HOWELL: Now we have this contingency plan in your book. It's under Tab 11 or in your computer system here and so forth. It's been reviewed and approved by HRSA. They've had many partners in it, and CDC is currently approving it.

Now one of the recommendations we need is whether or not we should agree to send this forward to the Secretary for coordination by the Office of

Secretary and all the other parts of HHS. Can we have a recommendation that we do that?

DR. DAUGHERTY: Can we have a chance to read it first?

DR. HOWELL: Well, it's in your book. You have had a chance to read it. Have you read it is my question.

DR. DAUGHERTY: No. I'm not sure it was clear to everybody that they were supposed to read it for approval at this meeting.

DR. HOWELL: I would urge everybody to go through their books, and everything that's in the book should be read, and we might discuss it.

So, Tracy?

DR. TROTTER: I move we send it to the Secretary.

DR. HOWELL: We have a motion to forward it to the Secretary. And obviously, the Secretary will coordinate -- is there a second? Excuse me.

DR. BUCKLEY: Second.

DR. HOWELL: We have several seconds, as Dr. Skeels and Dr. Buckley. Obviously, the Secretary will

get this report and coordinate it with other parts of HHS, et cetera. That will not be our job to do the coordination, but simply recognize that we've read this as an important part, and we can say that Dr. Getchell thinks this is a great idea.

[Laughter.]

DR. HOWELL: Is there further discussion?

Can we have a vote on sending this forward to the Secretary? Those in favor?

[A chorus of ayes.]

DR. HOWELL: Any opposition?

[No response.]

DR. HOWELL: We have one abstention? Denise has abstained since she --

FEMALE SPEAKER: Who opposed?

DR. HOWELL: No, Denise does not oppose. She just abstains because she's not had a chance to read it.

Can every voting person raise his or her hand?

[Show of hands.]

DR. HOWELL: And everybody, I think, is

raising a hand, and Dr. Dougherty --

I think we've got it. Do you have that?

It, ladies and gentlemen, is time for a break.

DR. LLOYD-PURYEAR: I have a question.

DR. HOWELL: You have a question.

DR. LLOYD-PURYEAR: Is it just to forward to

the Secretary? Is that the entire recommendation?

DR. HOWELL: We recommend approval and forwarding it to the Secretary.

DR. LLOYD-PURYEAR: That's not -- what do you want the Secretary to do? It's not a recommendation. That's not a recommendation.

DR. BOYLE: Yes. Actually, I think we just want to approve a plan, and then the plan goes to Dr. Frieden for approval and forwarding to the Secretary. That's my sense.

DR. HOWELL: I think the official --

DR. BOYLE: That's the protocol.

DR. HOWELL: Let's go back a little bit. I think the thing is to recommend approval and forward the plan to the Secretary for coordination by the

Office of the Secretary with the Office of the

Secretary emergency preparedness activities.

DR. BOYLE: Mm-hmm, we could do that.

DR. HOWELL: Is that good?

FEMALE SPEAKER: Can you say it again?

MALE SPEAKER: I think that's almost word for

word what I said.

DR. HOWELL: I think that --

DR. LLOYD-PURYEAR: Can we vote on that? Can I write up the recommendations so that we can vote after break? Oh, or vote tomorrow morning? Okay. Thank you.

DR. HOWELL: But for those of you who are going to be thinking tonight, the recommendation will be approval and forwarding the plan to the Secretary for coordination by the Office of the Secretary with the Office of Secretary emergency preparedness activities. That's what we are talking about. And so, we will clarify that again tomorrow and so forth.

We're going to have a break now. And after the break, we're going to have the subcommittees. Let me review where the subcommittees will be meeting.

The Laboratory Standards will be in the private dining room on the lobby level. The Follow-up and Treatment will be in the Mount Vernon Room on the lobby level, and I'm going to ask Dr. Bocchini if he would be good enough to join that group. The Education and Training committee will be in the Foggy Bottom on this level, and I'm going to ask Dr. Jeff Botkin to

join that group, if he would.

Time for a break, okay? And we'll go after the break to the subcommittees. And after that, it's the end of the day.

[Whereupon, at 2:30 p.m., the meeting was concluded.]

DEPARTMENT OF HEALTH AND HUMAN SERVICES/HEALTH

RESOURCES AND SERVICES ADMINISTRATION

Meeting of the Secretary's Advisory Committee on

Heritable Disorders in Newborns and Children

8:34 a.m.

Friday, May 14, 2010

Renaissance M Street Hotel

1143 New Hampshire Avenue, N.W.

Washington, D.C. 20037

P R O C E E D I N G S

DR. HOWELL: Before we begin with the subcommittee reports, you'll recall yesterday we heard a contingency plan that has been reviewed by a variety of Federal agencies, and we have looked at it and thought it was worthwhile. And Michele wanted to clarify the recommendation of this committee, and she's drafted a little note to clarify what she thinks that this committee should do.

Michele, you want to read that?

DR. LLOYD-PURYEAR: I think it's going to be put up on --

MS. HARRIS: I just need one more minute.

DR. LLOYD-PURYEAR: Okay. But I'll read it.

"In order to establish a comprehensive national all-

hazards approach to newborn screening incident response, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children approves the CONPLAN and recommends that the Secretary of HHS coordinate newborn screening emergency preparedness activities as defined in the CONPLAN within HHS's national response framework."

And that national response framework actually means something. I mean, that is the framework for HHS.

DR. HOWELL: Are there questions or comment about that? We discussed the plan yesterday. You have seen the plan, et cetera.

[No response.]

DR. HOWELL: If there is no further discussion, can we have a nomination -- can we have a motion to approve this recommendation Michele has made?

DR. VOCKLEY: Moved.

DR. HOWELL: Jerry moves. Is there second?

DR. BUCKLEY: Second.

DR. HOWELL: We have multiple seconds from Becky and Dr. Skeels.

Those in favor of that, please raise your hands.

[Show of hands.]

DR. HOWELL: Any persons opposing that? And did you oppose it, or were you just --

MALE SPEAKER: No. His hand was still up.

DR. HOWELL: Okay. There was no opposition.

Did anybody abstain?

[No response.]

DR. HOWELL: Unanimously approved.

So thank you very much, Michele.

And we'll now proceed. As you know, we had active subcommittee meetings yesterday afternoon, and we'll now go through the reports of those committees. And we'll begin with the Subcommittee on Laboratory Standards and Procedures. And we'll look forward to hearing a report from Dr. Vockley.

DR. VOCKLEY: Right now?

DR. HOWELL: Right now.

[Laughter.]

DR. VOCKLEY: I'm ready. So this is, indeed, the Lab Standards and Procedures Subcommittee. Sara

Copeland is my partner in crime from HRSA, and I was delighted for I think the first time since I've been the -- Windows has finished installing a new device. Does somebody want to clear that? I don't know how to do it.

Let's see if we can go back. I actually had a committee roster. So I knew who was on my committee

for this meeting. And we had four major agenda items this time around. The first was a presentation by Georgianne Arnold on a proposal that she is going to be bringing forth through the processes I think ultimately to the full committee for an outcomes study for FAODs. And while we're not the outcome committee, she wanted to run it past us because of its extensive use of the existing databases and programs that are in place where we do have quite an overlap with the new IT task force.

So she is looking to utilize existing newborn screening databases to prospectively mine information on disease outcomes. Now this is -- we had a lot of discussion about how this overlaps and is different from other current efforts, and I think number one is -- one of the main issues or one of the main points is

that she is sort of ready to go now and that this will allow some assessment in utility of the appropriateness of data collection within some of the databases that are already going.

So with a little bit of experience under our belt with whether or not we're collecting the right parameters, we may be able to improve the kind of data

that we're collecting, and that a part of that is going to go back to not only following up these patients, but then be able to feedback into validating standards for diagnosis and stratifying risk based on newborn screening result, with MCADD being a prime example. You know, are there determinants of good outcome versus babies who are at higher risk to have symptoms?

So, anyway, while we recognize that most of what was going on was the purview of the outcomes group, we did not see any obstacles to moving forward to full committee and endorsed her proposal from that standpoint.

We then had a nice really sort of Statistics 101 review, looking at parameters in terms of statistical significance of second-tier screening. We

focused a little bit on congenital adrenal hyperplasia, but really, it was a more general approach.

And Reem Ghandour joined us for that presentation, and we just kind of went through a lot of the formulas. It was a real interesting session, sorry, on balancing between sensitivity, specificity, clarifying differences between repeat and second-tier

screening, and discussed some of the formal mechanisms for looking at weighing costs and benefits of adding a sequential screen. So a second-tier screen to a first-tier screen.

And this was largely generated by, I'll admit it, Sara and me, who don't run newborn screening labs and don't necessarily think about these every day. And so, it was actually quite a nice session, and some interesting discussions especially around the second-tier screening.

We moved to a more meatier discussion on newborn screening parameter quality assurance measures, and Mike, in his capacity as a -- well, whichever capacity it was he was in. There he is. Hi, Mike. For this meeting as ACMG, Newborn Screening Consortia,

Translational Research, discussed a little bit about the existing QA systems to really start talking about the stage for standardization of pre- and post analytical best practices over the whole newborn screening mechanism.

So really the idea of developing national benchmarks for timing and quality of newborn screening

tests and the consequences of not meeting them. So we all have these -- we know that if you don't get a result in quickly for something where a baby can crash and burn, what the outcomes are in that setting. But what are -- how do those translate to some of the other diseases? Do you have a 2-day window if you miss your target for CF screening, I think was the example that Calonge made.

So looking to see how best to establish quality measures for each step of the newborn screening process. And so, it's not just the technical aspect of running the test, but each of the processes in the whole newborn screening paradigm, from sample collection all the way to reporting of results and following up of patients.

And I think Piero had the quote of the meeting. Piero Rinaldo had the quote of the meeting, which is to say that we need a transition from asking how many or talking about how many tests we can do to how well we can do them. And I thought that really nicely framed the discussion.

The last couple of meetings we've been having

discussions on specific technologies, just trying to stay ahead of the curve and look at the things that are likely to come down the road in terms of additional or some of the applications that are coming forth. Or in this case for SCID testing, as you remember, we approved adding that or recommended adding that to the recommended panel last time, and most of what we talked about -- in fact, I think all of what we talked about were DNA-based tests. And so, Ken Pass, one of our group members, has been looking at the Luminex platform, an antigen fluorescence readout-based approach to identifying proteins of interest and presented data using CD3 and CD45 antigens to try to capture the number of T-lymphocytes in newborn screening blood spots.

He did a very small pilot program in which he was able to correctly identify 11 out of 120 samples that he exchanged with New England, I believe, and maybe Wisconsin as well. And the nice thing about it was that the spot, once he did his extraction to get the sample out that he needed, that spot could be returned back to a molecular lab and still do a TREC

screening.

So one of the things that or one of the main points of discussion here is not so much this as a platform isolated to SCID. If it proves robust enough to do that, it joins a growing group of disorders where antigen detection is either already the norm, as in some of the endocrine markers, and may be improved with this technology and the lysosomal storage diseases, where one of the competing technologies currently is an antigen-based test.

So upcoming meetings where we will be focusing on looking at some of the QA information on existing systems and tests in collaboration with Mike discussing more about the role of routine second-tier testing and newborn screening, and we've got a number

of those paradigms that have been put forth lately. A lot of them coming from the Mayo program.

And what was that third -- development of network of regional specialization newborn screening labs. Oh, I know. I'm sorry. I had to stop and think about what we were capturing here.

We've had this discussion in the past to some

extent, but again, continuing to raise the idea that as newborn screening becomes a larger menu, and some of those menu items may be extremely specialized, that not everybody needs to do everything and continuing to put forth the possibility that what we really ought to be doing is developing labs with regional or with certain expertise that can serve a region or a network and make that the operative paradigm, as opposed to assuming that everyone is going to do every test.

And then one of the things that we've had an early read on at the last meeting was a comparison project that the Mayo lab is going to do on essentially all the competing platforms for identifying lysosomal storage diseases out of newborn screening blood spots. So we look forward to a more complete report on that.

We're not sure it's going to be ready for the next time around because it's just now getting -- it's up and running, but just barely. So I'll be speaking with Dr. Dieter Matern, who's running that project. And if he feels that it's ready to bring to the next meeting, we'll have him. Otherwise, it may be two meetings after that.

So that's it. I'm happy to take any questions.

DR. HOWELL: Are there questions of Jerry?

Are there any -- what has been your thought about how to develop this regional specialization network that's been discussed a lot, but how would you visualize the mechanics of doing that?

DR. VOCKLEY: Well, I think at least in the starting, it's going to have to be -- the labs are going to have to sort of define their interests, and so if you have a lab that is uncomfortable with molecular testing, maybe they don't want to do TREC analysis. But once, and where the committee might be able to make -- help with this process is trying to capture those data.

So we're not allowed to say "survey" or Jane will get upset at another task, but capture the menu of tests that individual labs would like to do and are already proficient at and/or are planning to set up. And just start making that available perhaps through one of the either the newborn screening consortium or the Translational Research Network to say you've got --

here is what's going on in New England. Here's what's going on in NYMAC. Here is what's going on at a national level.

And you should feel free as a program to utilize those resources rather than being compelled to do it all yourself. So I would think that cataloguing resources would be an important first step in that process.

DR. HOWELL: Any further questions? Do any of the efforts of your committee need to come before this group for any formal ratification or support from the committee?

DR. VOCKLEY: Not this time around, I don't think.

DR. HOWELL: Well, it seems like you've

answered all the questions of people. Thank you very much, Jerry.

And if there are no more questions, we'll move on now to the Subcommittee on Education and Training. And that's Jana Monaco and Tracy Trotter, and it looks like Tracy is moving to center stage here.

DR. TROTTER: Okay. Good morning. I'd like

to start on behalf of Jana and myself of thanking our subcommittee members. Each and every one was present yesterday, and the almost doubling of that number with interested folks who were very contributive, and it was a very good meeting with input from a wide variety of folks at all levels of both care and consumers and perspectives. It was a nice meeting and very enjoyable.

We, as usual, started with our reports from HRSA-sponsored programs that have to do with education. The clearinghouse being number one.

Number one. And Natasha Bonhomme gave us an overview of all the work they have done in the last year since they got going. It's pretty impressive. The beta Web site is now active. I urge you to go

there and start looking through and playing with it. It changes daily, hourly. But it's really coming along.

The obvious idea is to create a true clearinghouse. So we have access to all of the information you'd like to link to in some way in one place. The increased awareness at all stakeholder

levels has probably never been better than this, and the linkage is now 2,000-plus links to other Web sites that would be helpful to someone looking for information genetics and very specifically newborn screening. So that was a nice report. Appreciated the update on that.

The following people reported to us in various ways, presentations were given. Joe McInerney came up and gave us a nice update on the Family History for Prenatal Provider Project. You can see the partners are listed up there, which pretty exciting, interactive, computer-based family history project that hopefully will be going to some clinical testing and evaluation within the next number of months, and we look forward to, I hope, maybe this time next year

presenting some, at least a snippet of that to the committee as a whole, very well done.

Sharon Terry updated us about the HIT interface with education and training. Specifically, what types of things are we interested in? A lot of discussion around the table, which basically said it needs to be practical and it needs to fill some sort of

need for the primary care physician, or it's just one more thing for them to think about all day that they don't have time for.

Things that we felt maybe fit that category best is educational efforts on a just-in-time basis so that one is being more efficient in what they're doing. And creating a way to take care of, create care plans and coordinate care plans for complex patients, things that already take time and could be much better served with something of this variety.

And then Deborah Heine reported to us on a HRSA project on parental attitudes regarding newborn screening. Always interesting to get the perspective of the people we are supposed to be working for all the time, and there was a large group of parents with us,

and it was -- I hope will be an ongoing dialogue for us to continue to hear from them.

If your initials are up here, then your group was represented in some way. Kathy Camp gave us an update from the other advisory committee, not to be confused with the advisory committee.

[Laughter.]

DR. TROTTER: And representatives from the academies of all of the primary care groups updated us on what was going on in their venues.

I'm happy to say that there are -- at least in the last couple of years since I've had this perspective, the number of things going on are increasing. The number of things going on are more -- people are more aware of them, and they're getting more attention, and I feel like we're moving, albeit slowly, we're moving in the right direction in this effort.

Go back to the slide that I used 2 years ago that in pediatrics -- a number of the authors on this table and in this room certainly -- advances will give new challenge to the primary care physician, and that is true, and will require access to the information

collaboration, et cetera, et cetera.

So, with that as our basis, I'm happy to announce that I believe today is the contract availability for Genetics in Primary Care Institute, which was approved by this committee last September. And the contract will be out. It is going to have an advisory board, plus this committee as its advising

folk, development phase, implementation phase, and then report back to us.

And it is -- to remind those who don't remember my last two reports, it's the pairing of a primary care physician with a medical geneticist to create a 1-year project that will increase the awareness and utilization of genetics in that person's practice. And we hope that will be a "teach the teacher" approach and that we will get a lot of follow-up through those folks.

There are two focuses of this contract. Number one is to increase the number of primary care providers who are competent and confident in providing basic information about newborn screening and common genetic disorders to their patients and families.

And a second, somewhat different, in regions with limited genetic expert access, to increase the number of primary care providers who will be more knowledgeable and secure in providing care that is more comprehensive to individuals and their families with less common genetic diseases.

We came up with a number of targeted

knowledge areas that we felt, as a subcommittee, were appropriate for any and all of our projects to work on, and each works on little different pieces of this. We hope the Genetics in Primary Care Project sort of works on all of those in some fashion.

And again, I think we had a productive meeting. We have no formal requirements to the committee at this point, but our report. Question?

DR. HOWELL: Questions of Tracy and Jana, who chair that committee?

Oh, Chris?

DR. KUS: Tracy, the pairing of the geneticist and the primary care doc, how much is that going to be? How many do you think that will be?

DR. TROTTER: I don't think we have an idea

yet. I don't know if it's even going to be multicenter or single center. Maybe Michele knows that?

DR. LLOYD-PURYEAR: Penny Kyler, Dr. Kyler?

MS. KYLER: Hi, there. The contract calls for pairing of genetics expertise. So it's not just geneticists. It could be a genetic counselor, things like that. And in the initial phases, we're looking at

25 pairs. I think that's about as much money as we can fund, and that would be across the country.

DR. HOWELL: As you look at the news every day about newborn screening, most of which has to do with residual dried blood spots. But the issue is the lack of public information about newborn screening is enormous, and do you have a sense that there is really substantial progress being made in that area, and can you give us comfort that this is happening?

DR. TROTTER: No, I really can't give you comfort on that, sadly. We see that as a huge problem that has many heads to it. One of the problems is many of the folks who are providing care for these patients are also relatively not knowledgeable, at least not knowledgeable enough to address the issue straight up

and be our 200,000 ambassadors that we should have out there doing primary care. So that becomes one issue there.

And the other is something we all face every day, and that's the squeaky wheel gets the newspaper, so that the 90 percent of people who actually think it's a good idea and aren't concerned about it don't

get interviewed very often.

So we need to continue to be good ambassadors for this and be more vocal and to make sure that we know our part, whether it be the patients I see in the office or the people you all interact with understand the positive sides, the good things, the importance. I think we've been riding the wave of it is good and it's very well done, and isn't that nice? But complacency is not a good thing.

DR. HOWELL: Is there anything that this committee should be doing that we're not? Have you identified something that you said, "Oh, goodness, we should be doing that, be supporting that?" And we're not.

DR. TROTTER: I don't think we've looked at

that as directly as you stated the question, but we should. I don't have anything to bring forward today.

DR. HOWELL: And I think it's terrific that you've got a lot of parent input and consumer input into trying to figure out how to move along with that. But I think that the education piece is where we really have a problem in the public arena, I think.

DR. TROTTER: Well, I think we put that charge to the group that was with us yesterday. There were about 35 people in our room, many of whom are very influential in their spheres, and I think that that's not a bad way to let us focus for the next year.

DR. HOWELL: Outstanding. Are there other comments?

Coleen?

DR. BOYLE: Hi. Thanks, Tracy. That was great. And Jana.

I just -- I guess Rod's comments triggered a memory, a distant memory for me where we actually talked one time about making a recommendation about doing sort of formal campaign, consumer campaign about the benefits of newborn screening. Really to sort of

offset a lot of the perhaps fear and negative press.

But just like there's a national campaign on immunizations that rolled out, have you thought about something like that, or I don't know --

DR. TROTTER: I'll give that to Jana. Not in my term, but sounds like a good idea.

MS. MONACO: I think I know what you mean,

Coleen. We've talked about that. But one of our meetings, we all admitted the reality is that the funding is really what holds something back like that, and these national campaigns that have these issues out there getting attention have a lot of funding with them. And unless we have that to back it up, there is no foreseeable way to really realistically do that.

DR. HOWELL: I think Sharon has an idea. Oh, Bennett, will you --

DR. LAVENSTEIN: Well, I was just wondering. March of Dimes has taken a major role in publicizing in terms of this. Quite a bit of advertising, if you will, educational advertising, advocacy.

DR. HOWELL: Absolutely, and they were obviously at your committee yesterday.

DR. TROTTER: Yes. Alan was there. That's right.

MS. TERRY: And Alan and I have talked about this directly, and right to Jana's point, we've estimated between $2 million and $10 million would be needed to do like the "Red Dress" campaign or any -- the folic acid stuff that March of Dimes did. So a

really substantial sum of money, since advertising and public outreach just costs much, much more.

I mean, one of the things we're looking at is so if we all combine resources, do we come anywhere near that? And right now, the answer is no. But are there other things we could leverage in terms of social media, et cetera? And that's the sort of stuff that we're working on in the clearinghouse and other places.

DR. HOWELL: Well, you know, I think that if it's conceived that we really should do this and so forth, we then should make a decision to try to do it and then figure out how to fund it. Because obviously if it's an important thing, we should be able to identify a way to fund it.

MS. TERRY: Right. And Alan and I have

schemed what this could look like in a really nascent kind of way and are very ready and eager to do that sort of thing with all the other partners in this space. So we could get serious under the auspices of the committee and put together what that could look like and then look for funding.

DR. BOYLE: Well, I would encourage you -- I

just remembered the discussion from a number of years ago, and I think it's a very positive idea and one that really could have a continuing -- it could mature as it goes in terms of what the content of the message would be.

DR. TROTTER: Well, I think it's certainly timely with the explosion of information that's coming from other arenas.

DR. HOWELL: And I think Penny has a word.

MS. KYLER: Yes, I do. The other thing is that we have funded four projects that are coming to closure really looking at parental attitudes regarding newborn screening carrier testing, and these are across the country. They are providing both qualitative and quantitative data to give us some answers to the

questions about what do parents really think about this whole issue?

So when we're talking about a message, we hope that this will help drive the message or help give us the kind of mind cloud, as Sharon talked about, what parents really are thinking. Just as an FYI, I mean, some of the communities that are involved are we have

one project in Iowa that's looking at Sudanese refugees, something we really don't know a whole lot about, Old Order Amish. We have within this project the western States consortium.

So you're looking at a triad there where you're looking at the laboratory, the primary care doc, and the woman receiving the information. We have two other projects within Genetic Alliance that used online, what's the name of it?

FEMALE SPEAKER: Knowledge Network Survey System.

MS. KYLER: Thank you. Knowledge Network Survey System that has done a survey of over 3,000 women. So we're going to be able to bring you some concrete information, we hope, shortly.

DR. HOWELL: Well, Penny, you'll be sure to get that summary of those efforts to this subcommittee.

MS. KYLER: I will. And also in Iowa, I think most people know Janet Williams in nursing. And they have done a systematic review of the literature for us. So that's also coloring the landscape.

DR. HOWELL: Further comments or questions to

Tracy?

Andrea?

MS. WILLIAMS: I just wanted to -- thanks, Coleen, for bringing it back up. One of the thoughts behind, for our previous discussions was that we would prepare the primary care physicians for the onslaught of the public response to a public campaign. So I'm really happy that you guys are revisiting that because that is something that was on the table a few years back.

So I think it's really timely that we did address the physicians and their educational needs and then be able to have the right responses and be prepared so that they're not caught off guard when the public comes knocking at their door.

DR. TROTTER: Good point.

DR. HOWELL: Tracy, thank you very much for your excellent reporting. We look forward to great things coming from your committee.

We're going to now move to the Subcommittee on Follow-up and Treatment. And Coleen Boyle chairs that committee and will provide our report.

DR. BOYLE: Well, good morning. Last, but not least, we also had a wonderful committee, very productive committee meeting, subcommittee meeting yesterday. And I want to recognize our long list of subcommittee members, and we also have a number of new members.

So I think we have our sort of old and seasoned members, not -- old in a nice way. Not old in an old way.

[Laughter.]

DR. BOYLE: As well as our sort of enthusiastic new members. So it's really a delight to be engaged in this activity.

So most of the time was spent, we spent time on updating. I think you've heard about all of our

activities here, but I'll give you the updates on them.

So we spent time on updating everyone on our ongoing activities, and then we actually had strategic planning portion that Alex Kemper led us through.

So, for the updates, we have been, as you know, we have been focusing on long-term follow-up as a sort of primary focus of our subcommittee work. We

have the overarching objective paper that was published a number of years ago. We actually now have a draft of a white paper that follows the September meeting that we had, where we're looking at the overarching questions in terms of thinking about how to measure success from long-term follow-up.

There were a number of us that met on Wednesday with NCQA, the National Committee on Quality Assurance, to actually take those overarching questions and then try to develop quality measures for them. So thinking about HEDIS-type measures for some of them.

I think we actually made quite a lot of progress on that, and we're hoping to continue to work with NCQA. And I want to thank HRSA for providing support for that activity because I really do think

this is going to help provide some high-level framework for addressing long-term follow-up issues. And if anyone is interested in looking at the matrix, the matrix is really a crosswalk between the objectives of long-term follow-up and the actual principle systems that are engaged in long-term follow-up.

So I'd be happy to share at least a draft of

that matrix with the committee members at this point. It might be good to get some feedback on that.

Moving on to the next item listed there, you know we've been working on the issue of medical foods for quite some time from a subcommittee perspective. And the focus of our subcommittee really was to try to get more information to sort of fill those information gaps about the cost to families in terms of medical foods and the reimbursement-related issues.

So we have a survey that had been completed in three regions. And correct me if I'm getting this wrong because these genetic regions, I forget the acronyms for them. But I think it's the Mid-Atlantic, the Southeast, and then Sue Berry's region, which I don't remember the name of it.

So, anyway, those are the regions that we've been doing the survey in. The data analysis is ongoing. Mary Kay Kenney, who is on the HRSA staff, actually did a presentation last week at the newborn screening meeting, and we decided next steps there. I think there were some questions about the analysis, and we're going to have a small team working with Mary Kay

to actually look further at the analysis. And hopefully, by the next committee meeting, we'll give you a presentation, I guess in September, on that.

Last time, we brought back to the committee one of our issues on short-term follow-up. We did some brainstorming about -- since we've been focusing mostly on long-term follow-up, we did some brainstorming on what are some of the barriers and challenges from a short-term follow-up perspective. And the one that we identified that we thought might be a little bit of a no-brainer, although it's not really a no-brainer, is this whole idea of using the birth certificate as an anchor to do some type of ongoing quality control or quality assurance to make sure that newborn screening is actually happening. So making that linkage between

birth certificates and newborn screening to be more real time.

And Brad Therrell, who actually was doing the work on thinking through some of the issues around short-term follow-up, volunteered to draft a white paper to try to lay out the issues there from a State and a national perspective. So he has a draft that he

shared with our committee. We didn't really have a chance, all the subcommittee members, to actually review it and comment on it. We had a nice discussion around it.

I think there were some concerns about it from a privacy perspective and from an implementation perspective, but I think there are some good potential recommendations coming from that. So I don't feel like we're ready to share that with the full committee yet, but hopefully, by the September meeting, we'll have something in advance of that.

And then we did hear from Alan Zuckerman about potential HIT collaboration, and I've just listed a few that he identified, obviously thinking through whether or not HIT might be helpful in regard to this

newborn screening birth certificate linkage. He talked about our work on quality measures and, again, the role of HIT from a medical home care coordination perspective. And then he even brought up the idea, which I hadn't thought about previously, which was what we talked about yesterday on contingency planning and the family perspective and, again, the role of

information technology and facilitating that.

We do have liaisons to the HIT Workgroup and that's -- from our subcommittee, that's Robert Bowman, who is a new subcommittee member, and Alex Kemper.

So I also mentioned that we spent some time under Alex Kemper's facilitation to think a little bit more since most of our -- a number of new members have joined our subcommittee to think a little bit more strategically about where we're going because I feel like we're -- it's not like we're coming to the end of a pathway, but I do feel like we are filling in a lot of the information gaps on long-term follow-up.

So someone had the brilliant idea to actually relook at the subcommittee charge, which we actually haven't looked at in perhaps 4 years. Fortunately, I

did have it on my laptop. Everyone felt like it was still something that provided guidance to the committee. So we reaffirmed that charge, and then we started to brainstorm a little bit about sort of the barriers to short- and long-term follow-up.

I think we have a little bit more work to do in terms of providing guidance, future guidance to the

subcommittee. I have some ideas of how we can move that process forward between now and the next subcommittee meeting. Obviously, there is a lot of opportunities and challenges that our subcommittee could take advantage of, particularly in the area of IT as well as in health insurance reform.

But I think that the door is going to close fairly quickly for the latter. So we need to move fairly quickly. So if folks around this committee here have specific ideas, please share them with me or others that are on the subcommittee.

And then, as Jerry mentioned, we also had a presentation by Dr. Arnold. We didn't have a whole heck of a lot of time at the end, and she did a fairly quick overview of the two issues that she came to talk

about.

One was the work that she has done in terms of developing practice guidelines for specific conditions where there apparently is not appropriate guidance in place. And then she also talked about having more timely data, acknowledging the great work that's going on in terms of developing the

infrastructure to have this in the future. But she really felt this urgency to have more timely data about outcomes.

I think the subcommittee sort of endorsed both of these ideas as definitely important ideas perhaps this committee to consider in more depth, though I don't think we felt like we could endorse either processes.

So that's it. I don't know if anybody -- actually, this is not. This is from last time, sorry.

DR. HOWELL: You're not going to discuss your last slide?

DR. BOYLE: No.

DR. HOWELL: Okay.

DR. BOYLE: That was from my last

presentation, and I didn't delete it last night because it got really late.

[Laughter.]

DR. BOYLE: So are there questions?

DR. HOWELL: Any questions or comments for Coleen? Can we expect more recommendations from your subcommittee on the medical foods, nutrition situation

that you discussed earlier in your presentation?

DR. BOYLE: I think that we are not to the point where we have a good understanding of what we've found from that survey information. So, obviously, the reason we did that survey was try to fill the information gap. Because when we went forward to the Secretary with that original letter, there really was a dearth of information about cost reimbursement issues. So, hopefully, we'll give you more a sense of what that information is.

DR. HOWELL: Sure. I think the committee is aware of the fact that we sent a letter forth about medical foods some time ago to the Secretary, and the Secretary, quite correctly, said some of the things that we would like to do are legislative in nature and

that she was supportive philosophically but could not do those. And as you recall, then Senator Kerry's office took that letter and drafted the legislation that was introduced, and that currently has -- nothing really happened, it appeared, for some time.

But then recently, it's had some members of the House have signed on as co-sponsors of that

legislation. But I'm not aware that there has been any recent aggressive movement on that. Someone else may have a comment. Michele, do you have a comment about that?

DR. LLOYD-PURYEAR: No. I have another comment.

DR. HOWELL: Michele has another comment.

DR. LLOYD-PURYEAR: I was going to talk to committee staff -- and actually, somebody does have a comment. But this is a general comment for the subcommittee chairs to please review the Newborn Screening Saves Lives Act. There are several areas that we, one, have to write a report about as a committee, but the committee, subcommittees also need to really focus on and address.

And most of the specificity concerns the laboratory subcommittee around standards development, harmonization issues. So if the subcommittee could provide leadership or the subcommittees could provide leadership to the committee upon reviewing the legislation, that would be helpful.

DR. HOWELL: I had spoken to Michele about

this. I think it also would be helpful if we could ask the HRSA staff to go through the legislation and tease out the directives about what we are to report on because it's quite specific and then provide those to the committee. That would be helpful so we will not overlook something and come up with a deadline this next week, and we've not really thought about it. And I think that Michele, I think, felt that that could be done with the staff.

We have a comment.

MS. BROWN: If I could make a comment on the status of the Medical Foods Equity Act. I'm Christine Brown, the executive director of the National PKU Alliance and a new subcommittee member of the Long-term Follow-Up Subcommittee.

We currently are working to secure 100 co-sponsors in the House of Representatives by the end of June and working in conjunction with other organizations from the rare disease community, as well as SIMD and GMDI in getting those messages out. And we'll be bringing families to Capitol Hill June 9th through the 11th for direct visits with mostly people

from the House in hopes to be able to get enough sponsors where the bill can be voted on the floor before August 8th, which is the summer recess.

DR. HOWELL: Thank you very much, Christine.

DR. BOYLE: Christine, could you also just make a comment about the medical foods and children with inborn errors in metabolism from the health insurance reform?

MS. BROWN: Well, one of the things that we're starting to wonder is that with the recent passage of healthcare reform by Congress, what does that do in terms of impacting access to care and treatment for people with metabolic diseases? And what we're concerned about is that as HHS moves to creating the regulations around that bill, that it's going to be

very important that medical foods are included as essential health benefits. Currently, they are not listed in the legislation that was passed.

And in addition, we want to make sure that when they look at defining the high-risk pool in terms of people being able to access insurance, that metabolic diseases are included in that high-risk pool.

DR. BOYLE: So, in thinking about this overnight, I was wondering whether or not we could draft some type of letter to the Secretary. Obviously, this is within her purview in developing the regulations. I'm not exactly sure of the details of that, but I think that we should not wait until September to do that.

DR. HOWELL: Is there any reason we could not do that?

DR. BOYLE: No.

DR. HOWELL: Michele?

DR. LLOYD-PURYEAR: Yes. No, there's no reason.

[Laughter.]

DR. HOWELL: Yes, no. The bottom line, there

is no reason. And so, perhaps we can ask Michele and her staff to draft an appropriate letter that really deals really with our previous letter, but emphasizes that in the healthcare reform area, we should be --

DR. BOYLE: And it may be -- I mean, that may be a piece of it. There may be more details, making sure that all of the appropriate treatments are covered

respectfully and under the regulations. So I think we need to have somebody who's knowledgeable about a lot of these issues.

DR. HOWELL: Certainly HRSA has a large number of people working on healthcare reform.

DR. LLOYD-PURYEAR: Well, we do in this area. But to get a letter approved today or the recommendations approved today, I'd have to do something at lunch time so we can vote on it. Is that what you want?

DR. HOWELL: Could you get it done at lunch time?

[Laughter.]

DR. HOWELL: I think that will be soon enough. And so, perhaps if -- I mean, you ordinarily

eat lightly anyway. So the thing is if Michele could draft a letter at lunch time, perhaps we can look at it after lunch. And if it's suitable, you can make comments about it, and we can vote on it after lunch.

Chris?

DR. KUS: Yes. I think that goes in the context of healthcare reform in terms of coverage for

kids with special healthcare needs, and this population with the preexisting condition, we should highlight the food part but realize that that whole package of coverage is going to be -- needs to be addressed in healthcare reform. Because they talk about preexisting conditions, but what do you get if you've got coverage?

DR. VOCKLEY: Rod?

DR. HOWELL: Jerry?

DR. VOCKLEY: It should probably also reference nutraceuticals because that sort of falls into the same category.

DR. HOWELL: I'm sorry?

DR. VOCKLEY: Nutraceuticals, you know, are nutritional supplements that are not formula, but are not approved medications.

DR. HOWELL: Yes, that's certainly in the current plan. That's in the current legislation. That's excellent. So we will try to get that in and move along and so forth.

That brings to a close our follow-up and treatment things, and that will put us to move ahead to discuss the final report on the candidate nomination

for Hemoglobin H. And I think it's fair to say that as we go through these conditions for review and evaluation, each time there are new challenges that we address, and we need to keep those in mind. And the one that's consistent and certainly is present here in the Hemoglobin H review is a paucity of evidence for some of the situation, which we find very commonly in obviously the rare conditions we deal with.

Today, we've asked -- in order to consider some of these things today, what we've done is we've asked Jim Perrin to present some of the evidence review issues that we're going to have to deal with as we move ahead. And then, after Jim's presentation, we're going to ask Dr. Kemper to actually present the Evidence Review Workgroup report on Hemoglobin H.

And so, Jim, if you will walk us through some of the challenges that we need to think about and deal with? I think the question is dealing with these challenges and still be rigid and systematic in our approach, and it's a fine line.

DR. PERRIN: Thank you very much, Dr. Howell. And thank you to the committee for the continuing

opportunity to work with you and with the bureau. We've found this a fascinating and incredibly rich and rewarding experience of trying to provide evidence to the bureau and to the committee.

So I wanted to review, just very briefly, what we talked about a while ago with you with respect to the kinds of evidence that we would try to gather together to support decision-making by the advisory committee. And then to take you a little bit through what we've learned from our experience so far together and really to ask you to think with us and to give us some advice on what are the most relevant topics that seem to drive your thinking as you do make decisions together.

Back in 2008, this was the list of topics,

key review questions that we used in a general way in discussing or describing the evidence for any of the conditions that we were reviewing. A fairly lengthy list, and we have tried to stay on this list and to develop the best available evidence in these areas in each case.

Obviously, the incidence and prevalence of

the condition, something about its natural history, including what is known about when it shows up clinically, something about the variations in severity of disease, and something about the genotype-phenotype relationships. A good deal of information about the screening tests, including the methods of screening, their accuracy looked at several different ways, the methods of diagnosing screen positive children, and then the risks and costs involved with screening.

At the next level of treatment, we've looked at methods of treatment. We've looked at the evidence for whether treatment actually seems to help children, and we've focused -- and I think you have focused -- appropriately a lot on this question of does early treatment help, rather than treatment in the course of

disease once it is presented?

And what do we know about the availability of treatment? Now, this is not something that we've been able to do in quite a systematic way because usually this isn't published information. But we've tried to gather information on availability of treatment and something about risks and costs. And we've agreed in

every case to provide you with the list of the kind of critical information that we think is missing from evidence as we've done these reviews.

So, again, these are the topics that we agreed upon back in 2008 in our discussions with you. And as you know better than we do, you have sort of four major opportunities in how you review or what you consider how you vote on the recommended or proposed conditions here. And this comes from I think one of your recent reviews of the process here.

The level of certainty is probably the important area here. Where is there evidence that is quite sufficient and level of certainty is high, then you might recommend adding the condition to the panel. In situations where you don't recommend it, it's

usually that there's good evidence that it's not of value to add it. And often, though, I think you're focusing on the issues where there may or may not be sufficient evidence and have often gone back to something like recommendation number three and requesting more evidence.

So I wanted to just review quickly. I don't

want to spend a lot of time on this in detail, but to review quickly our experience to date together. These are the projects that we've worked on -- Pompe disease, SCID, Krabbe disease, Hemoglobin H, and critical congenital heart disease, which Alex is going to describe in more detail today. And then we're about to begin work, we actually have begun work on kernicterus and bilirubin encephalopathy. But we are not presenting any of those data today.

So my purpose here is just to review quickly what were the critical issues as we understand them from the advisory committee's discussions about these conditions. So, for Pompe disease, we believe that the committee focused on the lack of population screening in the United States or a similar population. There is

some evidence for population screening, but there are some questions that arise in that evidence, and especially, there were real concerns by the committee about its applicability to a somewhat different population in the United States.

Second, there were some really complicated issues in case definitions, and we're going to talk a

little bit about our newer approaches to case definitions later today. But specifically, in the case of Pompe disease, the issue of early versus late onset and how easy it is to distinguish between those two.

In general, here the evidence regarding treatment for early infantile Pompe disease seem to be pretty good from our viewpoint and from the committee's viewpoint, although there is a complication about kids who are CRIM positive versus CRIM negative in this particular circumstance. But in general, the weight of discussion did not reflect the issues about whether treatment is effective here.

For SCID, there are some challenges. There were some challenges in case definition of SCID. I think we worked through them in some real detail with

you. At the time of the initial review, there was a lack of population screening, and that led to the committee's recommendation to await better data from population screening, and indeed, more data are now available, especially from the Wisconsin trials. And there's a lot more work, hopefully, about to be going on in this particular area.

But that was, in many ways, at the initial time the limiting step here. In general, the evidence for early identification and treatment seem to be very good. This was not a matter of debate, I believe, at the level of the committee here.

For Krabbe disease, ones which you looked at fairly recently, the population screening data were really very nonconclusive, and there are real challenges in Krabbe disease about case definitions and really early versus late onset disease here. In the evidence that was provided, tremendous problems about false positives. I don't mean to say that the numbers of false positives were particularly high, but the evidence about the natural history of false positives was really quite marginal in the sense of really being

good and available to us.

And there were real question that were raised by the committee regarding how well the test identifies children who can and will benefit from early treatment. The diagnostic efforts here are challenging, had some evidence, some discussion by the committee.

And in this particular case, this is one

where the treatment side was a major issue of discussion with the committee. There is some evidence there that earlier treatment has better outcome, at least in the short term, very good evidence that earlier treatment has better outcome in the short term. But there were questions raised not so much in the published evidence, but elsewhere about long-term outcomes. So these were some of the particular issues for Krabbe disease.

We're going to talk shortly about Hemoglobin H and cyanotic congenital heart disease. So I'm not going to talk a great deal here about those issues, except to say we believe that the issues in Hemoglobin H that you will consider are that the natural history of screen positive children is really quite unclear.

And the evidence that early identification of children with Hemoglobin H disease helps is lacking at the moment.

There is some evidence, some good evidence that treatment helps, but it's not clear exactly for whom or at what point in the natural history of the disease that this treatment helps. And I'm not going

to talk about pulse oximetry because we will get to that shortly.

So just to really summarize some of these things, our sense is these are some of the things that have been most cogent to the committee's discussions. Some characteristics of the test, especially issues of test characteristics and their ability to distinguish effectively early versus late onset conditions. Now that isn't true across all four or five of these, but across a number of these.

And population testing data are particularly critical, and I think we recognized in the SCID circumstance especially, but frankly, for all of these rare diseases, that one needs to have, of course, huge populations in order to screen effectively and to

understand the characteristics of the test often if you're going to use population-based data to sort of make decisions. But these have been critical elements.

Another question that has been consistent across the discussions has been the value of early identification, rather than waiting until these children present clinically. In general, the evidence

in almost all of these cases is that treatment helps. And I don't mean to say it's 100 percent across the board, but in general, that's not been a major matter of debate for the committee. It's not a major question in most conditions.

And similarly, the severity in general has not been a major concern here. It may be in some of the ones we're going to be working on now with you, but in general, that's not been the issue. We're dealing with Krabbe or SCID or Pompe disease. These are clearly very severe conditions, and the debate has really appropriately gone in other areas.

Less critical data in general, but not again always in specific, have been really the incidence in prevalence data. Now, obviously, incidence in

prevalence plays a tremendous role in interacting with test characteristics with respect to positive predictive values and sensitivity and specificity and so forth, and the numbers of false positives. But in general, this has not been an issue that has been a major one on the specific conditions we've been dealing with. And natural history alone, i.e., forgetting

about treatment, has not generally been a major piece of debate within the committee.

So really, in summary, I think what we're saying is that certain topics from our view have been most relevant to the advisory committee's decision-making, and what we're interested in doing is simply fostering a dialogue with the committee regarding whether you agree with our assessment of what have been most important to you and how to help focus our evidence reviews to be even more supportive of the kinds of decision-making by the committee.

So that's really the purpose of this presentation. Thank you.

DR. HOWELL: Thank you very much, Jim.

Are there questions or comments for Dr.

Perrin about his assessment? Ned?

DR. CALONGE: So, Jim, I appreciate the opportunity to start thinking more in depth about as we look at applying recommendation and evidence and methodology that has been abstracted from diseases that occur more often to rare diseases. How does that play out? I think there are a number of ways that we can

start to think about having additional information that will help us.

Let me start, though, with kind of the output. So when we get to the end and we say we don't know, which is going to happen, I think the committee may want to explore a more robust set of decisions or next steps for what we do in the area of insufficient evidence. So now we have this kind of "we don't know" category, which says we need pilot studies or we need more information.

I think trying to think of more options in that box about this is the evidence gap we need to fill in. This is what would help us the most. If we could just answer this one thing, we could move forward. I think that more robust group of decisions would be

helpful, and I think that's a committee process.

I think when we look at our methods themselves, I think there are also opportunities to explore perhaps some new approaches. So, in addition to what you'd say, I'd say one of the first things you said prevalence is that's what it is, but that represents the entire universe of what we could

address. So if we're looking at two cases a year, you recognize that you can't do any better than helping two cases. Does that make sense?

So you understand the total potential benefit if you cured everybody, okay? So I think that's an important issue because that kind of bounds, puts an upper bound on what good we could do. And I think that can help put it in perspective.

The next area I looked at was treatment works, and you talked a little bit about this. And so, the thing we have to look at is what does that mean, treatment works? And I think we say, well, we can extend a life. But the kind of long-term treatment outcomes or things that we're -- since a lot of these therapies are new, we actually don't know beyond 5 or 7

or sometimes 10 years, and I think kind of

understanding what the life trajectory of that child is

beyond what we know, what treatment works really means

will be an important thing to kind of think about in

bringing to the table.

Also, there are other outcomes we have to be

cognizant of. So how this information can translate to

counseling for parents and making other reproductive decisions. And that's something we always talk about, but it's a researchable question that I don't think we have good research on yet. So I think exploring the other benefits.

The early treatment works is a concept of early treatment works better, and so that's what we really are looking at. And it's the issue, let me see, how am I going to say it? You have this tradeoff. Our tests are so good that they capture everybody. And I would posit that there is actually an overdiagnosis problem because there is a spectrum of disease associated with the kids who test positive, and that gets to another thing we need to strengthen up, which is what are the harms of screening?

In the adult world, we talk about the difference between screen-detected disease and clinically detected disease. And the problem, at least in the adult world, is those are different. That not all screen-detected disease needs to be treated. That's what overdiagnosis is. And part of the problem I see right now we're wrestling with is that for some

of these diseases, there are kids that need therapy and there are kids that therapy is not needed. And we can't quite separate that out.

So trying to delve more into are there expected to be differences between screen-detected diseases and clinically detected diseases? To me, SCID is a great example because, you know, I think you were able to convince us that if you got it, it's bad. And if you got it, detected it through screening, there is not these false positives or overdiagnosis problems. So the potential for harm goes down.

I worry that our studies don't look at harm enough, but at least we could bound the benefit and we could bound the harm by saying do we think there's a reasonable number of kids for whom we're either doing

overdiagnosis or creating false positives? Let's see if I have anything left.

So if we could -- I think what we're going to end up doing is having to take what we know and reframe it into questions of what's the entire spectrum, the entire universe of upside that we could do, we could benefit? And in the kids we're detecting through

screening, are there kids in there that are different than the ones we would have detected clinically? Do we gain health benefit by detecting them through screening versus benefit, and what are the tradeoffs of that? We capture everyone through screening, including kids we don't need to treat versus we wait and detect them clinically.

So those are kind of my thoughts about areas where we're going to have to move beyond the evidence and try to apply some logical assumptions about what we expect the diseases to do. And then we'll still end up with insufficients. We need a more robust process for saying how to fill in those evidence gaps.

DR. PERRIN: As always, an incredibly thoughtful commentary. And thank you, Ned.

And I think it, to a degree, by the way, in the paper that we had in Genetics in Medicine a couple of months ago, we tried to lay out some of these specific issues because we have been tremendously frustrated by our inability to gather exactly some of the data that you're asking for. So long-term outcomes are a key issue where we have very few data in almost

every circumstance.

Broader data other than child-specific data in relatively physiologic terms almost don't exist, and Lisa Prosser has been a colleague of ours on this, an economist. And we have almost no economic data of any kind, and I don't mean simply cost of screening, but we have beyond that very, very few data have been available there. So I think it's been a big issue.

The second issue that you raised that's quite interesting is the issue whether early identification and treatment is better than later identification and treatment. And again, we're dealing with the fact that we're going to have almost no RCTs here or anyone who has sort of actually done a direct comparison.

All the comparisons are relatively indirect,

actually, in that area, and that does create some very interesting issues about the quality of the evidence that we're dealing here. And I think that's particularly true.

And then, finally, your very thoughtful comments on screen-detected versus clinically detected children, of course, was a critical issue in Krabbe

disease, where we just don't know who the screen positive kids are, what their condition is. And of course, there are far more screen positive kids than there are children who actually have clinically apparent Krabbe disease. So that's a classic one where that really is true, and I think you're right, and again, we struggle to find that evidence as much as we can.

So thank you. These are very helpful comments.

DR. HOWELL: Mike, and then we have Chris, and then we have another Mike. Mike?

DR. SKEELS: Thank you, Rod.

These evidence reviews are fantastic. I greatly appreciate the work that goes into them. I

would like to make a plea for a little more in the way

of economic analysis when possible. I don't know if

that goes beyond the scope of the reviews or not, but

when it comes to translating these things into

practice, the first thing I get asked is how much is it

going to cost? And while that isn't known sometimes at

the point that you're doing these reviews, it would be

helpful to know the unit costs associated with the laboratory work, with the follow-up, but also the benefits of something that could help us at least make an educated guess about costs avoided in the future and so forth, that would really help us sell these when we go home and try to persuade elected officials that it's a good idea.

DR. PERRIN: Very helpful, and just came to my mind, Michael, as you said that was so we do have an economist who looks at published data, and there are almost no published data. But I think we could expand our expert questions because you know in our second phase of the work, we talk with people, both in this country and elsewhere, who are expert in the particular condition. And I believe we could expand our questions

in that area and do a better job than we're doing.

So I might get back to you and ask you for your help on the kinds of questions to put into that. But that's a great idea.

DR. HOWELL: I think in some of these conditions, you probably, in working with the experts, could come up with some pretty good data. And I'm

reminded of I was just in Miami recently, and an infant had been admitted who had been hospitalized in the intensive care unit in Georgia and Florida several times and had accumulated vast, vast bills. And this child, unfortunately, was an undiagnosed kid with SCID. And we know that -- I mean, you could simply take that one child and you have the hospital bills, and you could look at the cost.

And obviously, the child was immediately diagnosed and transplanted. But from Rebecca's data, we know that that child's prognosis is not going to be nearly as good. But you could probably gather a fair amount of information like that. It will not be excellent.

Chris?

DR. KUS: I mean, this is a follow-up on that. I think what happens when I've heard some of the discussions is we move into the cost-effective discussion, and it's not very structured, and we're not sure what the costs are because we talk about financial cost, but there is also costs of false positives, that kind of stuff.

And so, one thing is to help structure that discussion and be clear about what we know, what we don't know and not -- so at least we do go through that part of it. And I guess the other part, and I'll use Krabbe as the example, is who are we screening, what are we screening for in a disease where there is reported late onset, there is the early onset, which terrible outcomes. We're not sure a lot about the late onset. And how do you be clear about what you're screening for and what's going to be benefit for those severe cases, and what do you do with the late onset aspect?

DR. HOWELL: Well, I think it's clear that folks that work in inherited metabolic disease, to come back to Ned's comment, is the patients that we

historically know about are those that are diagnosed clinically. And when you start screening a population, you're going to find, oh, my goodness, there are other kinds out there that we did not know about.

Mike Watson, you had your hand up earlier?

DR. WATSON: Yes. Another issue is around what constitutes availability of treatment. And SCID

is probably the one we talked a little bit about this in the lab, surprisingly in the lab group yesterday. Bone marrow transplantation is available. Medicaid doesn't pay across States.

So I'm wondering if we need to look better at whether there are likely to be impediments to an organized system of service delivery for some of the conditions. And with healthcare reform and our work in medical foods, it's a bit of an extension of that whole area of involvement in healthcare reform about how we assure the availability of coverage for bone marrow transplantation in these patient populations because they --

DR. HOWELL: Coleen has a comment. And then Jerry and then Piero. Obviously, you've incited an

absolute flurry of --

DR. PERRIN: Well, it's great to have a couple dialogues here.

DR. BOYLE: Well, Jim, I appreciate all of your guidance, and the summary here is actually very helpful. And I was just going to follow up I think a little bit from what Ned said and maybe also from

Chris. Because I guess I kind of think of us taking, particularly in areas where we don't have good evidence or evidence is lacking, and actually, I think it's true for all of the conditions to take what we know, both about the benefits and the harms and the prevalence, the natural history, and do some empirical-based modeling.

So let's put some parameters on this. So it would be another piece of the evidence base, and it's not totally made-up modeling in that we take what knowledge we have and sort of see what the impact would be. And I think that's sort of what Ned was saying, but maybe not quite so maybe mathematically based.

But that's what I would do. I would try to actually develop a model and put sensitivity parameters

in it so you could vary them and see what impact it has. Many times, it has no impact at all, and we think it does. So I think that's really helpful.

DR. PERRIN: Super idea. Thank you.

DR. LLOYD-PURYEAR: I have a question. This is Michele Puryear.

Would it be helpful to pull together a

working group of this committee and other experts, similar to what we did when we began our evidence -- developing our evidence review and decision-making process? The issues that everybody is raising today are being raised in the area of rare diseases in general or actually in genetics in general of how to make decisions when the evidence isn't really all there.

And because I don't think you really mean fill the evidence gap, you mean how to make decisions when there are evidence gaps or --

DR. PERRIN: Well, both.

DR. LLOYD-PURYEAR: Yes.

DR. PERRIN: I mean, I think with modeling, you may identify an issue that you actually have to

have the information to fill in because your assumptions are to impact. Well, then you can't make a decision. So modeling actually gets you the same point.

But I want to be supportive of this concept because no one has quite figured it out. I just got an email from Al Berg, who's in the UK and said he just

got a very nice evidence review on six different newborn screening conditions, and it's probably from NICE. And it will be interesting to share those and see what they've done.

But I think bringing together people who are really worrying about this, because there is a lot of people who chomp at the bit to try to figure out a systematic approach to addressing these key problems that face us in evidence-based recommendations for rare diseases. So I think that's a great suggestion.

MALE SPEAKER: Sorry, Piero, I didn't mean to -- or Jerry?

DR. HOWELL: Jana and then Piero.

MS. MONACO: Ned, I agree with you completely. And I think because as wonderful as this

evidence review group is, it's been very helpful. The reality is with these rare diseases and getting into the areas that we are, there are never going to be the numbers to provide that kind of evidence that you want, and everyone knows that from the family perspective and I think really the professional side of it, too.

So utilizing and doing what's best instead of

kind of leaving it hanging because even if you go back and revisit it, I really don't see that these rare diseases that we're looking at are ever going to really change the outcome of the way we look at it once you go through the review. So we really have to make the most of it and get somewhere with it.

DR. HOWELL: Piero?

DR. RINALDO: Jim, I want to second what others have said. Actually, I enjoy reading these documents, very clear, very well organized, and they really address the issues. But I also see that as we make progress and we get used to it, we start thinking about what's next.

One of the things I would like to hear your thoughts is about the uniform panel really started as a

two-tier system, the primary targets and the secondary target. But it seems to me that we are dealing only with the mechanism to add to the primary targets, and is any thought given to what the process would be to add conditions that rely on the same biochemical, well, biochemical markers of primary targets, but they are really not recognized? And this, to some extent, might

be relevant to a discussion about Hemoglobin H.

So is there an option, or do you envision an option to say, well, maybe it shouldn't be added, a recommendation not to add to the primary of the uniform panel, but it certainly means this should be recognized as a valid secondary target?

DR. HOWELL: And that would apply only when you were looking at a condition whose diagnostic testing is already on the panel.

DR. RINALDO: Yes.

DR. HOWELL: That's an interesting thought.

DR. PERRIN: I think this is something the committee should really ponder and come to some discussion of. I don't think -- we will get into this a bit in the discussion of the Hemoglobin H, Piero. So

maybe that's the time to think about it.

DR. HOWELL: We don't want to get all of --

DR. PERRIN: But I think it's a very important question whether our evidence group can weigh in and say this is what you might consider, I think we could help with that. But I think this is a broader discussion for the committee to take on.

DR. HOWELL: Jerry and then Chris?

DR. VOCKLEY: Thanks. I just have a caution that I think we really need to be careful when we're going through the decision-making process to balance the extremes. What are the extremes of our evidence review?

The one extreme is that we will presumably, by basis of having been nominated for screening, identify some children who have a severe disease that will benefit from that identification early on. That is an extreme that gets very well represented in these meetings. We have parent groups. We all have our own patients where we can demonstrate that group of individuals very well, and it's very compelling.

The other extreme, though, is the one that

doesn't get represented very well, and that's the "do no harm" extreme. And I don't want to go back to any of the previous reviews that we've done, but I think it's sufficient to say that I believe that in some of those instances there was harm in proceeding. And I think we have to be really careful to be sure that when we're acknowledging one extreme, we are taking the time

to think through the other because if we have only the emotional appeal generated by the beneficial extreme, it will always counterbalance the potential for doing real damage by implementing something that either isn't well conceived or isn't ready.

DR. HOWELL: Chris, did you -- let's have Chris, and then we have Coleen.

DR. KUS: I just wanted to follow up one of the things Mike Watson said, and it relates to healthcare reform. You know, the comments that Medicaid programs don't pay across State lines. They can, and we do in some of the cases.

And the promise, I think, of healthcare reform is that that should be a better -- it should be facilitated that anywhere in the country, if this is a

recommended treatment, you can get it. And I just think we need to keep that in mind because it gives us a real opportunity to make comments to healthcare reform.

DR. HOWELL: Coleen?

DR. BOYLE: Just a quick follow-up from Jerry, I do feel like from an evidence review process,

the cards are stacked against thinking about harms. I mean, there is a publication bias issue, and then there's the expert biased issue. So that's been bothering me, and I don't know really exactly how to get at it.

So that's why I was thinking this empirical-based modeling where we can vary those parameters. And as Ned said, which I think is terrific, we can actually see where to guide the further gathering of information because we know that sensitivity parameter really makes a difference. Then we could drive research in that direction. So I think that's really important.

DR. PERRIN: I think it's an incredibly helpful suggestion.

DR. HOWELL: I think that there has been some

suggestion of developing a small workgroup to look at this, and I will visit with Michele and some others after this, and we'll try to identify a workgroup. And if anybody is passionate about being in that workgroup, let us know.

Are there further comments before we move on to Hemoglobin H?

[No response.]

DR. HOWELL: We will come back to some of the same issues. Thank you very much, Jim.

So we're delighted to have Alex Kemper, who's going to present the Hemoglobin H, and I think that the review of Hemoglobin H has precipitated a number of the questions that Jim has raised in his presentation.

DR. KEMPER: Good morning, everyone.

And thank you, Dr. Howell.

I really enjoyed hearing that very rich conversation, and one of the things that I'm going to be talking about later this afternoon when I talk about screening for critical congenital cyanotic heart disease is taking a look back at our experience in previous reviews and making recommendations based on

that experience about how we can move forward. And one of them actually hit the very topic that you were talking about in terms of thinking about how to do them in the future and even developing a manual that would lay out exactly what our process is going forward and certainly incorporating some of the modeling issues that Dr. Boyle brought up.

So I appreciate you all anticipating some of the stuff that I'm going to be talking about this afternoon. Let's see. So I don't know how to use thing, huh?

So before I start talking about Hemoglobin H disease, and again, in the presentation this morning, I'm going to be recapping our final review, which was submitted back in April, and updating the evidence as well as adding in what we've learned from talking to experts.

This afternoon, I'm going to be presenting our initial foray into critical congenital cyanotic heart disease, and a preliminary report was submitted in April 2010, and it's in your electronic meeting book. That presentation is going to focus on a summary

of the test characteristics, as well as using that as a jump point to talk about how we might do things differently moving into the future.

In terms of other activities, we had an overview paper about our procedures that was published just recently in Genetics in Medicine. The manuscript for the SCID paper was just published this month in

Pediatrics, and there was a thoughtful commentary by Dr. Botkin that was associated with it. And I have listed up there the Krabbe disease manuscript was submitted to Genetics in Medicine, and I was very happy to find at 5:00 p.m. yesterday that I got a little email that the paper was accepted. So we seem to be moving ahead nicely from that standpoint.

Again, I'd like to thank the workgroup team members, especially Alix Knapp and Danielle Metterville at MGH Harvard, who have been incredibly helpful in this process, and I've been very fortunate to work with Dr. Perrin in this process and have really learned a lot from him. So I'm very grateful for that.

What I'd like to do now is summarize some of the material that we presented last time related to

Hemoglobin H disease. I'm not going to spend a lot of time on that, however.

If you recall, Hemoglobin H disease is an inherited hemoglobinopathy. It's a type of alpha-thalassemia. It can be caused with by deletions or nondeletional mutations of three of the four alpha-globin genes. It has a variable clinical course, which

can include anemia, hepatosplenomegaly, cholelithiasis, or growth retardation. And there are certain mutations that are associated with worse health outcomes.

Again, this slide is something that we shared previously, and it shows what I'd like to highlight here is deletional Hemoglobin H disease -- again, three deletions -- versus nondeletional, which is typically two deletions and one mutation. And the one mutation that we most often talk about is the constant spring mutation.

Currently, if you recall, Hemoglobin H screening, it's considered a secondary target. Secondary targets are those conditions that are part of the differential diagnosis of the core panel of conditions or the would or could be identified in the

process of screening for the core panel conditions.

And certainly, because we all screen for sickle cell disease now, that's how Hemoglobin H became a secondary target.

Mr. Ojodu, through APHL, is in the process of conducting a survey to find out which States screen for Hemoglobin H disease and how they do it, and he has

informed me that at least eight States report hemoglobin Bart's, and that work is still under way. And I didn't see him this morning, but if he's here, it would be interesting to hear if he could update us with -- somebody is pointing out. He must be back there.

DR. HOWELL: He is here in the back.

DR. KEMPER: Oh, it's hard to see from up here.

Again, to summarize our methods of evidence review, we first conduct a systematic literature review, which summarizes evidence from those articles that appear in the peer-reviewed literature. That was presented back at the January meeting. We've updated that literature review and found two additional case series related to natural history that were published

in the interim period.

We also had consultation with multiple newborn screening and Hemoglobin H disease experts to try to identify relevant unpublished data. In the final review electronic document that we have, we have a detailed summary of the literature review method, the evidence, and a more detailed summary of the expert

unpublished data. There are also tables that highlight the key data from the abstracted articles, as well as a table of those articles that were excluded because they didn't meet our criteria, such as the need to have at least five cases for those papers of case reports, and a more complete bibliography.

So our systematic literature review, which I'm just going to again highlight briefly this morning, covered the period from January 1989 through March of 2010. And as before, we looked in Medline, as well as we searched for papers that were in progress. We did restrict to English language and human-only studies.

We also reviewed the references from the nomination form and the bibliography of reviewed papers, and at the end of the day, we ended up with 21

articles that met all of our inclusion criteria for abstraction.

This is a summary of all of those papers. Again, the thing that I would highlight is that the lion's share of these papers are case series papers of individuals who are identified clinically, not through screening.

I'm just going to go ahead and talk about the natural history. Of course, Dr. Watson points out that there's really nothing natural about the history that we present because all these people have been involved with the healthcare system. What I'd like to highlight, these are published data from the California experience. If you look from the period of 1998 to 2000, the incidence of really birth prevalence of Hemoglobin H disease was reported to be 1 in 15,000 cases.

There was a subsequent publication that covered the period of 1998 through mid way of 2006, and from that report, the birth prevalence of deletional Hemoglobin H disease was 9 per 100,000 newborns and was 0.6 per 100,000 for Hemoglobin H mutation, such as

constant spring.

We were very interested in the balance between deletional and nondeletional Hemoglobin H disease because they appear to have a much different impact on health outcomes. Not surprisingly, most of the case reports that we found were from Asia and the Mediterranean area because Hemoglobin H disease is

relatively more common there. And you can see that, in general, most of the Hemoglobin H disease is deletional, ranging from 43 percent to 84 percent in the non-U.S. studies. In the California report, about 78 percent of cases were deletional, and about 23 percent were nondeletional.

And from the available case series, children with nondeletional Hemoglobin H disease tend to be diagnosed at younger ages. They have higher rates of medical problems, including anemia and the requirement for blood transfusion, and higher rates of hepatosplenomegaly.

A key point that I want to make very clear is that there are no population or screen positive series for us to understand what the impact of Hemoglobin H

disease is. I know that at the last advisory committee meeting, one of the charges I got from Dr. Calonge was try to dig as deep as I can to find them, and unfortunately, we weren't able to identify that.

But again, in these clinically identified individuals in the newborn period, there could be anemia, jaundice, hepatosplenomegaly more often

associated with the constant spring mutation. There were some reports of Hemoglobin H hydrops fetalis. In infancy and childhood, there could be pallor, growth retardation, anemia, pulmonary function problems, mild cardiac anomalies, and hepatosplenomegaly. And then in adults, significant iron overload and cholelithiasis.

Now I'd like to move ahead into issues of the screen tests from the published literature, and again, there were three articles, two of which overlapped with some of the information I presented earlier. I'd like to highlight the California process because that's really been the model for how we've been thinking about things. They have a two-tier process.

The first tier involves the detection of elevated hemoglobin Bart's levels by HPLC, and then a

second-tier step, which is confirmatory diagnostic alpha-globin genotyping for newborns who are identified to have elevated hemoglobin Bart's.

As I discussed last time, there is a process where there's a trial period. And then the cutoff for the amount of hemoglobin Bart's you had to have to be considered screen positive was changed, and it's

currently 25 percent, where it's been maintained.

In terms of diagnosis, there are multiple strategies for alpha-globin genotyping that have been described, and the California newborn screening program uses multiplexed gap-PCR assay to detect common deletional and nondeletional alpha-thalassemia mutations in their second-tier screening. And I'm counting on nobody is going to ask me to describe exactly how that multiplexed system works, but it does, apparently.

[Laughter.]

DR. KEMPER: Which, you know, it's good enough for me.

Again, if you look at the papers from California, there were about 1.3 million children who

were screened. One hundred one of them were found to have elevated hemoglobin Bart's. And of those, only one of them was normal. So it's a very specific test, or I should say the positive predictive value is very high.

Now let's move into treatment, and this was the slide that I presented last time where we weren't

able to find any articles that dealt with the effectiveness of pre-symptomatic or early symptomatic treatment. There were no peer-reviewed publications, and there are no data published on the follow-up of the children identified in California. And also the last time, if you recall, I mentioned that there were no economic studies.

So now let's transition and really think about the important unpublished data. So we contacted Hemoglobin H disease experts through literature review, discussion with the workgroup, recommendation by the others, a really snowball process where we tried to find as much as we could, and we included experts from different Hemoglobin H disease domains, both newborn screening and those involved in clinical care. So I

think to the degree to which we could, we really tried to look everywhere.

This slide is listed as experts or advocates who either completed a written survey or interview with us, and sometimes both. Within the electronic document that we have, we have listed all the experts that we attempted to contact but, for one reason or another,

could not contribute to the process.

So, in general, experts corroborated our literature findings in terms of the natural history and the harms associated with having Hemoglobin H disease. There were no other data that we could find on the impact of pre- or early symptomatic treatment. We weren't able to find any systematic follow-up data on any screen positive populations, and there was insufficient data for economic analysis.

I would like to highlight, however, some information that we found from other State screening programs. So, Hawaii screens for Hemoglobin H disease, and unlike California, their first-tier test is isoelectric focusing, and their second tier is HPLC, and the same thing with Iowa. I'm going to be sharing

some specific data from Hawaii, although in our report, we have data from Iowa, as well as Missouri and Michigan, both of which use isoelectric focusing as a first-tier test.

And again, I don't want to -- this slide has to do with how California does their diagnosis, and I just wanted to be clear that their mechanism of DNA

sequencing seems to be effective. This, I think, is more interesting and important for the group and comes from Hawaii from the data that we provided between July 1997 and October 2009. They screened about 220,000 newborns. We were particularly interested in the Hawaii experience because Hawaii, as everyone knows, has a much greater prevalence of children born of Asian ancestry, which increases your risk of having Hemoglobin H disease.

In Hawaii, the way it works is that after newborn screening is completed, the newborn's physician of record receives the test result, and the positive test results is accompanied by recommendations for referral to a State hemoglobinopathy clinic or for genetic counseling and further alpha-globin testing.

Unfortunately, only about a quarter of the 214 screen positive children were referred, and some of this had to do with cost issues. So in 2008, Hawaii agreed to cover additional costs of the newborn parents' genetic testing, and they found that when they started doing that, referrals have increased.

So I suspect that over the coming years,

we're going to learn a lot more from the Hawaii experience. And I know that Ms. Au has been thinking about this in a very thoughtful and forward manner. So far, they have 48 confirmed cases of Hemoglobin H disease, although I'm not able to comment this morning on what their clinical case has been.

DR. CALONGE: Alex, can I just ask so that I saw 214 screen positives, 25 percent of those would be about somewhere around 50. Did those 48 come from those 25 percent of the 214 referred?

DR. KEMPER: That's my understanding, that those 48 are from the 214 that referred, again speaking to the high positive predictive value of screening.

DR. CALONGE: Thanks. Sorry.

DR. KEMPER: Does that answer your question?

DR. CALONGE: Yes.

DR. KEMPER: Okay. So let me just summarize real briefly and then lay out some of the issues. Oh, I thought Dr. Boyle had a question, but maybe the question is if we could turn off the heat.

So in terms of the published natural history evidence, there are studies on clinically identified

patients, and in general, it skews older children and adults. Children with nondeletional Hemoglobin H disease appear to have more jaundice, hepatosplenomegaly, growth retardation, and require blood transfusion more often and earlier than those with deletional Hemoglobin H disease.

The California data suggests the feasibility of newborn screening by HPLC for elevated hemoglobin Bart's, and I should add in that the Hawaii data certainly are that you can screen isoelectric focusing as your first-tier test and that there are validated methods for diagnosing Hemoglobin H disease by confirmatory genotyping.

So where are we in terms of evidence gaps? Well, here are some questions that I would like to lay

out, and I'm sure that you all are going to have other questions for me. But what proportion of children with Hemoglobin H disease would benefit from condition-specific treatment? There is a lack of systematic follow-up of data on the screen positive children. So it's hard for us to answer.

How does this vary across the United States

where the birth prevalence of Hemoglobin H disease may be different? Does early identification improve the health of identified children? Again, that is sort of hinged to the first question that I asked. What are the harms associated with delay in diagnosis, and what's the cost effectiveness of newborn screening for Hemoglobin H disease?

I apologize that those are questions I am not going to be able to answer this morning. But I think it raises some questions for you all, and some of these were anticipated in the conversation during Dr. Perrin's presentation.

So what's the threshold for moving a target from secondary target to one of the core targets? And I guess in the future, you're going to have to address

the other issue, too, if that ever comes up. What are the potential advantages for such a move, and what are the potential harms for it?

And what are the expectations for newborn screening laboratories, public health clinicians, and families if there is a move from being a secondary target to a primary target? So that's sort of the

infrastructure question.

And so, with that, I'd like to leave it open to you, and we'd be happy to entertain any questions that you might have about Hemoglobin H disease or our process.

DR. HOWELL: Thank you very much, Alex.

And let me also remind the committee that Dr. Vichinsky and Dr. Fred Lorey are on the telephone.

DR. KEMPER: Okay. Great.

DR. HOWELL: At least they're expected to be. Are you all there?

DR. VICHINSKY: [on telephone] I'm here.

DR. LOREY: [on telephone] I'm here.

DR. HOWELL: They are there, indeed. Thank you very much, Elliot and Fred.

Mike?

DR. WATSON: Yes, just to clarify, I don't think Hemoglobin H is on the secondary target list. At the time, neither the committee nor what we did, I think sickle cell was the core target at the time we did our analysis. And anything, any bad allele attached to an isoallele was a secondary target, but --

DR. KEMPER: I actually went back in the main body of the report, there is one sentence where it actually refers to other non-sickle hemoglobinopathies.

DR. WATSON: We allude to them.

DR. KEMPER: Yes.

DR. WATSON: I mean, there are probably 25 clinically significant alleles that could be in a list, and we didn't go into all of the non-isoallele related conditions. We made a comment there clearly are some, but I think regardless of whether you decide this is a primary target or a secondary, it might be worth looking, getting a group of hemoglobinopathy experts to look at the non-isoallele hemoglobinopathies. Just I think several States have chosen to make it one, but there is not a consensus as to which ones should be in

the secondary list.

DR. KEMPER: Okay.

DR. RINALDO: If I can add a comment? The official entry in the second, the list of secondary targets is variant hemoglobinopathies, and I believe, yes, somewhere in the 200 pages, there is a parenthesis that says including Hemoglobin E and H. That's the

only thing. But it says including.

And this is also relevant. You might remember at some point through the expansion of the panel, there was this interesting display of press conferences by governors or high officials who say, well, my State is better than others because we test for 94 conditions. Now I do 104, 77. And that's really about how many hemoglobin variants they were counting.

[Laughter.]

DR. RINALDO: And that goes back to the point of how many, how well. But, so, no, it's not a secondary target officially, I think.

DR. HOWELL: Other questions or comments and so forth? Mike?

DR. SKEELS: Thanks, Rod.

I just want to add a little more information that might be instructive about the Hawaii data. Hawaii is one of the six States in our regional program, and we generated the data that you're showing there, and Sylvia is doing something really unique with them.

But my point is that Bart's has almost become like a whatever is between primary and secondary target for us because we are using isoelectric focusing to identify hemoglobin disorders, and, oh, by the way, we also see these fast bands. And when we see them, and this is subjective, but when we can physically and visually see them, we then do HPLC. And if the HPLC result is between 10 percent and 24 percent Bart's, we report it as FAB Bart's. But if it's 25 percent or greater, we report it as elevated Bart's, FAB-EL.

And those are -- and Hawaii is the only one of our six States, thanks to Sylvia, who is actually following through on both categories of Bart's reports. When we find an elevated Bart's, our hematology consultant, our medical consultant contacts the primary

care physician in all of the States and say you need to have a diagnostic workup for possible alpha-thalassemia for this child, and we're done at that point.

I'd argue that that's really not a very good way to screen for alpha-thalassemia, even though we're doing it. We should switch to HPLC and do it right, if we're going to do it at all, and then have molecular

diagnostic testing. So you see what I mean? It's sort of in between.

There has been a lot of drift in this program, and I don't want anybody to think that at least that I would be promoting IEF as a good way to screen for alpha-thalassemia because we're finding some, but it's really not optimum, although I really want to acknowledge what Sylvia has done with it is pretty impressive.

DR. HOWELL: Kathy, can you comment? Kathy is at the microphone.

DR. HASSELL: Yes. Kathy Hassell from the hemoglobinopathy follow-up for Colorado and Wyoming.

We've had newborn screening for hemoglobinopathy since 1979, and I don't know how long

we've reported Bart's. But what I would say is our State lab, without sending a confirmatory sample, reports Bart's, which means every year 250 to 300 individuals are diagnosed with alpha-thalassemia in Colorado with only first 12 diagnosed with sickle cell disease.

And I think the primary care doctors in

receipt of a letter with the outcome information of that sample that's based on interpretation of an IEF, and the broader point I would make is whether officially recognized on a list, it is a secondary condition and/or a byproduct even of newborn screening.

And perhaps this committee and/or APHL should weigh in on what do we do with conditions like this where individuals believe they have a genetic disease, where they may or may not as a consequence of screening for something else? And perhaps some sort of guidance or statement ought to come out about that, if nothing else.

DR. HOWELL: Thank you very much, Kathy, for that very interesting suggestion of making a decision about that.

Any further comments for Alex about his very thoughtful report?

[No response.]

DR. HOWELL: Well, what would you like to do with his evaluation? This is their final report.

[Laughter.]

DR. HOWELL: And I am confident that unlike

some members that I'm sure that all of you have read this report, which is in your book and on your thumb drive. And so, you've had an opportunity to read and think about this in great detail before coming.

Jerry?

DR. VOCKLEY: I guess are we starting discussion of what the recommendation is?

DR. HOWELL: Yes.

DR. VOCKLEY: Okay. Well, I've heard absolutely no compelling information or evidence to suggest that this belongs on the screening panel. Typically, what we end up with is a disease or where we start is a disease where there seems to be some compelling clinical need, and we're trying to figure out what are benefits of putting that on the panel

versus not.

We haven't even been shown that there is a benefit to identifying these disorders. There was a whole column of zeroes in the treatment table of published data, and our experts, we're told, agree in general with what's been published. So I think that there is certainly -- there's a lot of room for further

study. But I would suggest that if there are groups who think that this should be on the screening panel, that it's up to them to generate the initiative to even meet the minimum sort of activation energy for us to consider it any further.

DR. HOWELL: Well, Dr. Rinaldo has been charged with initiating this discussion, and he will go through some of his assessments, and then we can -- then we'll come back to that. Okay? He also has slides.

DR. RINALDO: Jerry was trying to save time to all of us, I guess.

[Laughter.]

DR. RINALDO: But let's follow process. First of all, my impression listening to this reflects

what I said to Jim earlier that I have a feeling of deja vu, but actually is a good one. The fact that we're dealing with questions that we have sort of digested before.

Clearly, we're dealing with something that is related to other things we do, and the discrepancies in how we process, as Dr. Skeels said. We're also dealing

with a late onset disease because if you look at some of the papers, you see that the age of onset goes from 0 to 73 years for the deletional and 0 to 50-something for the nondeletional. So, clearly, we're talking a disease that can appear at any time in life.

I'm intrigued by a few of the findings in the report, and I would like to bring them up because it really goes back to the fundamental question is what do you do with the information? And there are things that are actually quite significant in some cases done to these patients. We talk about splenectomy. We talk about transfusions and the optimal time and intervals for these interventions.

There are several references to folic acid supplementation. I would like to know what is the

rationale and there is any evidence if it works beside the avoidance of iron-rich food. But there is also talk about modifiers that really could make a difference between this being a serious disease and not, at least some of the references that we have included.

And this whole issue about the severity of

anemia episode related to infections. One of the sort of clinical manifestations that I've seen mentioned several times is susceptibility to infection. So there are things that are done and could be done to these patients.

And so, I see that they are clearly part of the evaluation of the gaps. Because if we follow the analytical framework and eventually I think that the testing is there. There are different ways to do it. It seems to work, and there are programs like California and others that have decades of experience.

So I think that the testing is available and seems to be fairly effective. And so, perhaps following the framework. Is there anybody who would like to disagree with that or have comments about the

analytical aspect of testing for Hemoglobin H? I see a lot of heads just saying no. So that seems to be.

So we can go to the next level, and that's really about the treatment. Now perhaps somebody on the phone or somebody in the room can tell us -- right, you're there? I would really be curious to know about how many patients receive splenectomy, at what age, and

there are some reports I've seen the summary of the evidence that says that there were no transfusions needed after splenectomy. So perhaps you can comment on it?

MS. ODESINA: My comment is not about how many patients have had a splenectomy. But I want to comment on the role of consumer-based organizations when it comes to counseling regarding Bart's and all these other variants.

My name is Victoria Odesina, and I am one of the parents on the consumer task force for newborn screening, representing the Genetic Alliance. And with hemoglobinopathies, we know that consumer-based organizations perform the majority of the counseling because we have the material resources for counseling

for hemoglobinopathies.

And I think we will need some guidance from this group about what we do when we receive these results that says FAS and other because that's mostly the way it's reported. And when we call the lab, they tell us it's Bart's. We often don't know what to do with these results, and we are often faced with these

families asking us these questions.

And we also have programs where we train the hemoglobinopathy counselors, and we want to know how we convey this information so we provide the appropriate training to these families, or we give them the appropriate information so they can give the experience appropriate information. So I want your group to consider the consumer-based organizations and include them and provide us the guidance that is needed so that we are also included.

And those practitioners also, our primary care providers, they need to be brought up, included in this group.

So thank you.

DR. HOWELL: Thank you very much. And could

you, we're not going to have any further comments from the floor.

FEMALE SPEAKER: Just I have -- I'm from the community-based organization for thalassemia.

DR. HOWELL: We're going to stick with the group at the table, and then we'll come for public comment in just a minute.

Piero?

DR. RINALDO: Okay. Well, so I think the evidence might not be there, but I think there are definitely interventions that are fairly substantial. So, to me, this is not about lack of options, but rather initial lack of evidence of the benefits or harms of these options. And that's what we have done before when we are raising the issue about that that's what needs to be addressed.

Mike?

DR. SKEELS: Let me just ask a question, Piero. I'm not a clinician, and I couldn't tell from the readings how much difference it makes in successful treatment whether you identify alpha-thalassemia neonatally or later. Because for me, that's sort of

the crux issue here is if we're going to recommend it for newborn screening.

DR. RINALDO: Well, anybody want to answer the question? Somebody on the phone?

DR. VICHINSKY: Yes. This is Dr. Vichinsky. And tell me to stop when you like.

DR. RINALDO: Can you speak up a little?

DR. VICHINSKY: Yes. This is Dr. Vichinsky, who presented the initial proposal.

FEMALE SPEAKER: You have to speak louder.

DR. VICHINSKY: You raised an important question. The only time to safely make sure you can diagnose Hemoglobin H disorders is in the newborn period. It's an unstable hemoglobin, and what happens after the newborn period, the Bart's is gone. And when you send out the sample from a regular lab, it's unstable.

In at least 50 percent of the electrophoresis that are sent out, you can't even see it. And as the labs are sent out, the reliability of having them done in our first sample rapidly is so low is that basically on a study that I did comparing the diagnosis by

electrophoresis on send-out to immediate diagnosis in our program was over 60 percent of the cases are missed.

And so, you have to keep in mind that this is a poor group of patients largely, who will then be worked up for an acute hemolytic anemia by techniques that will largely miss them. And so, you have a very

special opportunity to diagnose them and educate them before the events happen, and there aren't any standards set up to accurate detect them through routine testing.

I don't know if that answers your question.

DR. RINALDO: Actually, it really addresses an extremely important issue that this is an information that is available within a limited window.

DR. VICHINSKY: Right. Exactly.

DR. RINALDO: And after that, it will be lost. And that, to me, is actually quite important.

DR. VICHINSKY: That is critically important in this because it's not able to be diagnosed, and these patients are lost. They're not transfusion dependent. So they're lost into the community health

system that largely cannot diagnose them correctly.

DR. RINALDO: So here is a question for Ned is that -- before we go back, just can this be construed as a harm of non-testing?

DR. CALONGE: Or, conversely, is the knowledge? I mean, I'm really stuck at the knowledge is critical in order to make the diagnosis, to make the

diagnosis in the newborn period. What I still don't understand is the critical nature of making the diagnosis.

DR. VICHINSKY: All right. In terms of clinical complications, which I hope to talk later, I'm about to publish the follow-up of long-term follow-up of the newborns from the California experience, and I have the follow-up data on 86 cases, 48 from the newborn period. I collect a lot of other patients who are sent to me.

Of the 48 patients we followed up on, in the first 3 months of age, there were 4 cases that required acute transfusions and the earliest one was 2.5 months to 2 months for a hemoglobin 1.9. Then the other cases were 6 hemoglobin and a 2 hemoglobin and I think a 5

hemoglobin.

These hemolytic events that occur in early infancy, which is a period the child would never be diagnosed, and it's unstable induced by infection. Overall, if you looked at the data, which was published recently by my group and Singer and all, and I think it's in your group -- Hemoglobin H Constant Spring in

North America -- the follow-up of a larger cohort, basically 24 percent of constant spring patients required chronic transfusion versus 3 percent at each deletion, and about 26 percent had a splenectomy of the constant spring versus 3 to 4 percent, and these were done when they were young.

The constant splenectomy, the splenectomies are complicated but beneficial. They have a high rate of portal vein thrombosis and other complications. Clearly, these patients need early education from a complex language to like sickle cell to provide them with the information about the hemolytic event, about the benefit of transfusion in preventing the need -- the benefit of splenectomy.

So I don't know if that helps you, but that's

-- well, I'll stop.

MALE SPEAKER: Alex has a question.

DR. HOWELL: Alex has a question.

DR. KEMPER: Well, my question, actually in response to Dr. Skeels's comment, too, was so one of the benefits that experts brought up to us often about early intervention would be that it was a time to

educate the family, both so they could for issues that would inform reproductive decision-making and testing in themselves, but also to teach them about what to look for in their child. For example, how to assess for splenomegaly in a young infant.

We couldn't find any systematically developed evidence around that either in the published literature or the unpublished literature, and I know that Dr. Vichinsky, you know, has talked before about this cohort of individuals that he's followed from early life. Unfortunately, those were data that we've not been able to see. So I can't comment on those in particular.

DR. VICHINSKY: But the data I mentioned to you is -- at least on the babies, there is a summary,

the report from the age TCRN study. They include newborns, but they're not a newborn natural history database.

The other thing that you mention I think is critically important. This is a high reproductive rate group who are often not in healthcare, and as the California experience reports, the number of alpha-thal

majors being born or dying in utero in California is dramatically increasing. And this is the high-risk group to get to.

In fact, that we've had in the State eight actual survivors of alpha-thal major without intervention, and there's been a large number of miscarriages or abortions or maternal complications related to the actual alpha-thal major. So this group is one in which would benefit from prenatal -- from counseling, which, frankly, isn't available prenatally. And this does identify a high target area to counsel.

DR. LOREY: This is Fred. I would just add to that. We've now picked up something like 10 cases of alpha-thal major where the newborn was born and survived at least long enough to have the newborn

screened. And last I heard, three of those were bone marrow transplanted and are doing fine. So that's an additional benefit, and relating to the earlier discussion, those kids would be dead.

DR. HOWELL: Jane?

DR. GETCHELL: I just wanted to point out the question of stability of Bart's hemoglobin in the

newborn dried blood spot. It's very important to test that spot soon after it's collected, or you may miss Bart's completely.

DR. LOREY: We found that not to be true.

[Laughter.]

DR. HOWELL: Well, that's interesting information. And now we go back to Piero.

DR. RINALDO: Jane will send you a survey, Fred. Don't worry.

[Laughter.]

DR. LOREY: No, but seriously, in that pilot, we did all sorts of things like mailing specimens various different ways, checking before and after. And we found that the information on stability was definitely overblown.

DR. RINALDO: Okay. So perhaps we're jumping up and down, but if I go back to key question one, the last question is are there potential benefits from the child's family? What I heard so far is that there seems to be potential benefits. Clearly, the strength of the evidence is a different story, but there are many things here that are on the table in terms both of

benefit of early intervention and early identification.

DR. HOWELL: Could you outline the ones that you would like to list there?

DR. CALONGE: Yes, I don't know which those are.

DR. HOWELL: That's Ned and I are on the same page.

DR. RINALDO: In terms of interventions?

DR. CALONGE: Yes.

DR. RINALDO: Okay. Transfusions, splenectomy, management of infections, folic acid -- whatever that is. The other thing that we tend to think in sort of silos, but the truth is there are several references here to something that we are looking at from a different angle, and that's jaundice

and hyperbilirubinemia.

So, in a sense, chances are that we will be screening, if that eventually is the decision. Perhaps the two things should have some touch points that if a child is deemed to have hyperbilirubinemia, should that trigger a different evaluation and reporting of the work already being done? I can tell you that for other

reasons the Minnesota newborn screening card was changed a few years ago to include the specific question in the risk factor section, jaundice, and then we put requiring treatment.

And that was not really in preparation for sort of perhaps a future addition, but rather because we know that is a quite significant cause of false positive results in the MS/MS profile. So we wanted to capture that information.

But that's certainly another thing we need to -- in other words, we're looking at the same thing for two different, and I don't see any thought being given so far about trying to put them together. What do you think?

DR. SKEELS: This is a little bit tangential,

but for those of us who are running screening programs,

regardless of what recommendation is made by this

committee, we still have to decide whether it's ethical

or not to ignore something that's right in front of us

every time we do IEF. And for us, we can turn over all

the rocks in determining how effective treatment is,

but it still comes down to a practical consideration of

having knowledge and deciding whether to share it.

It's a little bit -- I mean, not just because it's not analogous to identifying carriers for which there is no medical consequence. This actually is a different category, as far as I'm concerned.

DR. RINALDO: Yes, and that's exactly why earlier, I was bringing up the possibility of having a more granular definition of the variant hemoglobinopathy as a secondary target. That could, in a sense, I think that past history shows that inclusion in the panel has really led to changes in what several States have been doing or changed from what they were doing to a more consistent, to a level of uniformity right now that I think is one of the greatest achievements in terms of progress in public health, the

99 percent, more or less, consistency testing in the United States.

Remember, years ago, 2004, it was a 50-50 thing. So, in a sense, here we are approaching a remnant of that age where there are very diverse practices across the country. And so, providing some guidance of what should be done, I think, that could

actually lead to some harmonization and consistency.

DR. HOWELL: Ned, you had a comment.

DR. CALONGE: So I looked at the evidence in front of us. I appreciate the evidence by analogy. I think that's an important issue. But what I end up with is a large amount of uncertainty about potential harms.

There may not be any. I mean, I was just trying to keep track of all the kids. And is there a chance that we might intervene, label, or cause anxiety to a family in some negative way by identifying Hemoglobin H disease, or are there false positives? And it looks like the risks are low, but there is a lot of uncertainty there. So I have uncertainty on the harm side.

I can't really tell, other than I know why you're anemic, that it changes anything. I mean, would you do the splenectomy anyway? Would do the -- you would do the transfusions if you determine the disease. Or are transfusions actually, if we're being more proactive or starting them earlier, are we going to lead to more iron overload as adults. So there is

another potential harm.

So I have a large amount of uncertainty about other than I know why you're anemic, I don't have a good sense of benefit from knowing that it's anemia from Hemoglobin H disease versus I don't know what else it is. So what I end up looking at the literature is a large amount of uncertainty. So let's step back and say what our job is. Is there a reason then for all 50 States to test for this condition? Now that's a different question about -- if you're doing it, you're going to continue to do it.

I suspect California doesn't care what we say, and Hawaii, and will continue to test and actually add to the knowledge base going forward. But I can't see anything here that leads me to a large degree of

certainty that this test should be done in every child in every State in the U.S. And so, that's just kind of based on the evidence available.

New evidence would be coming down the line. The harms of not adding it now I don't see. I just don't have a large degree of certainty around that. So I'm really stuck with this issue of I want them to

continue to do it because they are. They're going to add to the knowledge base, and at some point in the future, revisiting this topic may say now we know the benefits or now we know the harms. So that just my summation, Rod.

DR. HOWELL: Jerry, and then Fred.

DR. VOCKLEY: I wanted to come back to the issue of here's a window where we can identify this, and so maybe we should. And I really think that's not a valid argument because unless we show there is a clinically -- there's a clinical reason to do it, to say that, well, if a child shows up with anemia at age 2, you can't use this test to identify their disease doesn't mean you can't identify it.

A qualified hematologist evaluating a child

for anemia is going to send off the molecular testing that's going to identify this disease and should know that they're not going to be able to pick it up on a hemoglobin protein study. So I think that's a nonissue. It will get diagnosed. It will get diagnosed appropriately. The question is, is there a clear benefit to diagnosing that in the newborn period

versus when the child shows up with symptoms? And I don't think we have that.

DR. RINALDO: Well, Jerry, that gets back to a point that Dr. Skeels brought up earlier that what's the cost of the workup of a symptomatic patient compared to the cost of reporting something that's already in front of you? That's actually something we --

Now if it's okay with Dr. Howell, I wonder if Jelili did his homework and -- Fred, sorry, it's you --

DR. HOWELL: Well, we're first going to hear from Dr. Chen.

DR. CHEN: Thank you.

Just two points, and one is that I would hope that the committee would -- has invested in and

respects sort of the methodology which we've all agreed to, and the fact that we have this evidence report, which is fairly clear in terms of its findings and as Jerry has summarized, I mean, it would be awfully hard to come to a conclusion that is essentially the direct opposite of what we have from the evidence report.

The second piece, though, is I do think that

a statement about the uncertainties about the evidence is quite helpful. Not only from a research standpoint, but from the primary care provider standpoint, trust me, we have as much uncertainty about what to do with a Hemoglobin H report like that or a alpha-thal report like that. I mean, it is a clinical condition that we diagnose and treat clinically right now.

And so, having a newborn screening report with that level of uncertainty around sort of what to do with it, A, I think it supports sort of the current reality of primary care that for this condition and that we're just not really sure what to do with that information right now. And two, it would be helpful to hear from the experts that you're right. We don't know, and we need to know. We don't know what to do

right now. It would be nice to get better evidence around that, et cetera, et cetera.

And so, I think that there is a value in sort of talking about and embracing that uncertainty, and that report could come from this group.

DR. HOWELL: You were interested in having Jelili present his data if he has it?

DR. RINALDO: I was just wondering if Jelili had a chance to give us at least a more detailed view of what's the current practice because, clearly, one thing if four or five States are now doing what California and Oregon are doing versus 30, 40. Jelili, can you please comment?

MR. OJODU: Thanks, Piero, for putting me on the spot.

Actually, I didn't come prepared with any results of the survey. Alex, I'm not sure, do you have the results of the survey with you?

DR. KEMPER: I looked at the link that you sent me a few weeks ago, where it said that there were eight States that did it.

MR. OJODU: Right. Yes, the survey just went

out about a couple of weeks ago to States, and I think we have about 30 States that completed the survey. And out of those 30 States, we had 8 States that reported.

DR. RINALDO: Out of 30. Okay.

MR. OJODU: Yes. So we're still continuing the survey, and I think --

DR. HOWELL: So, Piero, is it --

DR. THERRELL: So in the reviews that we've done in States, we've found it varies from State to State whether their hematologists even want them to report Bart's. So one of the things that might come out of this is a recommendation that States report Bart's. Because right now, fast bands are sort of grouped together, and they're just called fast bands. Some States say, okay, probably Bart's.

The States that do two screenings, on the second screening, if they don't see it and they saw it on the first, they say it was Bart's. So there is that kind of thing going on.

DR. RINALDO: But going back to a point that Dr. Chen brought up, basically we're having a discussion leading to anybody feeling strong enough to

make a motion for recommendation one of the categories, and I haven't heard that yet. And maybe it would be very helpful that that can be brought up on the screen?

Yes. So it seems to me that we are -- I don't think we'll ever go straight. Even SCID, I thought we struggled getting it as a Category 1. So I think that's a rather high bar, that it's unlikely that

we'll go there the first try at least.

DR. SKEELS: Piero, heaven help me for asking this question, but this is the most current version of this, right?

DR. RINALDO: Yes. That is Ned's baby.

DR. SKEELS: Yes, okay. So this is --

DR. CALONGE: Blame it all on me.

DR. SKEELS: Yes.

DR. HOWELL: Can I also add one thing? Dr. Vichinsky, who is on the phone, has said that he has a long-term follow-up paper pending, and that sort of information was something that the evidence review group did not have available.

DR. KEMPER: We did request it, and we requested to look at the primary data. But those were

not made available to us.

DR. HOWELL: Right. Would --

DR. VICHINSKY: Yes. We should have --

DR. HOWELL: If this were available to the evidence review group and so forth, would that be helpful to you in modifying or expanding on your recommendations or your observations?

DR. KEMPER: I can't comment on that because I don't know what's on it. Again, we requested it multiple times.

DR. RINALDO: So the question is --

DR. HOWELL: Well, I mean, the question was is that if that were made available, would it be worthwhile to look at that before we make a final recommendation? Because one of the key problems we had is no published long-term follow-up data.

DR. RINALDO: But that's one approach. What if we sort of can informally say how many people feel about leaning toward a Category 3 recommendation and then come up with the specifics of what we would like to see being addressed?

DR. HOWELL: Jerry has a comment.

DR. VOCKLEY: I don't see it as a 3. "Compelling enough to recommend additional studies to evaluate." I think additional evidence is needed, period. So I think it's Category 4.

DR. CALONGE: I agree. And recognize that that's -- it says now. So now means if we're going to vote it today, this is a Category 4. As additional

information comes forward, the things that are in Category 4 can come back to the committee and can change categories. But on the basis of the evidence, I agree with Jerry.

DR. VICHINSKY: Would I be able to make a public statement at the end of this? I'm just asking.

[Laughter.]

DR. HOWELL: Absolutely. We're not yet at the end.

DR. VICHINSKY: All right.

DR. HOWELL: Are there further comments about Category 3, Category 4 for the voting members? Jerry?

DR. RINALDO: Coleen?

DR. BOYLE: Actually, just a quick comment. I guess I also wanted to get some thoughts around the

table about making a recommendation of including it in the secondary panel or specifying it as -- and I don't know if that could be part of our recommendation?

DR. RINALDO: Could it be 5? Or that's a new category, but I think it's needed.

DR. VOCKLEY: Category 5 is do it regardless of what we say.

DR. RINALDO: Stop being cynical, Jerry.

[Laughter.]

DR. HOWELL: Mike, do you have a comment?

DR. WATSON: Is the committee only able to act in response to a nomination? I mean, it seems to me that there is Hemoglobin E. There are lots of other things or alleles considered clinically significant by various States, and I think it would be probably easier to put it in context if an independent group looked at the non-isoallele hemoglobinopathies and brought a recommendation forward, or else we're going to have to do this for E and lots of alleles.

DR. BOYLE: That's a great idea.

DR. RINALDO: Yes. Would you like to make a motion on it?

DR. WATSON: I don't get to.

DR. HOWELL: He can't.

DR. RINALDO: Ah, you can't.

[Laughter.]

DR, RINALDO: Jerry, redeem yourself. Make a motion.

[Laughter.]

DR. HOWELL: I think it asks the question does the committee have to make a recommendation? I think that once the committee has made a recommendation to send it forth to evidence review and that has been reviewed by the committee, I think committee is required to make a comment about that and categorize it in one of these areas and so forth.

DR. VOCKLEY: I have no problem with making what I think is a very reasonable recommendation to say that we've got this group of disorders that shows up on a screen that's done many places already. And that if you identify it, we need to know what to do with that. And so, bringing those as a group, as now a new nomination would be perfectly reasonable.

But based on for this nomination, based on

the evidence review that we have, I still say we're a Category 4 because there is -- it's going to take a lot more work to get it to the point where I think we have sufficient evidence to make this a clear primary target.

DR. HOWELL: Let's peel out -- there are several discussion on the table. The first thing is a

decision about what to do with this nomination today, and would you like to make a motion?

DR. VOCKLEY: Okay, yes. I move that we not approve this application and that we categorize it as Category 4.

DR. HOWELL: Recommending not adding to the nomination.

DR. TROTTER: I second it.

DR. HOWELL: Because of insufficient. And Dr. Trotter has seconded that. Is there any further discussion before we vote on that? We can come back to other issues and so forth.

[No response.]

DR. HOWELL: Those favoring that recommendation that it be a Category 4, all the voting

members have his or her hands up.

[Show of hands.]

DR. HOWELL: Anybody disagree with that? Is there any abstentions?

[No response.]

DR. HOWELL: So that was a unanimous motion.

The next thing, and I think that in sending a note

back to the nominators of this, it will be very helpful to have an organized list of things that evidence that needs to -- for instance, hopefully, it will come back in some form. But it would be helpful for them to know what we would like to see, rather than just a general comment. So we'll work on that.

Now the next question, Becky?

DR. BUCKLEY: Yes. Someone mentioned earlier that one of the recommendations that this committee can make would be to recommend that this condition be reported since it's already being screened for in most States. And I think the problem is that in many States, it's not being reported.

DR. HOWELL: Any comments about Rebecca's? That has been bounced around the table that a

recommendation from the committee that this hemoglobin, which is seen during the course of screening, be reported? Which would fundamentally make it a Category 2, which we recommend now, a secondary panel.

DR. SKEELS: I have a bias because we're already reporting it. But I think it would be very helpful to see what Jelili's survey generates to see

how widespread the practice is before we sort of recommend a change in that practice.

Jane, you're the APHL representative. You should be doing the talking here. Hello? The question was Dr. Buckley -- excuse me. Dr. Buckley is asking should we take action on I think it was Brad's comment about recommending that State labs report Bart's even if we're falling short of recommending that Hemoglobin H disease be added to the panel.

DR. GETCHELL: Yes. Given that most labs are doing isoelectric focusing, I would be very uncomfortable with that. At what point do you report and when do you not? Now, if we all switched to HPLC, that becomes a different question.

DR. HOWELL: Rebecca, it would seem to me

that your suggestion is an interesting one, and perhaps if we had the survey available and had a little more information about what States are doing that we might be a little more prudent, and that would be -- would you be comfortable in delaying that a bit and so forth, et cetera? I'm interested in the comment that Mike made because the thing is, is that it would be helpful

to look at this group of conditions in a more systematic way so that we don't have to think about this.

How would you suggest that we approach how should we do that? What would be -- Piero, anybody? Is that a good idea?

DR. RINALDO: Yes.

DR. HOWELL: And if it's a good idea, how would we do that?

DR. LLOYD-PURYEAR: We've begun -- HRSA and APHL on the National Newborn Screening and Genetic Resource Center have anticipated this issue and are having a workshop in California with many, many State labs on the 25th of May to look at hemoglobinopathies and Bart's. And so, we could begin -- if the committee

lays out issues that they think need to be addressed, we can make sure the agenda also includes those issues.

DR. VOCKLEY: Certainly, don't reinvent the wheel. If there's going to be a major confab on this, we should benefit from it. I think the guidance to send forth is that -- well, we've already sent, we've already said officially what we think about Hemoglobin

H. I think it would be valuable for the committee to note that there are a number of hemoglobinopathies that are identified through current methods being run through methods being run in current laboratories. And it is worth considering whether they should be reported as a primary or a secondary target. We don't have the formal mechanism for the secondary target business yet, but I mean, I think if we make that statement, perhaps it will encourage the next submission to be not focused on Hemoglobin H, but on hemoglobinopathies.

DR. HOWELL: So are you comfortable in waiting to get information from this meeting, which apparently is a sizable meeting, and have information come back to our next meeting?

MALE SPEAKER: That would be great.

DR. VOCKLEY: Our minutes will reflect this discussion.

DR. HOWELL: Okay. All right. Excellent. Excellent.

We've already taken a vote, and it was unanimous. Fred and Elliott, you're both on the phone. Would you like to make a comment? We are through with

our discussion.

DR. VICHINSKY: Yes, I'd let Fred go first, if he'd like.

DR. LOREY: Well, I agree with almost everything that's been said. There are a lot of issues. I think, yes, we're going to go on and do it no matter what. I understand the reluctance of some States to do it either because they're using isoelectric focusing or because maybe they don't have a large Asian population. So I don't think it's across the board.

Having said that, to me, it's no different than all those other Category 2 mass spec disorders that maybe actually aren't as clinically significant or don't have as an effective treatment as Hemoglobin H.

So I just think you should be -- with what's in

Category 2.

DR. HOWELL: I --

DR. RINALDO: Secondary, you mean secondary

target because Category 2 here is not good.

MALE SPEAKER: He meant secondary.

DR. HOWELL: And I sense that there is a

considerable agreement with your comments by many members of the table that it would fall really very sensibly in that.

If there are no further comments, we're running a bit late.

DR. VICHINSKY: I want to go. I want to say something.

DR. HOWELL: All right. Say something. We're about ready to leave it.

DR. VICHINSKY: Yes, I think the panel is relatively naive about the political healthcare delivery system. The comments that expect that a hematologist is going to work up these patients is unfounded. These are poor Laotian, other families. They don't get into the healthcare system after birth.

And to me, this whole thing is a deja vu of the arguments I listened to in the '60s and '70s about the benefit for sickle cell screening that geneticists were opposed to. Only after more political movement. So I think there is an opportunity to really improve the public health needs of this immigrant population who don't have access to care, and the prenatal alpha-

thal majors are going to happen. They don't get prenatal care.

And I think it has to be put in the social context of the access to these patients, and this is a particular period when you can access them and they do get -- the hemoglobin is unstable. It isn't just following anemia. They have an acute drop of 6 grams during a viral infection. So I think you need to rethink or at least think about this in the reality of healthcare delivery for minority people, and I'll stop there now.

Thank you.

DR. HOWELL: Thank you. Thank you very much for those comments. We appreciate those.

We are a bit behind, but we're going to take

a break at the current time. Let's return promptly, and let's get back at 11:15 a.m., please.

Thank you. I thought that was a good discussion.

[Break.]

DR. HOWELL: We're going to start naming names of talkers, I think. But anyway, as you know,

the President's Council on Bioethics report on newborn screening created quite a lot of discussion. And although within days of the inauguration of President Obama, he disbanded that group, their publication is out there, and this committee and the groups of this committee have significant concerns about some of the content and feel that it would be helpful to get something published that would at least be somewhat -- that would let it be known that there is some divergence of opinions from that report.

And Tracy has been working very hard on this report, and so he is going to report to us today.

DR. TROTTER: Thank you, Rod.

And thank all of you for your comments, which there were numerous, and suggestions. And this will be

a shortened version of what I presented last time. In that you've seen it before, the revisions will be obvious, and I think we can at least go through my part of this fairly quickly.

Just a reminder that the Committee Council on Bioethics members by discipline. The overarching question of that report was what ethical principles

should guide the practice of newborn screening in the United States? And the conclusions were grouped in seven elements that discussed what should be part of an ethically sound approach to public policy, and there were comments in each of those elements. And I'll go through each of them, but some very quickly.

Elements one and two I have grouped together in terms of the discussion of this in that they go together, reaffirming the essential validity and continuing relevance of the classical Wilson-Jungner screening criteria, which is element number one of the council's report. Number two is to insist that newborn screening be recommended to States only for those disorders that clearly meet the classical criteria.

The discussion in the report is that they're

clearly talking about what we think of as secondary conditions that were found with the primary screen. Just to go quickly through that, the Wilson-Jungner criteria, as all of you I suspect know, came out of a paper in 1968 to the World Health Organization describing criteria, 10 criteria, to include a condition in population-based screening.

This is really based on chronic adult disease at the time, has held up very well actually over the years in terms of criteria. And the three prime criteria had to do with a specific and sensitive screening test, a sufficiently well-understood natural history, and availability of efficacious treatment, which in that paper in 1968 meant direct medical treatment.

The National Research Council of the National Academy of Sciences in 1975 generally aligned with this criteria. It was a specific group tasked to deal with newborn screening, and they did broaden the concept of benefit to include not just direct medical treatment but to facilitate management decisions, to provide supportive treatment to the infant, to inform

subsequent reproductive decisions, and provide increased knowledge regarding rare diseases.

And the ACMG expert group, which was brought together in 2002, I believe, to come up with the core panel that we now utilize, reported in 2005 that their policy would be driven by what's best for the affected infant. I would hope we always do that. They felt

they considered both the classical criteria and the NAS/NRC and pretty much agreed with both of them with the expanded concept of benefit to be considered, although in the core panel, I don't think that actually happened.

A benefit to research study was not a criteria by any of these groups at that time. And of course, States make this final decision. These are recommendations, as we all know.

And then the genesis of this committee, which then produced and continues to produce what I think Dr. Perrin took us through earlier this morning, which is a really wonderful evolution of how we've thought about this and how we've tried to think about these rare diseases. And these workgroups have produced, I think,

fabulous reports that take on a very difficult subject.

We're clearly not done yet, but I think we have a process going that's working, and I am confident will continue to work, despite how hard it is.

So the response to element number one, which is the Wilson-Jungner criteria, should continue to have relevance I think is not an issue in that the criteria

for inclusion in the core panel, as far as we could tell, is consistent with those principles. The response to the secondary question, which was don't mandate anything that doesn't meet those criteria is, I think, really a misunderstanding from what I can understand of how the council looks at that group of disorders.

Secondary conditions, I think as we all know, are laboratory findings that are incidental to either the testing procedure or to the consequence of clarifying the differential diagnosis of a core condition and as such are going to be there inevitably. There is not a way for that not to show up if you do the job -- if your core conditions meet the criteria and you're going to do the job, it's going to be there.

The third element was to endorse the view that screening for other conditions that fail to meet the classical criteria -- read "Wilson-Jungner" when we say "classical" -- may be offered by States to parents on a voluntary basis. Our response to that is that classical criteria noted by the council needs to evolve, and in practicality, in real life, it has

evolved. We are a perfect example of that evolution today that includes the work of not only the original 10 criteria, which I think still hold very well most of the time, but the NAS/NRC, the expert group, and in fact, the ongoing work of this committee.

And when conditions do not meet those expanded criteria, and I think we are -- have been at least thoughtful about how we've applied that so far. I've been very proud to go back home and talk about how our decisions are made. Whether I made people happy or not, I felt that we did a good job of doing that. But if they don't, there is clearly a role for research within newborn screening programs, and we've talked a lot about that over the last year or two as well. And they will allow us to evaluate better disorders for

inclusion.

Number four, quickly, is a more difficult one for me, which is to affirm that when the differential diagnosis entails detection, i.e., a secondary disorder is picked up that would not otherwise be suitable candidates for the core panel, that these results need not to be transmitted, in fact, should not be

transmitted to the child's physician or parents unless there was informed consent at the time of screening. So, in the council's report, the States could choose to either suppress that information or obtain informed consent at the time of screening.

Our thoughts about that is back to the other question. If these are truly incidental and inevitable findings -- they're not somebody's agenda to get something out there, as all of you who do the testing understand better than I -- why reveal these findings? We feel that revealing them to parents who want to know that answer. There may be people who certainly don't want to know that answer. But is to not reveal them is unfair and unreasonable to disregard these results from a basic humanitarian process.

From a reality process, it avoids a diagnostic odyssey that for many of these metabolic conditions especially are arduous, very sad, and extremely expensive and seems to be unreasonable that one would go through that merely to suppress this data. To inform reproductive decision-making, very important for many families, and to provide early supportive

intervention for the child and family in a situation that you know is potentially not going to turn out well at all early on can be of more importance, I think, than many of us even feel in this room.

Clinical research studies might be available. Again, we've seen in the last couple of years, things come onboard that are now available to folks. If they knew about it, I suspect every parent would at least think about that. They would maybe not all use it. But they have the right to know about it.

Just a word about informed consent that I've already implied is, and the council agrees, that it's not appropriate for core conditions. I think we all agree with that. That's the point of mandatory screening. That it's absolutely required for research

studies, and we all agree with that, too. But it would be very confusing with incidental findings, incidental findings being, again, an inevitable outcome of screening for core conditions.

And I think there is a risk to the mandatory newborn screening program if that were to be instituted. The confusion level alone I think would be

enormous. Now that's not, I don't think, been tested very scientifically. So we may well be wrong there, and maybe somebody should look at that and see if that is going to make a difference or not in some fashion, but it worries me.

Encourage the States to reach a consensus. That's sort of like a softball. We've got element five taken care of. That's what we're here for.

And they urge a thorough continuing reevaluation of the disorders now recommended in inclusion. And I'm not sure that we have continually evaluated newborn screening in that many of your labs look at the process all the time, refine it, comment on it. We've changed a lot in the last 40 years due to those continual evaluations of the process going on.

But to actually look at the core conditions in a more specific way seems reasonable, and it just seems warranted. And our committee is actually tasked with doing that, and I'm not sure how we're going to approach it. But we have a group in place that could do that process.

And the last element was to reject the

technological imperative, i.e., because you have a multiplexed platform, you do more testing. And I think we have fairly clearly looked -- at least since I've been on this committee looked at all -- if all other criteria are met, then the review process looks at technology to answer three basic questions. Is a suitable test available? Does it meet a national public health standard? Can it be done? And is it economically feasible?

The conclusion being that newborn screening is a State-based, established, effective public health program. It is the model for early diagnosis and treatment I think in the United States.

This committee offers guidance through its recommendations. I think we have moved well beyond the

seven elements that were written in this council's

report. I think we've created a system of structured,

evidence-based assessment that supports a very

consistently rigorous iterative and very transparent

approach to making recommendations regarding broad

population-based screening programs in rare conditions,

and I'm proud of where we have come and would hope that

we can get your support as a committee for such a report.

DR. HOWELL: Thank you very much, Tracy.

This report has been circulated, and Tracy has received a number of comments, and those have been incorporated into the current document, et cetera.

Do we need to vote to approve this for publication?

DR. RINALDO: Can I make a comment?

DR. HOWELL: Yes, please.

DR. RINALDO: I think the message is there, but I really think that in the response to element number four, you really need to be very explicit that the distinction between a primary target and a secondary target cannot be done on the basis of

screening results alone. That will be known after the confirmatory testing and at that point is a moot point.

And the other one is that the technology imperative, the specific reference to MS/MS is also, I think, important to make a point that of the 60 or so markers, there are 2 or 3 that are really unique to a secondary condition. Everything else is part of the

pattern recognition and profile interpretation of the primary targets.

So it's just not that simple. But in other words, I think there is the assumption and the belief that you just look for everything you could possibly do just for the heck of it is fundamentally wrong and misinformed. You do it because it allows you to really make some progress, significant sometimes, in the differential diagnosis of these conditions. But still, you will never know until the confirmatory testing is done.

So overall, I think you've got it. But I think it could even be made slightly more specific about those two points because that's where I think the greatest level of misunderstanding transpires in that

report.

DR. TROTTER: And I couldn't agree with you more. I think that is exactly where the difference is, and I will take that suggestion and make sure that is as clear as possible.

DR. HOWELL: And Piero, maybe you could send Tracy an email with some specific wording that will be

explicit on that subject? Because that is an important point and one that is very hard to get over. It's the most common misconception about the entire ACMG report is the secondary panel, and I don't know whether people don't want to understand or will not understand. But it's a tough sell.

DR. TROTTER: That would be helpful. Thank you.

DR. HOWELL: Alan?

DR. FLEISCHMAN: And of course, Tracy will send it to the authors so we can see it, too.

DR. HOWELL: I'm sure he will, and so forth. The authors have seen it, but I'm sure in the final iteration, it will go around. The committee has approved sending such a document, and once this is

finally tweaked and so forth, it's your intention to submit this to publication. Where are you going to submit it?

DR. TROTTER: Wherever you tell me.

[Laughter.]

DR. HOWELL: Well, we'll have to figure out someplace that would be receptive to such a thoughtful

document. Ordinarily, we submit things to Genetics in Medicine.

DR. BUCKLEY: I have a point of clarification.

DR. HOWELL: Can you speak up a bit?

DR. BUCKLEY: Element number four, at the bottom where you talk about informed consent, you've got not appropriate for the core conditions and required for research studies. But what do you mean by confusing for incidental findings? Are people going to know they do or do not have to ask informed consent?

DR. TROTTER: Well, that's not clear on my slide. It's more clear in the paper. They are not going to ask for informed consent. The secondary conditions are really not that. They are really

incidental findings of doing newborn screening

appropriately.

DR. HOWELL: Any more comments and so forth?

[No response.]

DR. HOWELL: Thank you, Tracy. So you will

get word from Piero. You will amplify that, and you'll

send it to the authors and then get it sent along.

Thank you very much.

I'd like now to ask Mike to present, report on his State, on his lysosomal storage disease efforts and bring us up to date. And obviously, how that relates to the Newborn Screening Translational Research Network that I believe the members of this committee are certainly familiar with.

DR. WATSON: All right, and in the interest of keeping us on schedule for lunch, this shouldn't take the 30 minutes it's been allotted.

So we already -- this other one? Okay.

So I've already spoken and given an overview of the Newborn Screening Translational Research Network. This is -- aha. Thank you. All right.

So I won't go into the background on the

NBSTRN, and I'll cut straight to the activities that are taking place around lysosomal storage disease newborn screening. There are two major areas of activity that the NBSTRN has begun to look at around LSD screening.

Our ability to support the pilot studies that have been mandated in a number of States are already

progressing around both Severe Combined Immunodeficiency syndrome and the lysosomal storage disorders. We're also getting more actively involved in work around new technologies and tests and comparative assessments of different platforms for delivering the same newborn screening test.

I'll just cover this really quickly because Jim Perrin has actually touched on a lot of this in his earlier slides. The committee has looked at Pompe, Krabbe, Niemann-Pick, but has not been asked to look, as far as I know, at either Gaucher or Fabry.

DR. HOWELL: They were nominated.

DR. WATSON: They were nominated?

DR. HOWELL: They were nominated, and the internal evidence review committee felt that at the

current time it was not appropriate to send it forth

for a review.

DR. WATSON: So they realized the same fate

as did Niemann-Pick?

DR. HOWELL: Yes.

DR. WATSON: So Pompe had two specific issues

to be addressed. One was around the population in

which pilots were done. Another was the technology that was likely to be used in the United States. And even since that time, the number of potential technologies has expanded by a couple of new platforms.

Krabbe was not recommended for newborn screening at this time. Niemann-Pick did not make it to evidence review, nor did Gaucher and Fabry. But I will say that Gaucher and Fabry have additional issues attached to them that make them very interesting for newborn screening, and things we'll have to be very careful, attentive to as we go into the data collection activities.

At the current time, New York State is screening for Krabbe disease, has been for 4 years. Interesting issues have arisen around what was

perceived to have been the incidence of the condition, and some of this has been alluded to already in some of Dr. Perrin's discussions earlier.

They now have legislation that is coming forward to expand, to add four additional lysosomal storage disorders as listed in the previous slide, as well as SCID. Illinois has mandated the addition of

five lysosomal storage disorders -- Krabbe, Pompe, the same five -- with the intent of initiating this in October/November of 2010.

Missouri has mandated the addition of those five and any others that become amenable to newborn screening, with amenable presumably being the availability of a technology that allows you to screen for the condition.

Washington has been involved in a limited NICHD-funded pilot study around their development of new tandem mass spec-based screening technologies. And I think of importance is the fact that Perkin-Elmer laboratory is bringing forward a supplemental screening program for the lysosomal storage disorders, which would have patients potentially arise in any part of

the United States through a supplemental screening process of that type.

Lots of things are going to be needed in order to make these pilots go, as is needed for any condition that's actually even formally part of newborn screening. The pieces of this that we intend to address as we develop or evolve our own role in some of

these pilots, realizing that at the current time our interest in the pilots is as much in developing the infrastructure of the NBSTRN and using some specific conditions as was originally described in the contract to test those tools as they develop.

These conditions became an opportunity to both define some pilots, take advantage of the fact that they were going into pilot screening and use them to determine whether or not the tools we are developing actually work effectively or not. Among the things needed are provider networks. If patients are going to be popping up anywhere in the United States, primary care providers are likely to be told in many locations that a patient has appeared with this condition in their practice. And having those support materials,

such as ACT sheets and other kinds of guidelines about what to do in response to that notification, is going to be important.

We have been putting together groups of experts around the United States, trying to tie ourselves back to funded NIH activities, things like the Lysosomal Disease Network that was recently funded

as a rare disease clinical consortia. We've met with them. They're going to be actively involved in our pilot. They actually are beneficial in that they have experts and providers from all over the United States, not just in those States where these pilots are going to take place.

We're already in the process of developing ACT sheets. As with the non-isoallele hemoglobinopathies, we don't necessarily operate on the presumption that the committee has to have said something is a primary target or a secondary in order for us to generate support materials for primary care. And the mere fact that these are going to be done, whether in pilot or approved by this committee or not, justified to us having support materials made available

to primary care because the problem doesn't go away whether or not this committee has actually advocated on behalf of a particular condition or not.

We have some parallel activities. I had a group of experts chaired by -- an international group chaired by Olaf Bodamer in Vienna, and Bill Wilcox in the United States has just finished the penultimate

draft of a guideline on the diagnosis and management of the asymptomatic LSD patient. We didn't want to focus it on newborn screening, but that's obviously a way an asymptomatic patient could arise, as well as the diagnosis of an individual within a family, that it opens that family up to other asymptomatic, potentially asymptomatic, later onset forms of these conditions. We hope to have that done by the time that our expert groups meets at the end of June.

We're also developing the diagnostic algorithms that are associated with these conditions so that there is some guidance about how to work through the evaluation and laboratory diagnosis of the patients.

We're also looking at technologies, as I

implied earlier. We've talked about that a little bit yesterday in response to another question. So I won't dwell on that. But there are at least four competing technologies under consideration for lysosomal storage disease newborn screening, and a partnership between the folks at Duke University -- or Advanced Liquid Logic and the Mayo College of Medicine that was already

in the process of a comparative analysis of 10 mass spectrometry amino assays and other things is taking place.

I already said the first one, the second one, and the difficulty in having two different groups looking at different technologies will be how do we normalize these against the two laboratories doing this work and whether enzymology will serve as that normalization remains to be determined. But that's something we're talking about.

Next steps in our activities. As I said, we've already -- we had our first substantive meeting planned in late June. We had a meeting of a number of these experts at the American College of Medical Genetics meeting in Albuquerque earlier this year.

There was considerable enthusiasm among the diagnosis and management providers to have a coordinated approach, including protocols by which patients will be diagnosed and evaluated. Those will be done, and they will be supplementing the work we've already been doing around all conditions in newborn screening.

As I said yesterday, about 80 percent of the

data points are common among all the conditions. About 20 percent are unique to a specific disease, and this group will be coming together to work off of that first 80 percent and say what do we need to add that's specific to this condition as we develop the diagnosis and management protocols for those identified in the screening programs.

Algorithms, right now with multiple technologies, we obviously -- you probably can't see that worth anything at this point. But basically, what it says is that to the left of this, to this side of this slide is an algorithm that would stem from a tandem mass spectrometry approach to identifying these patients in screening.

The other side of the slide is through

immunocapture assay that would identify these patients. Comes down through the analyte levels that would trigger either a response that the result was normal or move you into more specific second-tier assays of enzymology for these particular genes involved in the conditions. This is Pompe as an example. So this is parallel to the other algorithms we've done to

complement the ACT sheets in all of the conditions in newborn screening.

Wrong computer again. And that's the Web site for the NBSTRN. As we develop these particular, more targeted studies, the NBSTRN Web site will begin to bring in summaries of actual projects on which we are working and try to keep people up to speed on what we're doing, what the protocols are that are associated with the studies we're involved in, and the results of those as they begin to evolve.

And on that, we're getting back on track.

DR. HOWELL: Thank you very much, Mike.

Are there any questions about the LSD pilot studies and how they're proceeding and so forth?

Obviously, I think that one of the things

that you have on the list is Pompe disease, which we've earlier reviewed, and hopefully, they will be able to with the pilot study gain the information we requested they needed there. And obviously, Krabbe will be in the same pilot study somewhere along the line.

DR. WATSON: And while I did focus largely on the diagnosis and follow-up side, we are going to be

engaging and, in fact, have engaged several of the States. Missouri has already agreed to begin to think about how pilot screening data itself might be brought into a platform such as the laboratory performance database in Region 4 as a way of beginning to capture pilot data from multiple States collaboratively so that those unusual situations of preemies and others that accrue much more slowly in any one State can actually come together collaboratively among a group of States. And hopefully, everyone can learn from playing together in this environment.

DR. HOWELL: Thank you very much, Mike, for getting us back on time.

We're now going to break for lunch, and we'll return promptly at --

MS. MONACO: I just had a question.

DR. HOWELL: Excuse me.

MS. MONACO: I just wanted to clarify, is there a central database that these States that are doing the pilot studies going to be putting their data into?

DR. WATSON: There are two different

databases. We're currently in the process of negotiating a subcontract with the Laboratory Performance Program of Region 4. It's been used as a retrospective tool to improve cutoffs, but all of the display tools and the way that whole program operates make it amenable to a prospective use in a pilot study.

So, yes, we have every hope of being able to resolve a contract within the very near future to use that as a centralized database, and we'll have to obviously work with the States who are involved in the pilots to ensure that they will participate in using it. I think the benefits are such that they probably will, but we have to make sure it's not a tremendous amount of work to be able to play.

One of the benefits of that program is that

it has gotten over the biggest hump of using big databases to develop big data and big science, which is behavioral science of people coming to play. And currently, I think 48 or 49 of the States are already participating in the program. So it's cleared that hurdle, and they have a relationship to the database and have found benefit in it that we hope could be

extended to the pilots themselves.

There are multiple formats by which clinical information can be collected, and I don't know that we have a definitive way. We can develop the protocols for diagnosis and follow-up, standardize the language, which can ensure compatibility of data, whether somebody is in an Epic EMR system capturing this data, whether they're using the DocSite data systems that Region 4 has used, or they are using the i2b2 system that the Clinical and Translational Science Award system, at least 40 institutions within that program use to capture clinical information remains to be seen.

We're actively reviewing all of those systems to see which ones have benefits, what are the pros and cons of these different tools for capturing information

at the patient-clinician interface to bring up into these sorts of databases.

DR. HOWELL: I think particularly those pilot studies that are funded by some national organizations will obviously require that the data be acquired in a similar fashion, or otherwise, the studies won't be very helpful and they will be in a similar repository.

Otherwise, it won't really be very helpful.

DR. WATSON: Yes, there is no doubt we would like to find mechanisms for funding more States to be involved in the pilots. That hasn't become available yet. We've taken advantage of the fact that a number of States mandated this to take place independent of the committee's decision.

DR. HOWELL: Any more comment?

[No response.]

DR. HOWELL: Well, now we'll go to lunch and return at 1:00 p.m. Thank you very much.

[Break.]

DR. HOWELL: It's 1:00 p.m., and we need to proceed. A number of our distinguished members have fairly early flights. So we need to have a very timely

afternoon.

And I'm pleased to welcome back to the podium Dr. Alex Kemper, who is going to go through a very preliminary review of the congenital heart disease and so forth. And after that, we will look at the letter that was drafted during lunch.

Alex?

DR. KEMPER: Thank you very much, Dr. Howell.

While I'm waiting for this time come up, I thank the advisory committee for allowing me to speak again, especially in this dangerous post lunch, second-day slot. I'll do my best to be entertaining as best I can, as Dr. Watson over there said.

So there are actually two things I want to talk about. One is to solicit your advice about future directions for the Evidence Review Workgroup and let you know about the thoughts that I, as well as other members of the group, have had. And then also to transition from that to talk about our preliminary review of screening for congenital heart disease.

And as you'll see, some of the stuff that I'm actually proposing in terms of our future directions

I've already adopted in our preliminary review for screening about pulse oximetry.

So, again, as we've spoken about a lot, evidence synthesis around newborn screening is challenging. Oftentimes, we're thinking about rare conditions so there's a lot of heterogeneity, obvious lack of data, emerging technologies and treatments, the

benefits and harms are not fully characterized, and yet there is some urgency in terms of making decisions to benefit children and their families.

And so, really spurred on by the work that Dr. Calonge has done, the way I think about weighing these potential benefits and risks is sort of very simple teeter-totter, where we have benefits on one side and harms on the other, and we're just trying to assess the degree to which there are net benefits. And so, I think that as we've done our work, it's been relatively straightforward to think about benefits in terms of decreased mortality, decreased morbidity, and improved quality of life.

But as Dr. Boyle pointed out in the earlier session, one of the things that's really difficult is

assessing harm. So what is the harm of a false positive? What about the difficulty in establishing diagnosis, carrier identification? What does it mean to identify an adult-onset condition during the early neonatal period? What if there's little prognostic information?

And then another issue that we've kind of

skirted around a lot is the issue of health services. To what degree do we need to look at the availability of health services for either diagnostic or treatments, and how does that play into how we weigh benefits and harms?

And this is, when I begin these reviews, these are things that really concern me. So let me just march through them, and it's a little complicated because they're all interrelated. But by time horizon, I'm thinking about are we just thinking about like the early childhood period, or are we following individuals through adulthood? What's the time period that we're talking about?

And then perspective. You can take -- when you are trying to assess benefits and harms, there is

different perspectives you can take. There is the perspective of the affected individual or the individual's families. There is a health systems perspective. There is a payer perspective. There are all sorts of perspectives that you can take on things.

Then there is the issues of laboratory and clinical validity, certainty as we review things, how

certain are we with things that we're finding. And then economic analysis often comes up. And I mean that in sort of the broadest sense, in terms of even counting up how many people we're helping.

So these are obviously all interrelated and difficult things. There are a bunch of unique challenges that we face as we've done these reviews. Issues of case definition, describing and evaluating harms, describing the benefit outside of early childhood, economic evaluation, and grading the evidence.

In the short period of time that I have this afternoon, I'm not going to go through all this stuff, but I would like to highlight three things and talk to you about how I'm thinking about moving ahead. The

first thing is case definition, and I think, as we've learned, getting the case definition right at the beginning of these reviews is really critical. It guides the review. It helps us know essentially what's in and what's out.

The previous approach that we've used is looking at the Nominations Workgroup, and then we make

internal decisions about what we really mean by the particular condition. And I've found, at least in the reviews that I've led, is my notion of what the disease is really changes as I start reading this, and of course, other people have said, well, of course, you should have thought about that. But these are conditions that I'm not familiar with in most cases.

So the new approach that I think we ought to propose is the use of the technical expert panel. That is a group of outside experts who can help us think through these things. Some of you may know that one of the things that I do back in my home institution of Duke is work with the AHRQ-funded, evidence-based practice centers, and this is a process that we've used to refine what it is that we're looking at.

And I think that we ought to expand the use of technical expert panels to the case definition, and of course, anything that we get from that, we would run past the Nominations Workgroup just to make sure that we're all in agreement.

The next issue is related to grading the evidence. So Dr. Calonge and others in this room

recently had a publication in Genetics in Medicine that talked specifically about methods for evaluating conditions. And there are four general domains that they recommended evaluating. That's analytic validity, the quality of data sources, study quality, and then the adequacy of evidence or the strength of the linkages in the chain of evidence.

So you saw earlier, for example, the analytic framework. So looking at how all these different arrows tie together and whether or not they tell a compelling story. So I'm going to just move ahead, but this group understands, I think, the complexity of looking at analytic validity.

In terms of quality of data sources, in the paper that was published in Genetics in Medicine, there

were five levels of evidence that were described, going from Level 1, which is usually good quality evidence, to Levels 4 and 5, which are poor quality evidence. And I won't repeat in this presentation, but you can certainly look in the publication the types of studies that would meet these different levels.

And then in terms of assessing the study quality,

there needs to be a clear description of tester disorder phenotype and outcome, adequate description of the study design and methods, interventions clearly defined, scientifically sound, and consistently provided. Adequate description of the basis of the right answer. So if you're looking at, for example, a study of diagnostic testing, avoidance of biases and appropriateness of the data analysis.

And I can tell you from having read a zillion papers in the process of this evidence review that certainly nothing meets sort of the high standards proposed by the study quality list. And I think it should be recognized, as I think most of you do, that there are lots of approaches to evidence review.

So there is the evidence review process that

is used by the United States Preventive Services Task Force, which I think is really the model for how this can be done in a domain that's more rich in data than we're often going to be.

Some people come up to me on the side and talk to me about the American Academy of Pediatrics approach to evidence review, and it should be

recognized that there are different levels that the AAP uses. So some topics are actually sent to one of these Agency for Healthcare Research and Quality funded evidence-based practice centers, and other things are done internally. And I can tell you that the degree to which those reviews are done in a sort of systematic way is really variable, and I'm now working with another committee to revise how the AAP does it.

The Institute of Medicine is actually developing a -- developing recommendations for systematic reviews, and I was hoping that that would be available by the time of this meeting. But unfortunately, it wasn't.

There is the Cochrane review process, which pretty much uses randomized trials. There is the EPC

approach, which again sort of combines some of the different approaches I've talked about.

I've listed the Web site in the slides, and I would encourage anybody on the advisory committee who really wants to understand how the EPC reviews papers to look at that particular Web site. And as you go on further, you're going to see that there is going to be

some things I'm going to liberally steal from the EPC methods.

And then the other approach I'd like to talk about is the GRADE process for reviewing papers. Many people have come up to me and asked me about GRADE, and I just wanted to discuss it in this forum so that everyone was on the same page.

So GRADE stands for Grading of Recommendations Assessment, Development, and Evaluation Working Group, and they have their own Web site as well. Their goal is to have a single system to evaluate the literature in order to avoid confusion because there is a gazillion different ways that this has been done.

In the interest of time, I'm not going to go

through all of the different criteria, but they grade everything from high to very low based on the estimation of the effect and the likelihood that their decision would be swayed by data that they haven't identified yet. And then there are different criteria that can raise or lower the grade, including things like study design, randomized trials versus

observational studies to the strength of the evidence in terms of the magnitude of effect. Really high odds ratio versus a low odds ratio, for example.

So the challenge that we face as the Evidence Review Working Group is that most evidence that we're going to find has just been low or very low by the nature of the study designs. You know, there are lots of very small case series or incomplete follow-up in the longitudinal studies.

And the other thing that we can't like completely co-opt what GRADE does is they're actually in the process of developing new strategies for evaluating diagnostic testing, which is something that we spend a lot of time doing. So I don't think GRADE is going to be the answer to how we evaluate evidence

fully, but I think there is some stuff that we can steal from them.

So what I propose as sort of a potential approach -- again, this is modified from the EPC -- is to have a technical expert panel to help guide us in the evidence abstraction process. And by that, I mean thinking about what our case definitions are and also

thinking about what the questions are in the analytic framework. So I think that we can do a better job with being explicit ahead of time in the analytic framework for each condition about what the potential benefits and harms are. I think that will guide how we both seek out the evidence and how we talk about it in venues like that, and I think it will make the decision process that much more transparent.

Now one of the things that I've done -- work that I've done with the EPC is once we've developed the analytic framework and the key questions for each topic that we're going to address, we actually put it up on a Web site for public comment. And it's not that we necessarily adopt everything that gets sent in, but I think, again, it increases transparency and helps us

think of things that we might not otherwise think of.

And again, remember that in many of the conditions

we're going to look at, we are not content experts.

And then once we get that feedback, then we

can review that again with the nominations workgroup

and then get going on the process. So I think the

advantages of co-opting some of these methods from the

EPC is that it increases transparency, and it allows us to have broader considerations before developing the report. The clear disadvantage to doing this is going to be time, but I think that if we limit down how long that the stuff is posted, I don't think it's really going to slow us down that significantly.

And my personal sense is that the benefit of doing this would probably outweigh that disadvantage.

The next thing I want to talk about is harms. They are often not reported -- I hate to use -- I just realized I had the word "report" there twice. I apologize about that. But basically, harms are often not recognized and included in manuscripts. I think authors, rightfully so, make judgments about harms and benefits, and it affects how reports are made. There

is publication bias. I don't have that listed here.

And just cataloguing harms based on expert opinion has been really challenging and prone to bias. And it's often difficult to understand these harms as well because we lack denominator information.

So I think that -- so sort of thinking about how to address this, I think that the technical expert

panel can help to clarify the case definitions and the analytic framework. Now I have this a little bit out of order, but I put Embase in there. Maybe just a little pause because this is an easy consideration.

We've used Medline as our major source for information about articles. Embase overlaps with Medline to a fair degree but has European literature that does not show up in Medline, and I think we ought to repeat things in Embase just for fun of it. It wasn't totally for fun, but I did look at Krabbe both in Medline and in Embase, and I didn't find any additional articles. But I think that just for completeness sake, we ought to look there.

We talked about posting things in the lab -- on the Web, rather. I think that we should have a very

explicit manual of procedures, and there was a conversation earlier about forming some sort of subcommittee of this group to put things together. I think there are different ways that we could do it.

I think that within the Evidence Review Workgroup, we could put together a manual of procedures and submit to this group, or if individuals in this

group would like to work with us to develop that. But I think that given that we now have some of these reports under our belt, I think that we can kind of revisit our operating procedure and really learn from what we've done.

And then the other thing that I wanted to talk about was modeling, which is something that we really haven't been doing. And there is this challenge because, as everyone knows, there is a lack of data. But if we're very explicit ahead of time with what all the benefits and the harms are, we can make estimates.

And for example, we could build a model where we could put in the most pessimistic estimations. And even with the most pessimistic estimations, if things still look kind of positive, then you can feel better

about things. Or if you put in the most optimistic estimates of how things play out, and it still doesn't look right, then I think that that says something as well.

This modeling wouldn't be trivial, but I think that that's one way that I think we could push the envelope in how this sort of evidence is included.

And I have no doubt that there would be a learning process in doing this because these conditions are complicated. But those were the main things I wanted to talk about future plans.

And Dr. Howell, should I open it up for conversation now about this, or --

DR. HOWELL: If there are any comments about this particular thing, why don't we hear those, and then we'll go ahead to the critical congenital heart disease. Alan?

DR. FLEISCHMAN: I just want to remind the committee and Alex, when we began to discuss the approach to the evidence review group, one of the very important issues was conflict of interest that is inherent in the experts. And it's important. They are

the experts. They know more about these disorders than anybody else.

But we were very careful in discussing the processes to try to maintain the evidence review group's not only transparency, but independence and not being even subconsciously affected by some of that work. So my question is could this be done

prospectively in the forms and in the materials that one receives when a disorder is nominated? Or could it be done later when the review group has already done some of its work and is now developing expert testimony?

I think we run the risk of being criticized in both directions, whether we make a recommendation or not, and I think we need to think carefully about this kind of technical expert group.

DR. KEMPER: I think that that's a great point. And I will tell you that for the technical expert panel, and I'm going to talk about how that played out for the definitions around congenital heart disease, we did get like a conflict of interest forms filled out and that sort of thing. But you're right.

It still opens us up to that kind of communication.

I just struggle with how to, being a non-content expert, make sure that we appropriately fill things out. But I totally agree with you, and it's something that I struggle with.

DR. HOWELL: And Ned, you had a comment.

DR. CALONGE: Right. I think it's in the

same area. I think you've really done some good work, Alex. There are a couple of ways to think about the technical advisory panel, expert panel. One is to think about it as an advisory panel. So the USPSTF does this by having task force leads who serve that role. So you ought to consider, we ought to consider, as committee members, being willing to sign up to be on the advisory committee for a topic, at least one member as kind of the lead for the committee in helping go through those decisions.

And then I think you do want to be careful about the rest of the experts and making sure that the evidence review stays pretty much germane to the evidence and not coerce. I think that's a good point. But I think you can achieve that that way.

The other way you include the experts is through your public comment period. And so, I would say as well as posting, you ought to be strategic in sharing the analytic framework, key questions, and work plan with the experts because they will help identify pieces of evidence that might slip through your fingers otherwise or will tell you that you've created your

clinical scenario wrong or other areas. So you can get that comment on the key parts of the evidence review without actually having them on the technical expert panel.

So I think those are approaches that we could think about to help make sure that there is ongoing guidance, especially for on the advisory committee and also input from other experts in the field, and then make sure that you cast a wide net to help you hone down the key questions and analytic framework.

I think all the rest of the ideas are target on. The manual of procedures, you can look at the EPC manual. You can look at the procedure manual for the task force and get an idea of the headings, and then I think you actually create a franchisable model, which

is what the EPC's are, if we ever need or want to expand beyond the unique relationship we currently have with you and Jim, et cetera.

So I just want to commend you on this direction. I think it's real good.

DR. KEMPER: Thank you, Ned.

DR. HOWELL: Outstanding. Any further

comments before?

DR. PERRIN: Can I just comment, Rod, just very briefly that when we work with experts, we are very explicit that we want information, we don't want opinion, and that we try to be very clear in stating that. And we don't ask for their opinions, or we basically turn them off when their opinions are being shared and only ask for what data they can provide us that might inform the questions we're asking.

DR. HOWELL: Thank you very much.

Alex, let's proceed, if you would, and go ahead and tell us where you are with the critical cyanotic congenital heart disease effort.

DR. KEMPER: I will proceed expeditiously. So what I'm going to talk about is our case definition

of critical congenital cyanotic heart disease, our planned approach to the evidence review, and then the preliminary findings regarding the accuracy of pulse oximetry, and then where we're going to go with all that.

So let me build up the definition. So congenital heart disease covers the entire spectrum of

structural heart defects that are present at birth, and critical congenital heart defects, or CCHD, cause severe and life-threatening symptoms and require intervention in their first year of life. And what we're going to be talking about is going to add yet another C, critical congenital cyanotic heart defects, and these are critical congenital heart defects that are present with hypoxemia in most or all cases. So not all critical congenital heart defects are associated with hypoxemia, and we're specifically interested in those for the purposes of this review.

And by background, congenital heart disease overall affects about 7 to 9 of every 1,000 live births in the United States. About a quarter of these have critical congenital heart defects, and the lion's share

of those are associated with hypoxemia.

So the rationale for review is that these lesions can cause significant morbidity and mortality, obviously because of the way we defined it. Newborn screening for critical congenital cyanotic heart disease, or CCCHD, I think I'm going to call it for the purposes of the talk, with pulse oximetry has been

examined in several large studies. I'm going to be showing that in a little bit. And early identification of infants with CCCHD can improve health outcomes.

So one of the things that we struggled with was the heterogeneity of heart defects and exactly what it is that we're screening because as we started looking at the papers that summarized the accuracy of screening pulse oximetry in the newborn nursery, we found that they lumped together different lesions. Some lesions were in. Some were out. And in order to really understand it, we needed to have a definition that was workable.

And so, with permission of the Nominations Committee, we actually convened a technical expert panel that included Drs. Beekman, Koppel, and Mahle,

all of whom are pediatric cardiologists, and we did have the disclosure forms and that sort of thing. And the question for them really was what are the heart defects that are potentially detectable by pulse oximetry? Which things would meet the definition of a critical congenital cyanotic heart defect?

And based on that and our other readings of

literature in the field, we've broken things down into those things that cause hypoxemia in most or all cases during the newborn period, broken down into outflow tract defects, such as tetralogy of Fallot, transposition, truncus arteriosis, and total anomalous pulmonary venous connection, or pulmonary venous return; right-sided obstructive defects, such as tricuspid atresia, pulmonary atresia, and with an intact septum; and left-sided obstructive defects, such as hypoplastic left heart.

So, with that in hand, we went ahead and completed a detailed literature review, and the methods are in the book, and I won't belabor that point. Today, we're going to be talking about the evidence from the studies published on pulse oximetry screening,

and the final report, again, is going to include the full systematic literature review, as well as consultation with investigators and advocates in the area.

One of the things that if we have time I'd like to talk about is by the way that we've set up the topic and the very nature of the topic, I don't think

that we need to spend a lot of time looking at whether or not detection of these lesions in the early neonatal period is beneficial, simply because that's really a core component of our definition. But again, I'd like to talk about that and find out how much evidence you'd like to see in that domain.

So we searched Medline for all relevant screening studies published over a 20-year period, and you can see the terms that we used, and we used the same methods that we've used in abstracting data before. And skipping to the punch line, there were 11 articles that met all of our inclusion criteria for abstraction. Again, what I'm about to present to you is just about the accuracy of screening pulse oximetry. And again, there were 11 studies that met that.

I am going to go ahead and talk about the screening method, and there are two tiers for the screening method. The first tier is pulse oximetry, which estimates the percentage of oxygen-saturated hemoglobin in the blood based on light absorption. I apologize for the misspelling there. I just noticed. It's noninvasive, and it usually only takes minutes to

measure.

If you have an abnormal pulse oximetry screening, then you move to a second-tier test, which usually involves an echocardiogram, but you can imagine it would also be done with clinical examination alone. I think that really, as you'll see in a second, we're really talking about echocardiograms to be able to directly visualize the structure of the heart.

So here's the big table, and this is in the book. What I'd like to do is highlight a few certain things about this table. So in the far left-hand column, you see the study and the year it was published. This table is organized by the year of publication.

The second column is the location in which

the study occurred, and you'll see that there were a number of studies that occurred outside of the United States.

The third column is the number of individuals that have been screened, and you can see that it ranges from a few thousands to a little bit over 50,000 in the different studies.

The fourth column is listed as prevalence, and as you look at the table, one of the things that I want to highlight is that this is a little bit different than the prevalences that we've talked about before because the prevalence here are the number of newborns who are born that were asymptomatic from a cardiac perspective and who were not known to have a structural defect based on prenatal ultrasound.

So it's not really a birth prevalence, but it's really the prevalence of children who were unknown to have a heart defect at the time of screening. And I think that accounts for, if you look at the table, the numbers vary from 1 per 10,000 up as high as there is one that's 12 per 10,000. But I think that explains the heterogeneity there.

The fourth column is another critically important column. If you're going to do the pulse oximetry screening, you can do it at different ages. And if you do it very early, so if you look at the third study up, the one by Sendelbach in 2009, they did the pulse oximetry screening at 4 hours of age for most of the neonates. The problem with doing it so early to

the time of delivery is that babies are still going through the transition to extrauterine life. And so, it probably doesn't really reflect where things are going to kind of settle down with. So you can end up with a lot of false positives because of that.

Studies can put the probes in different locations -- the hands and a foot, or just a hand, or just a foot. Studies use different thresholds for abnormal. So the lowest one was anything below 92 percent was considered abnormal, and anything above 92 percent was considered normal. Most of them, most of the studies, though, hovered around the 95 percent rate.

For many of these studies, if you go back and pull the studies, you'll see that the numbers that we

have down for true positives and false positives, true negatives and false negatives are different than what's reported in the studies because we actually had -- we were able to go back and take out those lesions that did not meet our criteria.

The other thing that was interesting, and I can show anybody who's interested later, is that this

is a big learning exercise for me is that sometimes the data reported in the abstract regarding test accuracy was radically different than what was actually in the body of the report. What can I tell you?

And so, to summarize, now that I've made everybody a little dizzy right after lunch, is that there's a wide range of calculated birth prevalence. But I've already told you it's not really birth prevalence, ranging from 1 to 25 per 10,000. All but two of the studies reported specificity above 99 percent. The study with the lowest specificity screened within hours of birth, and then there was another study that reported a specificity of 98 percent, which is pretty close to 99 percent. You know, in general.

And sensitivity itself was more variable, ranging from 42 percent to 100 percent. I'm not sure why there was such variability around sensitivity, and I think that's something that we're going to be able to explore as we talk to the experts and as we consider these data better.

So one thing I'm going to go back and look at

is -- one thing that I'm interested in doing is taking a meta analytic approach to this. I think that there are some studies that are homogeneous enough in terms of the cutoff they use and the time that they did it that we could combine those studies to come up with perhaps a more -- better estimate of, point estimate to 95 percent confidence interval around what the true test characteristics are, and that's something I hope to report back to this committee when we come back next time with the final report.

So let's talk about critical evidence that's still needed that we hope to dig up. How much does pulse oximetry increase the number of cases identified in the newborn nursery? And by that, I mean above what's picked up by, for example, prenatal ultrasound

and a careful clinical exam. The natural history, including the spectrum of severity of critical congenital cyanotic heart disease not identified prenatally.

Again, one thing I would like to ask you all to consider is we could spend a lot of time looking at each individual lesion and the benefits of early

detection, but I would argue that's probably for this particular condition less important than for us to be able to show that in general detection of these cyanotic heart lesions in early infancy is important.

Related to that, does pre-symptomatic or early symptomatic intervention in newborns or infants with CCCHD improve health outcomes? What are the economics surrounding newborn screening? What are the potential harms? Again, as you'll notice, I didn't talk about those during the presentation.

And something that I'm very interested in, although we probably won't be able to find anything from the literature, is how available are diagnostic and treatment services? And I'm particularly interested in the availability of diagnostic services

because if you're in a nursery that doesn't have access to a pediatric cardiologist, that kind of thing, what are the implications of that for the baby?

And I will say that there is a lot of very interesting work going on around telemedicine. So that may not be a big issue, but I think it's an issue that we ought to consider.

There we go. So we've identified an initial group of experts and advocates that we plan to contact to help fill in these gaps as we continue with our review. And of course, in the way that we've done this before, I expect that this list to snowball as experts and advocates refer us to other people and as members of this group and the other groups make recommendations to us. So that's the issues.

Dr. Calonge?

DR. HOWELL: Thank you very much, Alex. Ned?

DR. CALONGE: So great job, Alex. Good preliminary update. Can't wait for the final version.

This condition, actually, the condition -- sorry. The test for the condition represents, I think, something new. And we have representation around the

table from the affected groups for blood spot screening, but I'm not sure we have representatives around the table for who this would impact, which is the hospitals themselves.

And I would just ask us to think about how we incorporate that particular stakeholder because that's who we would influence with the universal

recommendation for pulse ox screening, the healthcare workers in the obstetrical services facilities around the United States. And I think we need to reach out as a committee to that stakeholder as well.

I mean, I know we've done this for newborn screening, but not through this committee, and that was a different time and a different condition and approach. And I just think we need to think about who we're going to ask to change their behavior.

DR. HOWELL: Jane?

DR. GETCHELL: Well, and related to that, would this be a program that would be part of a health department follow-up? Like, for example, hearing screening.

DR. KEMPER: Hearing. I think it's analogous

to hearing screening in that it would be a screen that would happen in the hospital, but there would need to be public health systems needed to track it and make sure that things were happening. Unlike newborn hearing screening, the diagnostic testing would happen in the nursery presumably before the baby went home, as opposed to having to have follow-up diagnostic hearing

testing after discharge.

DR. HOWELL: Chris?

DR. KUS: But I think that's -- it's parallel to newborn hearing screening and that system in getting the information to a health department. There is a lot of parallels with this as we think about it as to whose role plays in this.

DR. HOWELL: Dr. Chen?

DR. CHEN: Alex, nice job. A couple of questions just to help me sort of understand some of the clinical implications.

The first is your first evidence question that you had was how good is pulse ox in terms of identifying cases that you're not -- that aren't already blue? And is that not what you were telling us

that you did, though, as you reviewed these 11 studies? You were able to pick out -- your denominator issue was that you picked out ones that already were not apparent?

DR. KEMPER: Yes. So the denominator for those studies were the ones that were not apparent.

DR. CHEN: So are you expecting to get -- I

mean, does that not sort of answer that first question already, or are you expecting to get more data back?

DR. KEMPER: I think I'd like to learn more, and I'm going to go back. I'm sorry to make everyone blurry. But there was a pretty wide variety of estimates in there, and the way the studies are done I just want to talk to experts and clarify exactly who was in the sample and who wasn't. We did the best we could based on the way the reports were written to get rid of those people that didn't need to be in the denominator.

DR. CHEN: I personally think it would be helpful just to know sort of what the other denominator is, sort of how many of these cases really are picked up clinically then? And then, which is what I think

you are implying in terms of additional.

DR. KEMPER: Right. And what I'd like to do when I come back to present, and one of the other papers actually did this very nicely, was to have kind of like a bar graph where you had, well, these many are known prenatally. These many are picked up by clinical exam. And so, this is your potential benefit of

screening here.

DR. CHEN: The other pieces, I agree with you. I think that the clinical treatment of these conditions is not in question, that intervention, at least monitoring and intervention. But there is a time period, right, for many of these conditions that it's not that they all need to be immediately acted upon within hours to days of birth, correct? So I mean, there is some level of variability that happens for many of these conditions.

DR. KEMPER: I think, again, this is like completely anecdotal, and I apologize for that. But bringing sort of my general pediatric experience, that there are a lot of these babies that come back at 2 weeks of life, when you're there to check them for

their weight, and they're in heart failure. And that's when everything gets going.

But there will be some babies, for example, kids with hypoplastic left heart, who may go home from the hospital looking great and then before their first visit have collapse.

DR. HOWELL: Jane?

DR. GETCHELL: I'm just curious about pulse oximetry. Is it a test that is regulated and standardized? Do you know?

DR. KEMPER: It's in every hospital in the world. I don't know how it's regulated.

DR. CALONGE: The devices are FDA approved. But the application is -- no, there's no standardization.

DR. HOWELL: Alan?

DR. FLEISCHMAN: Yes, I think, Alex, that the fear that both family and physician will have with a positive test will result in no baby being just comfortably left alone with a positive test. And the real risk here that babies really do die.

So I think we're going to have to play out

this scenario in small community hospital that has --

may have an ultrasound machine but doesn't have a

technician who's going to be able to take care of a

neonate, even with telemedicine, or is going to have to

be a lot of new retraining and all the other things.

And the pediatrician's fears that they can't

-- they're going to have to transport this kid. And

they're not going to be happy with the automobile and the mother's arms or even the car seat. So I think these are real issues here that are very different from hearing screening.

DR. KEMPER: I totally agree with that, and I think the risk of harm to families because of that is not insubstantial. And that's why figuring out really what the specificity of testing is going to be critical.

DR. FLEISCHMAN: Right. And the benefits are tremendous, potentially, if you pick up children whose death can be prevented with very effective intervention. So I agree with you. I don't think you need a lot of work on the effective intervention side here. There is lots of effective interventions. We

know it. You can reference general articles about that.

The point here will be in the real world of this kind of screening, what are the harms to the false positives? Because the benefits to the real positives are going to be tremendous.

DR. HOWELL: Coleen?

DR. BOYLE: Just two quick things. It might be helpful in the next generation of this table to put some confidence intervals on those estimates, particularly because they're such small numbers there.

DR. KEMPER: Yes. Yes.

DR. BOYLE: And then just sort of a resource issue, not in terms of immediate short-term follow-up, but most States do have State birth defect surveillance programs, and part of --

DR. KEMPER: Oh, that's a good idea to look there to get the --

DR. BOYLE: Part of their charge is to connect families to services and monitor that. So there is some public health infrastructure there.

DR. KEMPER: Can I follow up on that? So, as

we do our evidence review as well, can we look to the CDC to help us get numbers?

DR. BOYLE: Yes. I'll connect you.

DR. KEMPER: Okay. Thank you.

DR. HOWELL: Any other comments before we move on? Chris?

DR. KUS: Yes. I mean, I think the issue of

risk to the false positives is a critical one in here because we talk about this, but we don't monitor it. And that whole idea that you tell a parent way back when that they had a heart murmur and their kid has a heart problem for the rest of their life and how that applies or doesn't apply to this is something we need to look at.

DR. KEMPER: Now I'll caution you that the amount of data to answer these questions is going to be limited. But I agree that we need to raise them.

DR. HOWELL: Let me make a comment, and then we'll move ahead. With regard to Alan's thing is that although you'll be detecting, hopefully, children in these remote hospitals, you would be in fundamentally the same situation if you, from your clinical exam,

came up with an area of concern. In other words, you would just be -- actually, you'd just be a little ahead of the game by having a pulse oximetry that would -- if you were in a small hospital and you find a significant murmur or something in a small infant, you would be in the same box as far as transporting and the whole 9 yards and so forth.

DR. FLEISCHMAN: Right. It's the false positives that the concern is. And the real positives, absolutely right.

DR. HOWELL: And so, we'll be particularly interested in false positive.

There are a number -- when we get to the public comments, which we're not to at this time, there are a number of persons that are going to be commenting about this subject and might add additional things that would be helpful in your review.

Are there any other comments before we end with -- Tim?

DR. GELESKE: Just to your comment, in our area, in Chicago, any baby who gets picked up with a murmur who still has the murmur by day two or three of

life is going to get an echo before going home. I think a question to ask might be for those kids that are picked up in rural centers that might not have access to an echo, how many of those kids are going home based on clinical exam alone, chest X-ray, EKG being normal, as physical exam is one of the screening tools that are used there?

Because not all murmurs that are detected are going to be a critical cyanotic heart lesion. So if you're comparing sending false positive pulse ox's versus, if you will, false positive murmurs from a rural center.

DR. HOWELL: Thank you very much, Alex.

DR. KEMPER: Thank you.

DR. HOWELL: I think you're off to a good study here, and we'll expect to have great detail when you come back. I think that this obviously does offer challenges of another point of care technology in the hospital. The newborn hearing screening has been complex as far as follow-up and so forth, and hopefully, we can work to get this a little more integrated into the system at the ground zero.

We have, as you recall, it was recommended and this group agreed that we would send a letter on behalf of the committee to Secretary Sebelius about medical foods and healthcare reform. And Dr. Puryear and her crew have drafted a letter that we will hopefully have soon on the screen for you to look at. And Michele, would you like to comment about the

letter?

DR. LLOYD-PURYEAR: Are you all going to put it on the screen, yes?

I have a couple changes that -- so if we could, if you could scroll down to the recommendations. Scroll down? Go down more. These three bullets. Stop.

On the second bullet, as you guys read it, I have some significant changes. It should read, "Individuals with those conditions recommended by the committee are high risk, and HHS regulations should ensure that they can access coverage for necessary medical treatments over the course of their lifetime."

The other change to the third bullet adds "after ERISA, the Federal Employees Benefit Program,

and Indian Health Service." So it's --

Can you change the second bullet, Alaina?

MS. HARRIS: I didn't hear all of your

comment.

DR. LLOYD-PURYEAR: Okay. "Individuals with

those conditions recommended by the committee are high

risk, and HHS regulations should ensure that they can

access coverage for necessary medical treatments over the course of their lifetime" -- semicolon. That's it.

MS. HARRIS: All right.

DR. LLOYD-PURYEAR: You just need to delete all the end.

MS. TERRY: I think you said medical treatments?

DR. LLOYD-PURYEAR: Necessary medical treatments. What are you doing? Should be "access necessary medical" --

MALE SPEAKER: Is that all right?

DR. LLOYD-PURYEAR: No.

MS. HARRIS: Will you read it to me one more time, Michele?

DR. LLOYD-PURYEAR: Okay. "Individuals with

those conditions recommended by the committee are high risk, and HHS regulations should ensure that they can access coverage for necessary medical treatments over the course of their lifetime."

No. But you are repeating words.

MS. HARRIS: Individuals with those conditions recommended by the committee are high risk,

and HHS regulations should --

DR. LLOYD-PURYEAR: Ensure.

MS. HARRIS: -- that they can access

treatment --

MS. TERRY: Coverage.

MS. HARRIS: -- coverage for necessary

medical treatments over the course of their lifetime.

MALE SPEAKER: You got it.

MS. TERRY: Is it high risk, singular?

MALE SPEAKER: Yes, it's singular. Take the

"S" off of risks.

MS. TERRY: Alaina, take the "S" off of

risks. High risk.

DR. LLOYD-PURYEAR: I wasn't sure. I was

like why were you asking?

I don't know if you want to -- those are the most important. If you want to quickly go through the letter? It's essentially a rewording of the last letter. Do you want to go through?

So I make reference to the last letter, summarize our issues, tell what the particular concerns are, say that we had a survey. The results of that

survey, although preliminary, shows such and such. And we ask that as HHS determines the regulations pertaining to the recently passed healthcare reform bill by Congress that the committee is recommending the following policy measures to ensure families of children with these disorders receive healthcare coverage for these essential components of treatment, and then the three recommendations.

I would like permission to go through these with the Office of General Counsel and also FDA to make sure that they're okay with these. Kellie?

DR. KELM: Well, I'm not --

DR. LLOYD-PURYEAR: I know. You're not that part of the FDA. So we would just want to make sure we're not stepping on toes.

DR. HOWELL: Well, that would be a requirement of letters going forth from this committee anyway. All the letters go through the Office of General Counsel at HRSA for review and so forth. But is the content of the letter satisfactory with the committee?

There may be a spelling or something that we

won't dwell on at this point. If the letter is -- if people are comfortable with the letter and so forth, we'll plan to polish it up, send it forth to the Office of General Counsel, but also try to get it sent forward fairly promptly in view of the fact that things do seem to be moving along fairly quickly.

Any --

DR. BOYLE: Just a caution for that second paragraph.

MS. HARRIS: Second paragraph?

DR. BOYLE: Second bullet. So would there be conditions that would require medical foods that aren't covered by the committee's high-risk list that we don't want to exclude because of this?

DR. LLOYD-PURYEAR: Why? Do you think it's

redundant?

DR. BOYLE: No. No, no, no. So there are some conditions that are not part of the committee's list, our 30 conditions?

DR. LLOYD-PURYEAR: Oh, yes, like --

DR. BOYLE: So I just want to see whether or not we're somehow putting those conditions --

DR. HOWELL: Like --

DR. BOYLE: Right.

DR. HOWELL: And the glycogen diseases and so forth.

DR. BOYLE: Right. Well, we obviously want healthcare coverage for foods for them. So just the wording seems a little restrictive to me. That's all.

DR. HOWELL: We'll be sure to include it. In the original letter, we were careful to point out that there were conditions that were recommended for medical foods by this committee not necessarily on our newborn screening panel. There might be other conditions that would be recommended.

DR. LLOYD-PURYEAR: Because, otherwise, Coleen, you open up to anything. So the caveat of the

original recommendation was those conditions not necessarily on the recommended screening panel. That's different.

DR. BOYLE: No, I guess maybe I'm not making myself clear. So as they're writing regulations for coverage for conditions that would require these special foods, obviously, there are going to be

conditions that aren't part of newborn screening. I'm just fearful that this might narrow that window or narrow those conditions to include just those conditions. No, you don't think that's a problem?

DR. KUS: Well, I don't think it says that.

DR. BOYLE: Okay.

DR. HOWELL: We'll be sure that that's not the case. That's important.

Any further comments? We'll go ahead and get that going.

DR. HASSELL: Can I add a public comment? Can I add a public comment very quickly to what you were asking? The reason why high risk is in there, originally, when we first looked at drafting this letter a few hours ago, the one piece in the healthcare

regulations that does need our work in terms of advocacy is that the high-risk pool will include those medical conditions that are looked at as high risk that basically would mandate insurance companies so they could not deny them coverage because of a preexisting condition.

So, in other words, if metabolic diseases or

inborn errors of metabolism are included in this high-risk pool, it means that insurers will not be able to charge higher premium rates by rating that as a preexisting condition. And so, that was what originally our intent had been in looking at the draft of that second bullet right there.

DR. HOWELL: And thank you very much, and so forth. Any other important comments?

[No response.]

DR. HOWELL: If not, let's move ahead to our public comment section. What did you say?

MS. HARRIS: Did we vote to move this forward?

DR. HOWELL: We have agreed to send this forward. We will not vote on it. There has been

consensus that we'll send it forward.

We have a series of public comments, and let me remind the public commentators is that although many of you will be commenting about conditions that are not only important to you, but to all of us and that you could probably spend the next afternoon talking about them, we will be very, very strict in trying to limit

your comments to 5 minutes each so that we can move the program along.

Let's start with Anne Marie Saarinen, who is speaking again, the first person speaking about critical congenital heart disease.

MS. SAARINEN: Hello. Thank you.

I really wasn't sure whether I was going to say anything today since there is a couple of other people --

DR. HOWELL: Can you get closer to the microphone, please?

MS. SAARINEN: Thank you. Oh, gosh. This seems germy when I get this close.

[Laughter.]

MS. SAARINEN: Anyway, I really -- actually,

you all heard from me in January, 4 months ago, when the nomination for critical congenital heart disease was made, and I primarily wanted to thank you as a committee and for having the process you have in place and for having an external workgroup that works so diligently -- and what am I trying to say? -- methodically, thank you, to sift through hordes of

data. And as someone who has read thousands and thousands of pages on pulse ox studies from around the world, it's just a lot, a lot to digest.

And having these experts taking the time and having the committee move forward with its consideration of this is just I know a herculean effort, and I'm grateful, as a parent and a parent advocate, for your time on all the issues you work on because I truly believe lives are being saved because of the work done in this room. So thank you for that.

I will just remind the group, as an advocate, about 3,500 more babies have been born in this country in the 4 months that I've seen you with congenital heart disease, and using your numbers, that's, what, 875 of them probably had critical congenital heart

disease. And with the literature suggesting we could have a sevenfold increase in detection rates with this one extra tool we could put in the toolbox, I certainly hope we're heading in that direction.

Thank you, Dr. Fleischman, for your comments earlier. I hope what we're doing in Minnesota and what a lot of other States are doing on their own already

will help address these sort of rural issues and making sure kids and families in rural areas are being identified and getting what they need in as real time a fashion as possible. I think we're doing that in the Minnesota study, and I hope we play through on that in the research being conducted here.

Thanks again. Appreciate your time, and looking forward to seeing everybody in September.

DR. HOWELL: Thank you very much, Ms. Saarinen.

And our next spokesperson is Olivia Easley, who again is going to be addressing the situation of critical cyanotic congenital heart disease.

MS. EASLEY: Good afternoon. Thank you for giving me the opportunity to speak.

My name is Olivia Easley, and I am speaking on behalf of my daughter, Veronica Jane Easley, who died suddenly and unexpectedly last summer of undetected critical cyanotic congenital heart disease.

I believe that the data speak for themselves, and I won't reiterate them. I am here to provide a face for the tragedy of missed diagnosis of critical

congenital heart defects.

Veronica was my third child. She was born on April 29, 2009, and was seemingly perfect. She weighed 8 pounds, 7 ounces, and her Apgar scores were 8 and 9. Her hospital discharge physical examination stated ironically, "a perfectly healthy newborn baby girl." At the time, though, there was no reason to think otherwise.

She experienced newborn jaundice, and that resolved by 10 days. And otherwise, she did great her first month of life. She was eating well. Her color was good. She had gained a pound by her 4-week checkup.

At 6 weeks of age, she began to develop some difficulty feeding. She spit up more often and seemed

uncomfortable while nursing and vomited on a couple of occasions. But I'm a third-time mom. I wasn't really alarmed by her symptoms. I contacted my pediatrician's office. They suggested perhaps she had reflux or maybe was intolerant of something in my breast milk. I cut out caffeine, gas-producing foods to see if that would help Veronica.

When her symptoms didn't improve in the next few days, I called my pediatrician's office to schedule a visit. Unfortunately, we never made it to that appointment.

The night before the visit on June 18, 2009, she died suddenly at home. She was 7 weeks old. An autopsy conducted the following day at the Maryland medical examiner's office found that Veronica died from a critical congenital heart defect. She had total anomalous pulmonary venous connection with an atrial septal defect. All four of her pulmonary veins returned to her right atrium, and her heart was nearly four times the normal size.

I was beside myself. I had no idea she was critically ill. She was never cyanotic. Her breathing

was never labored. She had gained weight appropriately. She seemed fine.

After she died, I read about the symptoms of heart failure in babies. None of them really rang a bell. She only had one, difficulty feeding. It never crossed my mind that this mild and nonspecific symptom could have been a sign of a life-threatening anomaly.

When I was pregnant with Veronica, I had perfect prenatal care. I had a chorionic villus sampling and a 20-week ultrasound performed by a highly respected maternal fetal medicine specialist. At the time, though, I did not know that prenatal ultrasound misses more than two-thirds of major congenital heart defects, and I also didn't know that congenital heart disease is the most common birth defect and affects 1 in 125 live births.

Veronica's heart was a ticking time bomb. The symptoms of heart failure in babies are too nonspecific. Heart disease is, therefore, in my opinion, ripe for a delay in diagnosis. Veronica's disease escaped detection by me, my husband, my extended family, my perinatologist, the newborn nursery

nurses, and by her own pediatrician.

A screening test like pulse oximetry was, I believe, her only chance. I would give anything to turn back the clock and demand that this simple test be performed on my baby girl. She might be alive today.

I am happy that you are considering this important issue, and I hope that in the future you will

vote to recommend universal neonatal pulse oximetry screening and help to prevent other families from suffering the tragedy that ours did.

Thank you.

DR. HOWELL: Thank you very much, Ms. Easley, for those thoughtful comments.

Our next person is Vi Kennedy, again speaking on critical congenital cyanotic heart disease.

MS. KENNEDY: Good afternoon to the advisory committee and the evidence review subcommittee.

Thank you for your time and allowing me to share my story with you.

My name is Vi Kennedy, and I'm from Colleyville, Texas. It's a suburb of Dallas-Fort Worth. I'm here with my husband and brother, and I

stand before you today as a registered nurse of 9 years and an applicant for congenital heart defect screening.

Our story, the information that case studies and autopsy reports don't include. I did not have a high-risk pregnancy. My husband and I did all that we could to prepare for our daughter's arrival. We took classes, conducted interviews, reviewed information

with the Texas Medical Board, read inspection summaries from the Texas Department of Family and Protective Services to help us choose daycare options. We secured college funds for our daughter, and additionally, I changed jobs and followed the prenatal rules and performed all of the safety checks.

Taryn was the first grandchild on both sides and the first great-great grandchild on my side. When she was 27 days old, she suffered an unexpected cardio-respiratory arrest at home, and I had to perform CPR on her until EMS arrived. I remember the ambulance ride and seeing my life fall apart before my eyes.

Taryn was stabilized at a local emergency room and then sent by air ambulance to Children's in Fort Worth. At this point, SIDS, metabolic disorders,

seizure disorder, and meningitis were being ruled out.

Later the same evening, the doctors pulled us aside and explained Taryn had two congenital heart defects, total anomalous pulmonary venous return and atrial septal defect. The pediatric cardiologist explained to us that 1 percent of all babies have a congenital heart defect.

Taryn had jaundice after being discharged from the hospital. By the time she was 27 days old, she saw her pediatrician three times and the home healthcare nurse two times for jaundice.

She did not have a heart murmur. She passed her birth weight by 2 weeks and grew an inch. She reached all the milestones of a healthy baby. She never experienced any difficulty breathing until her event, which doctors believe was a pulmonary hypertensive crisis.

By the time we found out, it was too late, and she suffered significant brain damage. Her health declined over the next 24 hours in the PICU, and surgery was not an option by the time her heart defect was detected. I read many books while I was pregnant.

Nothing prepared me for what was to come.

I realize that there are no guarantees for survival if her heart defects were identified earlier and surgery was an option, but we weren't given that chance. Not to be given that chance of a better outcome is unfair and unacceptable. The lack of early detection is taking a gamble that we might find out

with a minimal chance of a successful outcome. Early intervention is key. You cannot fix the problem if you are not aware of it.

Some key information points I'd like to give you. Her Apgar scores were 8 and 9. I read her medical records, and it indicated "healthy baby" on multiple accounts.

Her autopsy results did state, "Total anomalous pulmonary venous return is a known cause of sudden, unexpected infant death. In a small proportion of patients, prior symptoms may be either completely lacking or so subtle as to not raise the possibility of this diagnosis."

You are aware that according to American Heart Association, this is the most common birth defect

and the number-one cause of death during the first year of life. In the study by the AAP in 2003, effectiveness of pulse oximetry screening for congenital heart disease in asymptomatic newborns does state the screening and test is simple, noninvasive, and inexpensive and can be administered in conjunction with State-mandated screening.

The recent study that you all have been reviewing by the American Heart Association and AAP does continue, stating, "Critical congenital heart defects is not detected in some newborns until after hospital discharge, which results in significant morbidity and occasional mortality. Furthermore, routine pulse oximetry performed on asymptomatic newborns after 24 hours of life, but before hospital discharge may detect critical heart defects. Routine pulse oximetry performed after 24 hours in the hospital that have onsite pediatric cardiovascular services incurs very low cost or risk of harm."

Our actions. I stand before you today as an advocate for change. My plea is not just words. I've taken an action to ensure children born with these

defects have a fighting chance. I've contacted two of the largest hospital systems in the Dallas-Fort Worth area, the chief of neonatology, to provide them with the information and ask for change.

I've contacted the AAP, and I actually received a letter from the American Academy of Pediatrics in 2009, saying "I'm sorry for your loss.

More research needs to be done." So I was acknowledged, but not heard.

I've been working with my regional March of Dimes representatives. I reached out to the Texas Department of Health and Human Services, and they referred me back to you. I contacted the American Heart Association. They sent me a pamphlet about congenital heart defects after my daughter died.

My husband and I formed a 501(c) nonprofit organization called Bless Her Heart, and I wrote a pamphlet for distribution to go into prenatal packets so that families can be educated and can be their own advocates for early detection. These pamphlets are available outside.

We've worked with other organizations for

congenital heart defect awareness and advocacy such as Safe Babies Through Screening, and I've come here to ask you for your support to require pulse ox as a standard of care after 24 hours of birth.

Our request for how this committee can support or be an advocate for children like Taryn. Advise the Secretary regarding the most appropriate

application of universal newborn screening tests, such as pulse ox screening for infants prior to discharge from the newborn nursery, and also develop policies or guidelines and standards for pulse ox screening to reduce morbidity and mortality in newborns with congenital heart defects.

My closing statements. It's in your hands. How much more information do you need? How many more years do we need to implement change? How many more babies have to die to make a difference? How many more families have to suffer the loss of a child due to lack of screening for the most common birth defect?

You have the power and the authority to make changes which would have the greatest impact to screening babies for congenital heart defects prior to

leaving the hospital. We all do our best with the information that we have. Based on the information that we have, now that you have this additional information, it's in your hands.

I appreciate your time and consideration.

DR. HOWELL: Thank you very much, Ms. Kennedy.

And our final commenter about critical cyanotic congenital heart disease is Gerard Martin.

DR. MARTIN: Thank you very much.

My name is Dr. Gerard Martin. I'm the senior vice president for the Center for Heart, Lung, and Kidney Disease at Children's National Medical Center.

And after listening to those last two parents, I apologetically would admit I'm a late adapter. You see, about 3 years ago, I was asked to receive an endowed professorship at my hospital, and I began preparing for my lectureship by reviewing the literature the same way that Dr. Kemper reviewed the literature today and the same way that the American Heart Association, the American Academy of Pediatrics reviewed the literature a little over a year ago in

their position statement on pulse oximetry.

I did make a mistake, though. I called Mona Barmash, president of the Congenital Heart Information Network. It's a group of parents who feed information back and forth. I said, "Tell me what would be an important screening issue for heart disease in children." And she gave me the quote that not nearly a

week goes by when she does not hear from a distraught parent who has lost a child with congenital heart disease.

These are not two rare parents that are speaking to you today. Congenital heart disease is the most common birth defect. Fetal echocardiography, although promising, is accurate in detecting these lesions only in about 30 percent of instances in the best of hands -- in the United Kingdom, where they've been most organized over the years.

Then we get to physical exam. Physician exam is accurate about 50 percent of the time. That's a coin toss. That's been proven and shown in large European studies, as well as some studies in the United States.

Yes, pulse oximetry does have misses, and I'll speak to that in a second. But the issue is we are missing these babies, and they are getting sick. And they are showing up in shock. And not only that, we, as physicians, are teaching for failure. Over my 25 years, one of my favorite things to teach the pediatricians at my hospital is that a 1-week old baby

comes into the emergency room in shock, what is it? And the answer is critical cyanotic congenital heart disease. I've been teaching failure, not trying to prevent it, and I apologize to the parents.

Now, to the facts. As Dr. Kemper said, there has been a lot of work, and in fact, the sensitivity has ranged quite variably from as low as 40 percent to as high as 90 percent. A lot of that has to do with the non-cyanotic conditions, particularly coarctation of the aorta.

The specificity has been excellent, typically over 90 percent. There are false positives. But with newer equipment and, as noted, with proper timing after 24 hours of life, sensitivity as high as 99 percent is now being achieved. The meta analysis has been

performed by Thangaratinam, which is in the CV -- the bibliography that was presented here today.

Now, and the hospital impact I think is very important. The same way the American Heart and American Academy of Pediatrics has noted, implementation is key. How do you do it?

What we've done is to develop a toolkit. We

have studied this in a community hospital in the Washington area and have screened 7,000 babies in the last just over a year. We have three false positives. So that the false positive rate with teaching, proper teaching and application of the technique, and new pulse oximetry monitoring equipment can be minimal.

We've had -- in addition to the three false positives, we have had one true positive, and we've had two positives not for critical cyanotic heart disease, but for other heart disease. So I hear you about the issue of false positives. But as we've come down to it, and I think as one of the members of the panel noted, shouldn't we know that some of these children don't have oxygen saturations of 95 percent or greater before they leave the hospital?

Regardless of whether or not it is cyanotic congenital heart disease, a pulse ox of less than 95 percent is not normal. And as been shown in the European studies, both Mayberg and Granelli, which are also in your bibliography, these babies have pneumonia, sepsis, PPHN, and a number of other conditions that are leading to them not having a normal oxygen saturation.

This will be different than hearing, which I might add, the hearing screen, although very important, has a much higher false positive rate. It will be different than some of the rare metabolic conditions, also very important. But this is a spectrum of conditions, and I think you framed it nicely by putting in the critical cyanotic because you may miss and parents need to know that we still may miss coarctation of the aorta. But we will find babies that have lung disease that should be treated before they're discharged from the hospital as well.

We are now implementing at 11 other hospitals in the metropolitan Washington area, some as far away as 100 miles from our hospital. We have implemented in Kuwait, at a hospital in Kuwait, and we are traveling

there next week to implement at the largest birth hospital in Kuwait and starting in Qatar as well. This is happening around the world. We just happen to be behind.

Thank you.

DR. HOWELL: Thank you very much, Dr. Martin.

We're going to proceed with our public

comment, and we're next going to hear from Gina Cioffi from the Cooley's Anemia Foundation.

MS. CIOFFI: Thank you.

I want to thank everybody today for a really great, robust discussion about Hemoglobin H and including it on the core panel, and I think that we have a really good idea of how difficult it is to include the rare disorders.

And to include this on that core panel, which is great to have that understanding, except I think that we also now have some reasons to encourage further discussion and further inclusion. I mean with the alpha-thalassemias, we're really losing an opportunity if we don't get the newborn screening. So maybe they don't qualify for the core panel, but I think we need

to look at doing them on a secondary panel -- that criteria, what it would mean and how we also kind of look at that and make those considerations.

We don't want to lose these patients, and we will lose them unless we catch them during this window. And that would be very tragic because the whole purpose of newborn screening is to be able to do

education and to be able to inform the families, especially in the first year of life, what they can do to watch out for the child's health, to protect them from infections that can become very, very severe and life-threatening. So I do think it's important for further discussion, and I really encourage it.

I think that right now, there is a really great opportunity with the new registry for the surveillance of hemoglobinopathies, which is a cooperative program with the NIH and with the CDC, and we'll be able to get some population-based evidence on outcomes from people with hemoglobinopathies. We'll be able to look at the impact of treatment. We'll have some case studies.

I think that we'll also have an opportunity

to look further at the States that are doing the screenings right now for Bart's, and we'll be able to sort of have more discussions on these incidental findings and how we process them and what we do about them. So I do think it's really important.

I know that there was a suggestion for a working group. I don't know if that was made formal?

If we can make that as a formal process to continue this conversation, I think that having the CDC, the NIH, other experts, the community-based organizations, and maybe even getting some more feedback from the Secretary's Committee on Genetics and Health Outcomes and Healthy Society would be important as well.

So I think let's continue that work. If somebody can give us some sort of assurance that we will be looking at that, that's great.

I think in terms of public education and the things that the community-based organizations are doing, we have really terrific materials that we provide to anybody that needs them on trait screening for Hemoglobin H for thalassemia in general. We have them in a variety of languages. Our foundation has

translational services where if a family wants to talk to us more, we'll have somebody to interpret whatever language or cultural outcome there is.

And we do all this work with a cooperative agreement through the CDC. So we already have a lot of systems set up to be able to help, as a community-based organization, the States and others communicate to

potential trait carriers how they might be able to understand this genetic information that they'd be provided.

And I know it's not within your purview to look at trait screening for adults. But if you are a parent with an alpha-thalassemia trait, and there is a possibility that your child might have hydrops, the idea that now we can cure them is amazing, phenomenal. It sends chills up my spine.

When you see anemia on a slide, you think it's something so benign. And then, when you look at this remarkable ability to transfuse these children in utero and save their lives, it's something that you really do want to speak up and fight for.

So I hope we'll have more of these

conversations. It's my first time here, and I hope to be part of this continuing process.

So thank you very much.

DR. HOWELL: Thank you very much, Ms. Cioffi.

We're next going to have discussion relating to the dried blood spot issue, and I'd like to welcome Ms. Catherine Crump from the ACLU.

MS. CRUMP: Good afternoon. My name is Catherine Crump. I'm with the American Civil Liberties Union. I work in our Speech, Privacy, and Technology Litigation Program.

Genetics in general is an issue that's of increasing interest to us and, of course, newborn screening in particular. That's probably not surprising. It encompasses the blood specimens of a wide range of people, of essentially everyone born in the country. People who have lots of different views about the privacy and autonomy interests that are implicated through those blood spots.

So far, our involvement in this issue has been modest. We have a position on the Community Values Advisory Board of the Michigan Biotrust Effort,

and we submitted some preliminary comments in response to the residual blood spot report.

There is a good deal that we like about the report. We appreciated the recommendations that States place increasing emphasis on educational programs. However, we were concerned that the report did not contain a strong statement that consent, parental

consent is necessary for the long-term storage and research use of blood spots. Instead, the report said that States should consider whether consent or dissent from families is necessary for uses other than newborn screening and, if so, under what circumstances.

We would have hoped for a stronger statement in favor of consent. Parents have a lot of different views on these topics, and we think those views need to be taken seriously, and people should have the ability to opt out.

The ACLU is certainly not opposed to newborn screening. We think it's an important public health program. We're not opposed to residual blood spots being used for research purposes. Our only issue here is with the issue of consent.

We go into more detail in our written comments. I won't reiterate that here, and the ACLU would love to have the opportunity to work together with the committee on these consent issues regarding residual blood samples because we would like to make sure that this important public health program evolves in a way that also protects civil liberties interests

at the same time.

So thank you.

DR. HOWELL: Thank you very much.

The committee has received the letter from the ACLU commenting about the dried blood spot, and we are fortunately getting a lot of responses, which is very good, and all the members of the committee will get all the responses to review once we have those in hand.

And our final commenter for the day is Jennifer Weisman from HHS, the Office of Civil Rights. She is local, and perhaps she was called away on some urgent issue at HHS and so forth, since I do not see her here.

That's the end of our public comments, and we

will now briskly move to committee discussion. Are there issues that should come before the committee before we move on? Any other specific area that is in limbo that we need to discuss?

[No response.]

DR. HOWELL: Hearing none, we'll move to -- oh, I'm sorry. Chris?

DR. KUS: Yes. Just following up on the NCAA issue that we had discussion on, did we come to any action in that area?

DR. HOWELL: Yes, I think so. Do you want to comment on that, Michele?

DR. LLOYD-PURYEAR: Well, we could come back with a general recommendation for that workgroup, or we could wait for the workgroup to come back to us. But there was sort of general discussion that if the committee did not, in fact, agree with screening following on KOF's comment of why should we teach someone to do a bad thing well, Tracy suggested to just have one recommendation. We recommend not screening.

DR. KUS: But did we --

DR. LLOYD-PURYEAR: No.

DR. KUS: That's what I'm bringing up. Because I would recommend that.

DR. HOWELL: I think the sense of the group, and obviously, we'll have that at the next thing, the sense of the group I think has been that we would not recommend carrier screening for sickle cell disease and so forth. And again, following on KOF's classic

comment -- and maybe it's not original with him, but it was original to me -- that you can't teach someone to do a bad thing well, can't teach someone to do a bad thing well, I think that's correct.

Any other comments, and so forth?

DR. LLOYD-PURYEAR: Wait, wait. What I think Chris is suggesting --

MALE SPEAKER: We write something. We do something.

DR. LLOYD-PURYEAR: He's suggesting a more formal recommendation?

DR. KUS: Well, I don't know what, so we -- what I'm hearing is that we don't recommend screening of athletes, but I don't hear how anybody is going to know that other than through our midst.

MALE SPEAKER: The letter.

DR. LLOYD-PURYEAR: Because the working group is coming back with a brief to the Secretary with a recommendation to be approved or not at the next meeting. You want it to be sooner?

DR. KUS: I guess it seemed to me that people were pretty clear, or at least I thought people were

clear we shouldn't screen. It seems like a long time to come back in a process when this is happening right now.

DR. CALONGE: So, Michele, I understand we have a process that we want to adhere to. I think maybe there is a way to do both, one, that would it be possible to send a letter saying that we are looking at this issue and we have concerns without reaching the conclusion that we want to go through the process in order to get to? So we could at least put a stake in the dirt saying that we have concerns about your policy, and we're looking at it. And then, when we get the final conclusion and we vet that, then we can take the next step.

DR. HOWELL: Our recommendations all go to

the Secretary. That's the only place we can send recommendations.

DR. KUS: I don't know whether we're ---

DR. LLOYD-PURYEAR: You don't know what?

DR. KUS: It just sounds like there was pretty strong statement, and I would actually adapt it to say we shouldn't teach people to do bad things well.

And how do we communicate that without waiting for a longer period?

DR. LLOYD-PURYEAR: If somebody is ready to make a recommendation.

DR. HOWELL: Is a member of the committee, a voting member of the committee prepared to make a recommendation that we vote on today?

DR. TROTTER: I'd be happy to. You know, last night, I looked at the report from the material, the whole of the material that Kwak gave us yesterday. And the very first paragraph is we don't -- his group does not recommend that they do anything to identify these athletes and that they, instead, adapt the practice and play, much as the military has done, so that they don't become singled out.

We don't need to identify them, then we don't need to identify them. It doesn't make any sense. Forget all the other problems. And I happen to agree with his thought. So I would move that we do not recommend at this time screening for carrier detection of sickle cell disease in athletes.

DR. HOWELL: Is there a second to that

nomination?

DR. CALONGE: I would second that.

DR. HOWELL: Is there any discussion?

DR. SKEELS: This is just a question. I agree completely, but what's the purpose of this? NCAA isn't going to change their recommendation. They had to issue it as part of a lawsuit, right? So are we just getting on record in case somebody wants to use what we say to counter the NCAA? I mean --

DR. TROTTER: Well, we were asked to recommend, have preliminary recommendations to this committee specifically noted, number four and number seven are noted to this committee for a response. And we can choose to put it off. I'm just suggesting that I don't want to.

DR. SKEELS: No, actually, I agree with you, Tracy, completely. I think it would be great if we could get this on record now and not wait until September or whatever. But I think the way we craft this depends on the intended audience and the purpose. And I think all we want to do is just issue a statement that says here is what we don't like about

the NCAA policy. That's fine. I'll shut up.

DR. LLOYD-PURYEAR: Well, what do you want the Secretary to do?

DR. SKEELS: Yes, that's it. Like what action are we asking?

DR. LLOYD-PURYEAR: I mean, this is the committee's position, but it's you're recommending something to the Secretary. Do you want her to look at the issue? Do you just want to tell her this is your opinion? Are you recommending some action, or are you just saying this is the way we feel?

DR. TROTTER: I have learned never to tell any lady that this is just my opinion.

[Laughter.]

DR. TROTTER: Well, I think the whole subject

needs significant review. I'm just concerned that this committee was -- a preliminary recommendation from that workgroup, or whatever it was, was for us to comment on this, and then we were supposed to come up with a resuscitation plan. And I can tell you when I go down, I don't want a lot of geneticists resuscitating me.

[Laughter.]

DR. TROTTER: So I think the whole thing needs to be looked at, and I'm just responding to his request for our concern.

DR. BOYLE: I think a statement has to be prepared. I don't think we -- I said I think there needs to be a statement prepared. What is the committee recommending? We just can't say that we don't endorse it. So someone has to have a prepared statement that the committee can get behind.

DR. HOWELL: Rebecca, Jerry, what are your thoughts?

DR. VOCKLEY: I don't think one precludes the other. I think we can make a statement that says we don't recommend it and that gives us we can still come back at the next meeting or through an interim email

vote to approve a slightly longer and, if necessary, more detailed recommendation.

I guess I don't know what we're being asked. We're being asked to say do we support this? We're replying, no, we don't support it.

MS. MONACO: Question. Would whatever we decided to do, would this be sent on to the NCAA?

DR. HOWELL: We advise only the Secretary. We do not advise others.

MS. MONACO: No, I mean, do they -- are they informed of anything coming out of this committee?

DR. HOWELL: I'm quite sure they will be informed, but not by us.

[Laughter.]

DR. VOCKLEY: Rebecca is going to talk to Coach Kay next week.

[Laughter.]

DR. HOWELL: What did you say?

DR. BUCKLEY: I think we should take action today.

DR. HOWELL: Piero?

DR. RINALDO: We have a motion. We have a

second.

DR. HOWELL: Do you have any comments?

DR. RINALDO: No.

DR. HOWELL: We're in the discussion period.

DR. RINALDO: I just agree.

MALE SPEAKER: Call the vote.

DR. HOWELL: All right. Everyone seems to

have spoken. Alan, would you like to comment? All right.

Those favoring a recommendation that we send a note forward to the Secretary saying that we do not recommend carrier screening for sickle cell disease. That's what the thing is, and I think your motion is.

DR. TROTTER: Correct.

DR. HOWELL: At this time, I will elaborate a bit. We obviously should not get into the methods of resuscitation, et cetera. That's clearly not our bag. I mean, that's clearly beyond the purview of this committee. But that's the motion, and we have a second and so forth. Those favoring that --

FEMALE SPEAKER: Excuse me, Rod. Can I get a clarification on that statement? Because whatever you

say, we have to put in that letter. So are you recommending not screening for carrier screening for sickle cell or -- we need to make sure it's worded exactly correctly, please.

DR. HOWELL: We have a written word here so that you'll be able to have it quite accurately done. We recommend that we do not recommend carrier screening

for sickle cell disease for athletes as a prerequisite for participation in Division I sports, which is what they said.

MS. TERRY: Could you use the microphone? I think they're having a problem hearing.

DR. HOWELL: Oh, they're having a problem hearing? It's late in the day. Do not recommend carrier screening for sickle cell disease for athletes --

MALE SPEAKER: Sickle cell carrier trait.

DR. HOWELL: Yes, for athletes as a prerequisite for participation in Division I sports. I think that was it.

DR. GUTTMACHER: May I ask just a point of clarification, or whatever? I'm not sure what this,

point of something, point of my confusion. Do we want to say it as that, or do we want to say that rather than we do not recommend screening, do we want to say we recommend not screening routinely for sickle cell disease trait as a whatever for athletic participation, et cetera?

DR. HOWELL: That might be a little clearer.

Let's see how that comes down when --

MALE SPEAKER: That got a plus. That's good.

DR. HOWELL: -- our handy scribe to my right puts it on paper.

DR. GUTTMACHER: While I have the microphone, though, I might say that as I believe the only medical geneticist that has ever run an intensive care unit, I resent the idea that medical geneticists are not supposed to resuscitate people and --

[Laughter.]

DR. TROTTER: Well, then you stay close to me.

DR. HOWELL: And if we say that we would recommend that medicine geneticists who've run ICUs are in charge, that would be one in the world. So that's

you.

DR. LLOYD-PURYEAR: So is this the recommendation. We recommend not screening routinely for sickle cell trait as a prerequisite for participation in Division I sports? Is that --

MALE SPEAKER: Yes. That's good.

MS. TERRY: So does, is that the only thing

that the -- so the only thing I wanted to not do is narrow that too much, and if it's then once you're in, you can be screened, and it can be required for everyone. We don't want to leave that door open, do we? Because this is about prerequisite to participate. Once you're a participating athlete, can you be required then to be screened, and then we're okay with that? I just don't want to make it too narrow.

DR. TROTTER: They're going to do what they're going to do. I think we just have to make a statement about what we were asked to make a statement about.

MS. TERRY: Which is the --

DR. CALONGE: It might be as a condition instead of as a prerequisite, as a condition for

participation.

MS. TERRY: That's better.

DR. HOWELL: Do you want -- let's read this.

DR. LLOYD-PURYEAR: Read it again. We recommend not screening routinely for sickle cell trait as a condition for participation in Division I sports.

DR. HOWELL: Okay. The motion, is that good?

MALE SPEAKER: You bet.

DR. HOWELL: Okay. Those persons favoring this motion? We're not going to have any comment from the audience. Those persons favoring this?

[Show of hands.]

DR. HOWELL: Piero left me his vote is a yes.

Those who are abstaining?

[Show of hands.]

DR. HOWELL: Do we have one abstention? We have one abstention.

MS. TERRY: Two abstentions.

DR. HOWELL: If you have some very brief comments, we'll hear them. We're running far behind.

DR. GRANT: This is Althea Grant, Division of Blood Disorders, CDC.

I just want to encourage -- even though you voted already, I encourage you that this actually is a more nuanced issue because people can't opt out of screening. So when you create your statement, it needs to be a lot more detailed and a lot more nuanced.

The other thing I should also alert people to is that increasing the number of people with sickle

cell trait who know their status is a Healthy People 2020 developmental objective that we're proposing. So we need to make sure we balance by saying we do support people knowing their sickle cell trait status.

Thank you.

DR. HOWELL: Thank you very much and so forth, et cetera.

Please note the calendar dates for 2011. Our next meeting is September 16th and 17th. After the meeting, you'll get a note from Altarum about the meeting, and please fill out that and let them know what you have to say.

Are there any other materials that should come before the committee?

DR. CALONGE: Move to adjourn.

DR. HOWELL: We have a move to adjourn.

DR. SKEELS: Second.

DR. HOWELL: And a second? I'm sure that we have a second, and I think I see nodding that we'll agree that we'll see you in September.

[Whereupon, at 2:40 p.m., the meeting was concluded.]