25TH MEETING OF THE SECRETARY'S ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

RENAISSANCE M STREET HOTEL

1143 NEW HAMPSHIRE AVENUE NORTHWEST

WASHINGTON, D.C. 20037

SEPTEMBER 23, 2011

COMMITTEE MEMBERS PRESENT:

R. RODNEY HOWELL, Chairperson

DON BAILEY

JOSEPH A. BOCCHINI, JR.

JEFFREY BOTKIN

REBECCA H. BUCKLEY

BRUCE NEDROW CALONGE

FRED LOREY

ALEXIS THOMPSON

TRACY L. TROTTER

GERARD VOCKLEY

CHARLES HOMER

STEVEN McDONOUGH

CATHY WICKLUND

ANDREA WILLIAMS

DIETERICH MATERN

EX-OFFICIO MEMBERS PRESENT:

COLEEN A. BOYLE

ALTERNATES:

CARLA CUTHBERT

DENISE DOUGHERTY

KELLIE B. KELM

SARAH R. LINDE-FEUCHT

SARA COPELAND, Secretary

ORGANIZATION REPRESENTATIVES:

FREDERICK M. CHEN

MICHAEL S. WATSON

JANE P. GETCHELL

CHRISTOPHER KUS

BENNETT LAVENSTEIN

MARY J.H. WILLIS

SHARON F. TERRY

ALAN R. FLEISCHMAN

CAROL GREENE

(Begins in progress.)

DR. HOWELL: -- yesterday. And so, we will miss him. Dr. Alan Fleischman has asked that I give him a few moments of a personal note before we begin the meeting today.

Dr. Fleischman?

DR. FLEISCHMAN: Mr. Chairman, on behalf of the March of Dimes, its President, Jennifer Howse, its 3 million volunteers, its 1,250 employees, we would like to present you with this lovely, little plaque, which was displayed last night at the Genetic Alliance meeting, which reads, "Rodney Howell has led the transformation of modern newborn screening and saved countless lives," and Dr. Jennifer Howse, President of the March of Dimes. "A charismatic leader, a marvelous political, clinical, scientific, and dramatic person, who has helped the women and children of America and across the world."

Dr. Howell?

(Applause.)

DR. HOWELL: Alan, thank you very much. And, obviously, I thank Dr. Howse, who, as you know,

was an original member of this committee and a very big contributor. And the March of Dimes has always been very, very helpful.

And let me congratulate Sharon on the 25th birthday of the Genetic Alliance. And she hosted a marvelous festivity last night. Many of you were there. And she had an enormous number of excellent folks there.

So congratulations, Sharon.

We are now going to move into our subcommittee reports. You know, the subcommittees have been historically extremely productive and full of suggestions, and so forth, for the future directions of the committee. And the first report will be from the Laboratory Standards and Procedures Subcommittee and Dr. Vockley and Lorey.

And is Gerry going to speak, or are you both going to speak?

DR. LOREY: He's going to speak.

DR. HOWELL: He's going to speak? All right.

Dr. Vockley?

DR. VOCKLEY: Thank you. I'll start off, as I have typically, listing the members and, in this case, pointing out the addition of Dieter Matern to the committee, who will be joining the full committee as of next meeting.

And, in keeping with Sara's charge yesterday, we spent the day really, kind of, reviewing the progress over the last, I don't know, two, three, four years in the committee and in looking at the topics that we've wrestled with in trying to generate a platform for going forward for our new Chair. And, to start off with, I went back to read what we actually were supposed to be doing, because I think that's always a good place to start.

And the subcommittee charge here is on this slide. And I think it actually has some areas where there is a lot of room for the committee to move.

So the subcommittee charge is to define and implement a mechanism for the periodic review and assessment of the conditions included in the uniform panel. That's like a time bomb. And it's probably about ready to go off.

To review and assess the infrastructure services needed for effective and efficient screening of the conditions included in the uniform panel, and the laboratory procedures utilized for effective and efficient testing of the conditions included in the uniform panel. And I'm going to come back at the very end to talk about the direction that the committee will look to to go forward in the coming years.

Not to be outdone by Dr. Willis, I'm going to list all of my acronyms up front. You know, it's not just the military. And so --

(Laughter.)

DR. VOCKLEY: There.

(Laughter.)

DR. VOCKLEY: You know, for those of you who are laughing and going off the committee, I know why I'm being thrown off. What's your excuse?

(Laughter.)

DR. VOCKLEY: It won't be the only time, I fear, that gibberish has entered into the federal register, as long as Congress is in session. But nevertheless, we'll move on.

So in looking at what we've done over the last couple, three years, we have the longstanding and very tardy second screen project, which we continue to be told is almost ready. I won't elaborate on that, for those of you who haven't been here for the whole process.

One of the things that has evolved as a real role for the subcommittee has been the Health Information Technology Work Group, where we are collaborating with -- look at all these acronyms -- the National Library of Medicine Information Technology Initiative and specifically helping out with the assessment of new medical language, specifically LOIN codes, as that group has been bringing them forward and in regards to newborn screening results and the medical record.

We've also spent a fair amount of time looking at and evaluating novel molecular technologies. You know, this is really the, sort of, transformative piece over the last few years in newborn screening, as we moved to primary molecular-based testing as opposed to molecular-based testing as

follow-up of a metabolite or an analyte. And, in keeping with that, we have had an ongoing dialogue with the CDC over their development of Q.A./Q.C. materials for the SCID testing and also for the lysosomal storage disease. Oh, man, look at those acronyms. Love it.

And have had several presentations from Bob Vogt over the time of the last few committee meetings. And then, finally -- or, at least the ones that we're going to talk about in this list -- we spent considerable time reviewing the various technologies that are out there now and competing for the LSD newborn screening market and recommended a project for direct comparison of these alternative techniques. And although we won't take credit for having started that, we do note, with satisfaction, that the Mayo Clinic, indeed, has a project now going forward funded, I think, by HRSA.

Dieter, is it a HRSA project?

DR. MATERN: NICHS.

DR. VOCKLEY: NICHS? So it's a project to compare competing technologies directly to see whether

any of them has a clear advantage in the newborn screening arena.

There will be a number of committee changes, as Rod noted yesterday. I get to step down from this committee as of the end of the day. And Fred Lowry will be taking on the duties as Chair.

And, in recognition of the, sort of, evolving -- what we see as the evolving pattern of responsibilities, we spent some time deciding whether the name of the subcommittee was actually correct. And we thought that it could be more accurate and that something like the Laboratory and Information Technology Subcommittee would better fit the evolution of the scope of the committee and recognize the increasing role of information technology in newborn screening infrastructure.

I'm going to leave it to Sara to figure out whether or not we can just, like, take that name or if there's something official that has to be done. But that's a recommendation, a formal recommendation from the committee.

In moving forward, I actually pulled this

slide out of a presentation that I did at one of the meetings in -- I guess it was the January HRSA meeting. And it's still quite pertinent.

While there are many potential areas that the subcommittee could become involved in, and especially looking at the idea that screening is not, by definition -- and does not, by definition, have to be newborn screening. Nevertheless, we recognize that, with the likely applications and agenda going forward for the full committee, that newborn screening is really likely to be all-consuming for the committee in the near future.

So if there are other areas that suddenly burst on the scene, the committee certainly should be open to examining them. But I think we really will be focused on newborn screening for the near future.

As an initial agenda for the immediate future, we talked a lot about what the committee could or should be doing. And the list is almost endless. But we really came up with three pieces that we thought where the committee could make an impact.

The first is really a continuation of the

role of the committee in reviewing new enabling or disruptive, transformative-type technologies. And, by definition, we don't know what they will be, but we can anticipate that they will come. And so, the committee should continue to aggressively monitor that and bring in speakers for presentations to stay abreast of those technology.

Number two is likely to be a more important piece going forward. That is to provide guidance for states making decisions about implementation of new screening tests, comparative performance metrics, overview of technologies, and then, a discussion -- an ongoing discussion of the point of origin versus traditional laboratory-based newborn screening-type tests.

So these are all things that are going to be necessary for the committee to be successful in the future. And we've boiled those down into four specific goals.

One is in -- and the reason I showed my subcommittee charge at the very beginning is to really remind the committee at large that one of our charges

is to actually review the standard panel as it goes forward. And therefore, the committee would be happy to take a lead role in trying to establish a process for -- processes for regular review and revision of the standard panel. So removal of disorders and a slightly less dramatic change: altering status of some targets that are listed currently as secondary to primary, if that becomes appropriate; as a second goal, recommend specific changes to technologies, when indicated.

And we think there's one right now that really needs some adjustment: the use of tyrosine levels to identify Tyrosinemia Type I, which is the one you really want to identify in the newborn period, has been superseded by succinylacetone. So this is a disorder that's already on the panel, but there's a new technology that eliminates almost all of the problems related to the original methodology. And we think that there should be a mechanism for making that notation and adding it -- a specific recommendation that this is the technology that should be used when screening for Tyrosinemia Type I.

And then, the other two are a little bit more nebulous. We think that the information technology component of what the committee does is going to continue to be very important. And so, we want to maintain that interaction with the I.T. Work Group and keep that collaborative. And then, as I mentioned in the previous slide, the monitoring of new technologies will be very important, going forward.

So I will stop there. Thank you for your attention and the forbearance of the last five minutes and four years and call it quits. Happy to take questions.

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

Chris?

DR. KUS: (Off-mike) a conversation. I guess one of the questions is you're talking about lab technology. But how about other physiological tests like pulse oximetry, hearing screening? And how does that fit with your committee?

DR. VOCKLEY: Well, that was the implication when I talked about point of origin testing. So that

really does bring us to all of the other technologies. That could be a lab test, as in the bilirubin discussion. But, in a lot of cases, it's going to be other technologies. So this brings us to this is where the congenital cyanotic heart disease would fall.

DR. HOWELL: I'd like to ask about the second screen. You had that listed, and so forth. And you said it's almost ready, which it's been almost ready for several years, as I recall. What's the status of that?

DR. VOCKLEY: It's almost ready.

(Laughter.)

DR. VOCKLEY: Joe Lilly, are you here? Oh, Harry's here. Harry's here.

DR. HOWELL: Dr. Hammond, certainly, can comment on that. I see him coming to the microphone.

DR. HAMMOND: We are through collecting data. We have decided that what we have is all we're going to get. And we have most of the data we had planned to get. We are cleaning up the database. We have asked some questions back from those who have

submitted the data to get it polished up. We're compiling, and we'll start evaluating the data. And we'll have a report to the committee in the next meeting.

DR. HOWELL: That's great. I think the bottom line is that, you know, obviously, everybody should be doing the second screen, or nobody, depending on what the data can show you. I mean, if persons are being missed with important conditions, that's a problem.

DR. VOCKLEY: And, for those who don't remember the history of this, the project really has just struggled with IRB issues. They wrestled with having to pool information and get multiple state IRB approvals. And that's something, I know, we've discussed in the past. But really is a major problem in dealing with these multiple-state projects and trying to deal with newborn screening pilot projects. So it may be something that the committee ultimately wants to come back to and think about making recommendations for alterations in procedures.

DR. HOWELL: One of the technologies that's

obviously going to be before this committee very soon and in a big way will be whole X-on sequencing, and so forth, which will be a very big issue. At the same time, I think that one of the biggest issues in that area have to do with ethical/legal issues.

And have you all talked about how you will -- in other words, a technology such as sequencing, that's one thing. But it's hard to deal with that in the real world without having the ethical issues at the same time.

DR. VOCKLEY: I'd say that we exhibited some benign neglect at that level, largely because, while that technology is really looming heavily over us right now in many clinical situations, the application to high-throughput newborn screening environment is probably still technically a few years away. So it didn't hit the highest level of -- in terms of the subcommittee's agenda for the next couple of years.

But beyond that, I think we're definitely going to have to wrestle with it. But it's going to have to be -- if it starts -- whichever committee it -- subcommittee it starts with, it's going to clearly

cross over to all of them. And the ethical issues are probably only going to be outweighed by the I.T. issues.

DR. HOWELL: Yes.

Jeff?

DR. BOTKIN: Yeah, just a quick comment on that. The Bioethics and Legal Working Group of the Newborn Screening Translational Network is planning a small meeting in November in conjunction with the meeting of that work group that's going to focus on unanticipated findings, secondary results, a variety of different terms for the phenomenon of generating results on testing that aren't your primary target and what the ethical and legal obligations are to disclose that information to families and clinicians.

So that's a current problem. But, as just mentioned, this is going to be that much greater once we get DNA-based platforms.

DR. HOWELL: And there's no reason that this committee can't inform this subcommittee. I mean, that will be helpful.

As far as I'm aware, no one disagrees with

the observation that the primary screening analyte for Tyrosinemia Type I is succinylacetone. Is that not correct?

DR. VOCKLEY: It is correct.

DR. HOWELL: Is that --

DR. VOCKLEY: It is correct, but not implemented in a uniform fashion across the states. So a specific recommendation that that be the analyte would be helpful from the committee.

DR. HOWELL: Well, it seems to me it would be, too. I mean, I think the science behind that is clear; is that right?

Does anyone have any concern about that?

DR. BOTKIN: (Off-mike) in the context of, well, why isn't everybody doing it now.

DR. HOWELL: Yeah.

DR. BOTKIN: And I think, because just the way it developed, instead of having a brand new recommendation --

DR. HOWELL: Yeah.

DR. BOTKIN: -- you know, we've had Tyrosinemia.

DR. HOWELL: Right.

DR. VOCKLEY: Well, it does ask the question, how do we reevaluate something that's already there. Do we need a full evidence review? Is this something that goes back to the Evidence Review Committee? In which case, we probably need to double or triple its size.

Or is it this is a very technical, very specific piece? And if the Technology Subcommittee is able to put forth a statement to the committee at large that says, we recommend that -- or we recognize that succinylacetone is the metabolite of choice to be analyzing for Tyrosinemia Type I, which is already on the recommended panel, that may be sufficient.

DR. HOWELL: Well, I think that when something goes on the panel, ordinarily we don't make formal recommendations of exactly what you measure.

DR. VOCKLEY: Right.

DR. HOWELL: But, on the other hand, it would seem worthwhile for this committee to look at the data and come forth with a recommendation that this be the analyte. And I don't see any reason that

can't be done.

Does anyone see a problem with that?

MALE SPEAKER: I don't, because the problem as it is now, is people will still say they're screening for Tyrosinemia Type I with tyrosine.

DR. HOWELL: Yes. And we know that's not the case.

MALE SPEAKER: And they should not be able to say that.

FEMALE SPEAKER: (Off-mike.)

DR. HOWELL: Okay. About this? Okay.

The bottom line, it would seem prudent to come up with a specific recommendation for this committee to come to this -- for the subcommittee, so it could come to this committee and say that we have reviewed -- your committee could say that we have reviewed the evidence, and you can get the evidence from a number of sources. And it's clear that this should be the recommendation. And that recommendation just can come forth in the committee, would not change what we are screening for, the condition.

Jane, question or comment?

DR. GETCHELL: A comment. Is this on?

DR. HOWELL: Yeah.

DR. GETCHELL: I did a little investigation last night, after we had the discussion in the committee meeting. And not being an MSMS chemist, bear with me here. But, as I understand it, there is one commercial manufacturer available that will provide the succinylacetone assay. Many of the labs that aren't doing it are using what I will call a home brew assay.

And for that assay, it would require two separate processes, two separate MSMS runs, increasing he cost, for example, to the state of Texas by about half a million dollars to do it on their population. So that's the reason that states have not implemented the succinylacetone screening, as I understand it. It's a cost.

DR. HOWELL: Well, let's -- why don't -- we have several people at the microphone. But the bottom line, it seems to me, that the subcommittee should gather the information, including what Jane has said, and so forth, and come forth with a specific

recommendation.

But, Ann?

DR. COMEAU: Thank you.

DR. HOWELL: Let's be brief, please, at the microphone, starting with Ann being brief.

DR. COMEAU: Thank you, Dr. Howell.

I wanted to --

DR. HOWELL: Ann Comeau.

DR. COMEAU: Thank you, Dr. Howell.

I wanted to go back to the second screen issue, and, because I think it has general implications for everything. My understanding is that the second screen study came forward to try to determine whether or not babies are missed by one method or the other. And, in that it's very likely that having two screens with a particular algorithm and/or using just one screen with a different algorithm will -- that they will both have the same sensitivity and specificity.

And if that's the case, then I would hope that the committee is not determining that all states have to follow the same algorithm, because I think

it's good for us, on many levels, whether it's the second screen or a particular assay that we're using, that states do use different assays and algorithms. It helps when there are reagent problems, whatever.

So so long as we can -- sorry. So long as we can assure that the sensitivity and specificity and predictive values of any particular assay and algorithm are good enough for the population, I would hope that that would be the standard that we'd be following. I think that's probably what you meant.

DR. HOWELL: I would assume that that will be embedded in the study.

DR. COMEAU: Thank you.

DR. HOWELL: I would certainly hope so.

DR. ZUCKERMAN: Thank you, Dr. Howell.

I'm Aaron Zuckerman from National Library of Medicine. I just wanted to remind the committee that Sharon Terry and I chair an ad hoc HIT Work Group, which has now disbanded because they had finished their look at evolving federal policy. And our recommendation was that the HIT Work Group activities move within the standing subcommittees because of the

logistic difficulties of having individuals attend two different work groups.

So the very important ongoing activity of HIT requirements for laboratory data reporting and exchange need to become an official part of the work of the Laboratory Subcommittee as well as Follow-Up and Treatment and Education. So I'm hoping that the committee will officially charge the work group to create a sub-group within its own organization, or at least to take on that ongoing task, since there is no longer an Ad Hoc HIT Work Group to carry on that activity separately.

DR. HOWELL: Thank you.

And our next person is Dr. Dieter Matern.

DR. MATERN: Yeah, just back to succinylacetone. So historically, it's true that there were two second-tier assay for succinylacetone that was done when you lowered your cutoff for tyrosine and then, you do a second-tier test. So you do another analysis.

But then, it was revised. So we did it. And then, others, too, that you actually had only one

tandem mass analysis, but you had your sample prep divided in two. But in the end, it's run on the same equipment, at the same time.

And then, other people have done it so that the sample prep is the same for succinylacetone and the amino (inaudible) all at the same time. But there is no need to double your equipment needs, so just to keep that straight.

DR. HOWELL: Well, anyway, I think that the subcommittee should look at succinylacetone and analyze the data and come up with a recommendation to this committee to approve. And you've heard a lot of -- and, apparently, Sara has some wisdom.

DR. COPELAND: Yeah.

MALE SPEAKER: (Off-mike.)

DR. COPELAND: Okay, now we're on?

DR. HOWELL: Yeah.

DR. COPELAND: Okay. One thing to keep in mind is this is just a one issue, which is tyrosine, succinylacetone, et cetera. But I think what's really important is maybe the process of getting there, just doing a one-time shot without having the operating

procedure, et cetera, will put the subcommittee at a disadvantage. I think that we need to come up with a mechanism for formally doing that, because I think, at this point in time, it's the most obvious issue.

But I think that, as screening technology evolves, et cetera, that we might have better markers, better technology. And so, I think that coming up with a process and then, maybe using succinylacetone as the mechanism to do that will probably be the mechanism to go by.

DR. HOWELL: I think that's a good idea. This is the first time this has been done. And so, it'll be good to have a systematic way of looking at it.

Is your group committed to changing the name of the committee now? Or would you like to wait until the new committee comes? What's your sense?

DR. VOCKLEY: Do you want to think about it a while? Or you want to --

DR. HOWELL: If you've deliberated about this and think that you should do it, why don't you make the recommendation to the committee? And the

committee will approve it. We're a committee of action, as you know.

DR. VOCKLEY: Whoops, sorry. I hit the wrong thing.

DR. COPELAND: But, Gerry, we also -- we thought about including methodology in there. I thought it was Laboratory, Technology, and Methodology Subcommittee.

DR. VOCKLEY: Oh, I thought that Methodology -- I would think the Methodology would go into Laboratory. It, sort of, covers it. But, I mean --

DR. COPELAND: But when you say Information Technology, we were thinking of other types of technology as well and just remembering from the conversation yesterday. So I --

DR. VOCKLEY: It's up to you guys. I'm quitting.

(Laughter.)

DR. HOWELL: Denise has some thoughts.

DR. DOUGHERTY: Well, I was just thinking that maybe we should consider all the subcommittee recommendations before we -- because some of these

seem to overlap. Some of the recommendations for what the subcommittee would do seem to overlap with some of the other committees. Or maybe a new Committee on Methodology. So I think voting on it right now would be premature, because we're not sure that this subcommittee would be the right place for all of these things.

DR. VOCKLEY: Well, I would remind you of the subcommittee charge. These are all straight out of the charge.

DR. HOWELL: I'm not aware of any overlap between the Laboratory and the I.T. I mean, everybody will have a little bit. But, I mean, I think that's where they reside.

DR. DOUGHERTY: Well, establishing the process for reviewing the existing conditions, for example, might be a broader task than just assigned to the Laboratory Subcommittee.

DR. VOCKLEY: Well, except that the first bullet there -- I mean, this is the charge of the subcommittee, to find and implement a mechanism for periodic review and assessment of the conditions

included in the uniform panel, and then, the third bullet, laboratory procedures utilized for effective and efficient testing. So the charge is clear.

And it's not to say that it is the group that makes the decision. The subcommittees make no decision. They just bring the information forward to the committee at large.

DR. HOWELL: Right.

Ned?

DR. CALONGE: I guess what I would recommend that we take the things that the subcommittees are supposed to do as a long list. There may be other things that the incoming Chair wants to add to the list of subcommittee duties. And that I would think that that would be a good Chair activity to think how to best sum those up into the number of subcommittees that he thinks will help move the work forward. And so, I'm, kind of, supportive of Denise's approach, that -- I'm not so much concerned about overlap, just that the whole list might be long, and there might be other aggregates of that list that make more sense.

DR. HOWELL: And you had commented about

that yesterday, about the fact of looking at the subcommittees as a group and decide if the right ones, and so forth. So maybe that makes a good -- does that seem sensible? We'll let that roll over and let the new persons decide about what's there.

Any further comments to Gerry?

So the new committee, straight out of the thing, will have a report on the second screen. That'll be great.

DR. CALONGE: I think we should recognize Gerry's leadership. This is actually a whole lot of additional work that, clearly, you have to do after the parties on the night before the second meeting. And he's been a good leader, has helped move us along. And I just wanted to recognize his leadership.

Thank you, Gerry.

(Applause.)

DR. HOWELL: And, again, thank you very much.

And we are now going to move to the Subcommittee on Education and Training, Don Bailey and Tracy Trotter. And it looks like we're going to hear

from both of them.

DR. TROTTER: Well, lucky day.

(Laughter.)

DR. TROTTER: Good morning. Also following Sara's charge of, in some way, dealing with past, present, and future of our subcommittee, I went back into the historical archives. This was established in January 2005 after, I guess, probably about a year of the committee meeting. And our charges here, as you can see, to review existing educational training resources, identify gaps, make recommendations regarding newborn screening to five groups. And if you are not in one of these five groups, you do not exist.

(Laughter.)

DR. TROTTER: This represents the world. So we have work yet to do.

The first meeting, Jennifer Howse was our Chair, interestingly enough. And those were the four members of the committee. These have been the Chairs over the years, with Don taking over at this point.

Our current committee -- and all of our

members were there, either there or on the telephone yesterday. Plus, we had probably another 20 interested contributors who were there. And we had a chock-full meeting trying to get the three hours done in two hours. But we got it done, knowing that the cocktail hour was coming up.

So, in the past, the accomplishment-type things, which are a little less straightforward, sort of, than what we do, is -- but I look back at minutes and talked to members with better memories than myself, and, sort of, looked through and listed a few things. The ongoing dialogue that the newborn screening issue with the primary professional organizations is important. They were not actually involved initially as members of this subcommittee and as active participants and now are an extremely important part of that.

The subcommittee has been expanded over time to now include parents, advocates, newborn screening staff, nurses, genetic counselors. And we continue to -- and Don and I have talked about -- and Able have talked about our need for probably continuing to

expand expertise as we get into more complicated issues of education.

A list of vetted Web sites that had to do with newborn screening resources was come up with a number of years ago. National Repository of Educational Materials -- there were three or four major organizations that played a role in that.

We have, over the years that I've been involved, provided input and feedback from various organizations. I merely list some of them here, who have -- obviously, most education is going on at some other levels, not because we put it together, but we're often involved in looking at material, suggesting ways to go, and, probably more importantly, benefiting from the tremendous amount of work that goes on at these levels.

One of the first things I was involved in was a workshop on genetic education topics. And we had a sub workshop sponsored by HRSA called Developing a Blueprint for Primary Care, Physician Education in Genomic Medicine. It should say Education. Sorry.

This was in June 2009. We had 30

representatives of primary care physician organizations in the United States and looked at three areas: the knowledge, barriers, and interventions. Out of that, there came a summary and recommendations, which was published. Alex Kemper was a senior author of that in Genetics in Medicine in February 2010.

And from those recommendations, this committee approved a recommendation from our subcommittee to develop a program or a plan for some, what we called at that time, a learning collaborative, Genetics in Primary Care Training Institute. And the future is now. The future is here.

The Genetics in Primary Care Institute contract was recently, about three months ago, awarded to the American Academy of Pediatrics. Bob Saul and Beth Tarini are the Medical Directors. Most of you heard this before, as we presented our proposal about a year ago.

The idea is to pair genetics experts with -- in this case, they're going to be with 20 practices with three-member teams from those practices, which would include probably a physician, a nurse, and maybe

a family member and have a program that's a three-year program that will create, they hope, a community of learners, who will then be -- you know, teach the teacher-type thing, a technical assistance center, which will be basically a Web site that's designed for the primary care physicians, and to take a really big bite out of this, attempt to assess and address residency training needs.

I think we know what the needs are. Trying to change those is a little bit larger struggle.

We had the members of our subcommittee give their updates, as they frequently do. You've heard yesterday updates from the clearinghouse regarding Baby's First Test. You also heard about the consumer task force program, which will have applications out soon and challenge awards, which they had -- the first ones were last spring. And we've seen the results of those.

They're on the Baby's First Test Web site by next week, I believe. And a number have -- we have been able to watch that from its inception. And it's really an amazing progress. I urge you all to go to

that Web site.

This was the previous challenge awards. Again, the reports are available to you on the Web. And these were our other somewhat routine programs we instituted about a year ago using the regional collaboratives' time to highlight, if you will, one program somewhere from some one region. Debra Rodriguez did this year's from NYMAC. And that's been very helpful to all of us to, sort of, see what's going on in various regions from an education standpoint as well.

The usual updates from the primary care organizations, Kurt, as well as a special highlight, if you will, from ACMG Translation Group from Mike Watson. And that's going to be an ongoing thing as well. Each meeting, there will be a targeted, highlighted education program that will be looked at from that group.

To go back, as Gerry did, looked at what are we really supposed to be doing. Well, this is what we're supposed to do. And to that point, the provider of public awareness, as you heard yesterday, has led

us to the National Newborn Screening Awareness campaign.

We have -- we, being the subcontractor -- and Jennifer Nichols did a nice report -- completed the first part of phase one, which was the media and environmental scan. She attended our subcommittee, and we had a good dialogue about what further things they might look for. And she's going to do that.

We will then -- at some point, the Chair and Dr. Copeland are going to come up with a work group to facilitate the second step, which is a strategy summit to try to define what are our real goals, what do we really want from this, is it appropriate to go forward. It may not be. If it is, how do we do that? So stay tuned for further information there.

And figuratively and literally, passing the microphone.

(Laughter.)

DR. BAILEY: Thank you, Tracy.

And good morning. So we began our meeting yesterday by thanking Tracy for his fine leadership in this committee over the last two years. And so, as a

large group, we should do that again right now.

(Applause.)

DR. BAILEY: So just a few comments about future directions. I think the first statement is pretty obvious, that we feel that there's a continued need for the Education and Training Subcommittee. This need will only grow in the future as we learn more about different conditions or different technologies and the various ethical issues that come up. All of these will come to the Education and Training Committee in one form or the other. So we're going to be in business for a while.

One of the questions that we discussed a little bit yesterday was, to what extent should this committee address issues of education and training after newborn screening, and in the follow-up and implementation phase. And, of course, we know that there is a Subcommittee on Follow-Up and Treatment. And we're not completely sure the extent to which that committee is also dealing with education issues associated with follow-up and treatment.

It actually brings up a bigger issue about

collaboration across the different subcommittees. We feel like education really pertains to all the subcommittees in one way or the other.

And so, perhaps in the future, Joe, we might consider some mechanism where the subcommittee Chairs meet periodically to discuss collaboration at, kind of, intersections among the three subcommittees. But, of course, especially in the education arena, but I suspect in everything, there's quite a bit of blurring and overlap of missions. And we would all profit from some interaction there.

We would certainly benefit from some increased participation from ACOG. And we are considering recommending that we have a nursing representative as well on the subcommittee.

I think, Sara, we may have to have some kind of formal process for going through that. And so, we'll discuss that with you afterwards.

There was also some discussion about the various training initiatives for physicians about genetics and genomics in medicine. But what about specific information about newborn screening to be

included in those? And so, we're recommending that those initiatives make sure that information about newborn screening is a part of the genomics and genetics training.

So another big challenge for us is, as this larger committee expands and moves beyond -- it already has -- to issues beyond newborn screening, should the Education and Training Committee change its charge. Actually, I think our written charge says Education and Training related to newborn screening. But, in fact, this committee deals with things much larger than newborn screening. And so, we suspect we'll probably need an official modification in our charge.

And then, as we discussed yesterday a little bit in this large committee meeting, as we were talking about our audiences -- and even though Tracy said, well, if you're not in one of those five groups, you don't exist, we were wondering about advocacy groups as a potential target audience for the subcommittee as well, not necessarily working on a one-on-one basis with advocacy groups, but helping

advocacy groups understand what it will take to help bring a condition to the nomination and then review process.

Many of these organizations -- I have been affiliated with one over the years -- often will push for newborn screening without realizing what might be needed to get it to that point. And if we can provide some blueprint beyond just the nomination form, examples and strategies that advocacy organizations might take in order to advance their cause and get us to the point where we have the evidence necessary, that would seem to me to be a very useful product.

Whether that can become an official recommendation of the committee, we don't know. But I think it could be a point of discussion and interaction among the three subcommittees.

And finally, I think -- it's not on the list here, but just to say a word about being strategic as we go forward in the future. We've got lots of a variety of initiatives going on with different organizations. And I think the Education and Training Committee we'd like to step back and say, okay, in the

big landscape of things, in terms of our different audiences, are we addressing each one of them in an appropriate and sufficient way, where are the gaps, what do we need to be doing strategically over the next two to three years to really make a difference.

And also, how can we add a -- maybe probably not as rigorous a process as the evidence review group, but how can we add a research and evidence component to the Education and Training Committee so that we evaluate the work that's being done out there and have data on both what are the objectives of these initiatives and whether those objectives have actually been accomplished?

So I would like to invite any of the other subcommittee members who were there yesterday to chime in to see if there are any other things that I have forgotten to list. Okay.

DR. HOWELL: Any other comments or questions of Tracy or Don?

Jeff?

DR. TROTTER: I would like to take a moment, as I'm finishing, to thank all of you. Thank you for

the opportunity that I've had the last four years to work with this bright and talented and interesting group of people. I will tell you your work ethic, both as individuals and as a group, and your, literally, uncompromising commitment to quality care for children has been inspiring to me. It really has.

All of you have been more than generous with your time. And I have learned an enormous amount. And I appreciate that piece of this more than you know.

In my 37 years of medicine, I've served on, I don't know how many, committees, more than I should probably. This is one of the very few that where I've worked this hard and spent this much time and energy and still enjoyed almost every minute of it.

(Laughter.)

DR. TROTTER: And that's -- yes, I did say almost, everybody.

(Laughter.)

DR. TROTTER: And a few folks, if you indulge me, deserve a special thank you. Alaina Harris and Penny Cuyler, who I don't think either are

here, and Lisa and the rest of the support staff for the untold thousands of things you do all the time to make this thing happen, because we see the tip of the iceberg, I'm sure.

To Michelle Puryear, Rod Howell, and Jana Monaco, who made me feel like I was a part of the team from day one. And to Jim Hanson, Piero Ronaldo, who are not here, and Alan Fleischman, who is, for making me believe that occasionally my contribution was actually important.

So I went into medicine with a very idealistic attitude and a great admiration for and respect for physicians and scientists. And I have to tell you a bit of that has eroded in the last decade or so. And I refreshingly found that the committee members here that I've been fortunate to work with, at least, are those role models that I envisioned. And it's been an honor and a pleasure. Thank you.

(Applause.)

DR. HOWELL: I think Jeff Botkin had a question.

DR. BOTKIN: Well, I can probably make this

in the context of my presentation. But just to say our group, as well, highlighted the potential need to have the Chairs of the subcommittees have an opportunity to talk. And, of course, in the context of the larger meeting here, we have the opportunity to hear what everybody's doing. But we thought, too, that that might be a new opportunity that would be valuable.

DR. HOWELL: But thank you, again, Tracy, for your hard work. And, Don, we look forward to your carrying on this tradition. Great.

We are now going to move on to our next subcommittee report. And that's Coleen and Jeff. And Jeff will be presenting that. This is the Subcommittee on Follow-Up and Treatment.

I don't know whether Coleen's on the phone today or not.

DR. BOTKIN: I don't know, either.

Coleen, are you with us?

DR. HOWELL: Is anybody on the phone? Well, that's settled. Nobody's on the phone. Okay.

Jeff?

DR. BOTKIN: Well, and Coleen has a long history with the subcommittee and has provided outstanding leadership (inaudible) committee. And so, if she's able to join us on the phone, most welcome. We have a large and diverse group who participate with our subcommittee, many of whom are here today. And so, once I finish my comments, I'll welcome comments from other subcommittee members about their perspectives on our wide-ranging and fascinating conversation yesterday.

Thanks to Jill Sugar for her support for the subcommittee. She put together a wonderful document that summarizes the work of this subcommittee over the last number of years or so. I'm going to touch on a couple of highlights here. But hopefully, that document will become part of the record to illustrate all the work that the subcommittee has done.

I just wanted to highlight a couple of publications that have come out of the work of the subcommittee. First, this question, "What Questions Should Newborn Screening, Long-Term Follow-Up Be Able To Answer." That is now in electronic publication

ahead of print from June of this year in Genetics in Medicine. So you see the authors on that paper, all longstanding contributors to this subcommittee.

Let me go backwards here. "Long-Term Follow-Up After Diagnosis Resulting From Newborn Screening," published in Genetics in Medicine back in 2008, Alex Kemper, first author, and, again, a lot of familiar names on that substantial publication.

Quite a few meetings and discussions fostered by the subcommittees. And I've collapsed those into these general categories. The subcommittee has been tracking health policy reform and the implications of those reforms for newborn screening services, and particularly, within the domain of this subcommittee, what are the implications for the care of children.

In particular, I'll emphasize here the notion of medical foods. I'll be coming back to that on several occasions during my comments here to illustrate the importance of that domain.

Health I.T., another significant focus of the subcommittee over time, with the recognition that

that's a rapidly-changing landscape and offers some real opportunities, longer-term, to capture the type of data that heretofore has not been readily available on the outcomes of children with these conditions and the ability to compare different treatment modalities in real-time, in real-life. And so, health I.T. has been a significant focus as well. So quite a few professional presentations in these domains, as well as fostering a number of meetings within the subcommittee to address these topics.

A number of issues that are in progress at this point. We have a hospital-based point of care screening. This conversation, of course, emerged out of the congenital cyanotic heart disease statement, but also relevant to considerations like hyperbilirubinemia and illustrating the clear change in the direction of some of these screening modalities.

And this goes along with the implications of whose job is it to engage with these technologies and to follow the kids up longer term. So, at this point, there is an early draft of the paper led by Nancy

Green and Alex Kemper. A small group of us are helping with drafting of that.

That will come to the full subcommittee, hopefully, before the next meeting or so, and then presented to the Advisory Committee, presumably, within the next six to nine months or so. So this is a significant effort.

In addition, there's Brad Therrell and Colleen Buechner's paper that they've been working on for a period of time, "Improving Data Quality and Quality Assurance in Newborn Screening by Including the Blood Spot Screening Collection Device Serial Number on Birth Certificates," a fairly specific, narrow issue, but really quite important in follow-up and data collection for kids identified through newborn screening.

And this has now been finalized. And this paper will be ready for submission to the full Advisory Committee for this committee's evaluation, presumably, at the next meeting.

So thanks to Brad and Colleen for all their work on this.

This is also a substantial effort. "Parents' Experience with Limited Insurance Coverage for Medical Foods Used for Treatment of Inherited Metabolic Disorders," Susan Berry and this list of authors, again, has been working hard on this survey, has this paper in almost final form. It has to be reviewed by several federal agencies and at that point, will be ready for subsequent submission for publication.

So no question, our subcommittee felt that our subcommittee does valuable --

(Laughter.)

DR. BOTKIN: Clearly, the whole system's notion of newborn screening with all of the linked services that, hopefully, should be available for children after the time of diagnosis is under the purview of our committee, and a clear consensus that those complex set of issues need further attention and evaluation.

What we spent quite a bit of time on was the question of implementation. And I think what some general sense that the committee function may benefit

from additional attention to some of the closer-to-the-trench issues.

What does it mean to say we're going to initiate a certain type of screening and follow-up? Who has responsibilities for conducting those services? How should data be collected to assure that children are benefiting in a maximum way from those services?

So the implementation issues, we thought, were something that required additional attention and discussion. Now, this, of course, is a huge set of issues. And we're cognizant of the need not to get overly ambitious with what can be supported with the subcommittee.

But we also thought that this was worthy of additional attention and collaboration with the other sub-groups, because implementation refers, of course, to the testing itself as well as the diagnosis and longer-term follow-up. So the specific implementation aspects, we thought, were important. And, as you'll see with our revised charge, we've added this term to the charge to highlight our attention to this aspect

of newborn screening.

So here is our revised charge. I didn't put up the original charge for you. But I'm going to offer this language. And it's perhaps slightly broader than the original charge, but not shockingly so.

So it identifies barriers to post-screening implementation and short and long-term follow-up, including treatment relevant to newborn screening results; secondly, develops recommendations for overcoming identified barriers in order to improve implementation of short-term and long-term follow-up, including treatment relevant to newborn screening results; and, thirdly, offers guidance on responsibility for post-screening implementation, et cetera. Judicious use of acronyms here.

(Laughter.)

DR. BOTKIN: So we felt that this highlighted the implementation issues. Treatment is in the name of our subcommittee, so we thought that ought to be reflected within the charge itself and some discussion as well about what we mean by long-

term follow-up.

And I think our group, consistent with the publication that came out of the Secretary's Advisory Committee, long-term follow-up, beginning at the time of diagnosis and ending at probably 21 years of age. I think we decided, based on the legislative mandate of the committee itself.

Although, as I'll mention in a minute, transition to adult care is a critical issue in terms of long-term follow-up. But, given the purview of the larger Advisory Committee, our attention was going to be focused on the sending end of that transition and perhaps not so much on the receiving adult end of that transition.

Do we need new people on the subcommittee? Here were some suggestions. I don't think there was a great deal of time to talk about this in detail or any clear consensus on this.

But to the extent that we'll be focusing more on point of care issues and perhaps thinking about implementation and issues around education within the nursery environment, a neonatologists might

be a good addition, a nurse practitioner involved with kids who were receiving long-term follow-up care consideration, and that question of the adult clinician. Again, if we want to focus on this question of transition to adult care, perhaps getting input -- additional input from folks who were responsible for the adult care end of things might be helpful.

So what are the future issues? Implementation we've talked a little bit about already. We had some discussion about whether there should be greater opportunities to collaborate with the regional collaboratives.

Given the fact that the regional collaboratives may, in some circumstances, be more tightly linked with the individual programs and the trenches that those folks live in, might there be an opportunity for the regional collaboratives to help garner additional input on the work of the Advisory Committee from state health departments and might our subcommittee be a potential avenue for help garnering some of that feedback from the regional

collaboratives.

We didn't come to any consensus on this. But I think there was some general sense that it might be valuable to enhance that communication process with the collaboratives, and then, the collaboratives, of course, with the individual states within their regions.

Roles and responsibilities we've touched on already. Whose job is it to do these things? And we had a good discussion that changed our terminology from accountability to responsibility so that, perhaps, a little bit less legalistic. We wanted to have the opportunity to talk about whose responsibilities would be entailed with the long-term follow-up and treatment aspects.

Again, medical foods -- we want to highlight the importance our subcommittee places on this. And we wanted to make sure that, as the federal process moves forward for determining the minimal care elements, that medical foods was highlighted once again. And we understand that the committee has had communication with the federal government and had

feedback from the Secretary about this issue, but we wanted to highlight it just to make sure that, as this process moves forward, that it reflects the importance that our group gives to it.

Health I.T. issues -- that's been mentioned a number of times. I think I.T., clearly, a significant focus of discussion for our subcommittee as well as the other subcommittees and the larger Advisory Committee.

And then, some discussion at the very end about whether we might entertain a specific focus on some of the long-term follow-up issues and treatment issues with children with sickle cell disease. It's a condition for which the efficacy of the early interventions is unquestionable. But, at least to my understanding, fairly good data that a lot of these kids are falling through the cracks.

We know there's been a lot of attention to this, so I think we might need to specifically address, you know, what questions would be most relevant for our subcommittee to attend to in this particular domain. But I think some general sense

that this is such an important disease for which the long-term follow-up aspect could be improved to enhance the overall efficacy of the newborn screening program. So that was a tentative direction that we may want to further explore.

And I believe that's it. So I very much want to welcome additional comments from our working group, anybody who may want to emphasize another issue that I missed or recharacterize any of that conversation.

DR. HOWELL: Well, Jeff, thank you very much. And I think that I can say that the committee as a whole also values your committee and does think it's a committee of value.

(Laughter.)

DR. HOWELL: So rest assured in that.

(Laughter.)

DR. HOWELL: I think we should, in addition to thanking you, we should certainly thank Colleen, who has worked very hard on this committee. And she will continue to be, I'm sure, a very strong participant as you move forward.

DR. BOTKIN: I hope so.

DR. HOWELL: Any other questions or comments for -- oh, we have a couple.

Ned?

DR. CALONGE: So (inaudible). It's for things that aren't on the list for the next Chair to consider as potential subcommittee or work group work. Is this an appropriate time to bring those up?

DR. HOWELL: Sounds good to me.

DR. CALONGE: One of the things that we've talked about at now two subcommittee meetings and yet, I think we haven't necessarily captured it as work that we need to pursue, is the concept that I think we should look at diversifying the outcomes or the products of the recommendations of this Advisory Committee. So right now, the, kind of, final common pathway for considering conditions is that they end up on the uniform list.

And what that brings with it is a mandate that these conditions and the screening for them become provided on a state-wide basis with the usual implementing activity being state government. I will

tell you that there is many issues for which -- like, especially blood spot screening -- where that's exactly the right thing to do.

There may be other, though, screening activities where state government isn't the most effective, efficient, or appropriate source for implementing the recommendation. And I would point out that, you know, well over 99 percent of all medicine is not mandated. And yet, we still manage to have some consistency, quality improvement, and population-based rollout of many services.

So I think thinking about additional routes to bring screening forward on a population state level that aren't necessarily we recommend this be added to the uniform panel is something, I think, the committee actually really should think about. Other routes are professional guidelines, which are implemented to varying degrees by the specialties. Hospitals actually pay quite a bit of attention to JCOA, the Joint Commission on Accreditation. And that's another route.

Medical standard of care is how most

medicine is defined in a legal and torte approach in most states. So, as we looked at pulse ox screening for congenital heart disease, some states recognize that this isn't something they do or know how to do. And they may want other routes.

So I think thinking about a broader implementation strategy for our recommendations that actually match the systems that are out there so that the only final common pathway is that it's added to the uniform panel or it is not would be in the best interests of newborn screening across the country and is something I hope the next Chair will think about and think about either a work group or assigning that to a subcommittee.

DR. HOWELL: That's, obviously, very interesting and important. How would you -- if you were thinking of a charge that Joe might consider, and so forth, what would you charge this committee to do? How would the charge read?

DR. CALONGE: It really would be looking at the way other recommendations and guidelines and even standards are implemented in medicine across other

systems. So ACIP, just by example -- they don't mandate the use of any vaccine. They just approve it.

Now, approving it, then, has a number of different ramifications in terms of rollout. But we've actually done a pretty good job of getting uptake of vaccines through that mechanism. So I think looking at other routes of population-based implementation of recommendations would be the charge. And then, figuring out the criteria for when the Advisory Committee would, say, recommend adding this to the panel, versus, recommend rolling this out in population-based medicine through a different route, would be the charge of the committee.

The last thing I'd say is that, you know, we have these categories, one of which is needs pilot studies. And I would urge us to also look at the ability to go back to this concept of a provisional recommendation. And you say, well, what's the difference.

The issue is that pilot carries with it the connotation of research. And research carries with it the connotation of informed consent.

If there were a way to do population-based data gathering on something we really think shows promise or we think there's a high likelihood of effectiveness, benefit versus harms, if there was another way to provide a category where informed consent and research wasn't part of the concerns so that we could get higher uptake implementation within uniform screening with the mechanisms we already have, and then, the discipline to look at it later to make sure it worked, I think that would be another helpful category. So those are all charges I would give the sub-group.

DR. HOWELL: Well, that certainly is an interesting collection of stuff to go into the -- and, certainly, our incoming Chair has a lot of experience with vaccines. And so, that recommendation should work neatly.

Fred?

DR. CHEN: Our subcommittee also had a discussion about implementation, and especially in the context of these new technologies that move beyond heel spot screening.

So I think what you suggested about having at least the subcommittee Chairs talk, but especially around this issue of implementation, which we recognize really doesn't -- Jeff, what I thought I heard, at least part of what you were saying, was about implementation, sort of, post-screening implementation. I think you mentioned a couple of times.

And our subcommittee was talking really about, sort of, well, who's taking care of the screening implementation piece that goes outside of the laboratories, and which seems to be an area that we continue to move more and more into. I think that builds very much on what Ned was talking about, too, which was we do need to start thinking in a different way about many of these implementations, the strategies, and the different types of methodologies we could be using.

DR. CALONGE: Well, I would say that we wanted to promote exactly this sort of dialogue, and, again, particularly as we move into things like pulse oximetry and echocardiography. It wasn't clear to us

whether that was something that the Laboratory Group would find to be within their natural home or whether it didn't quite fit in with Long-Term Follow-Up. So it seemed to be in a gray area, where we wanted to make sure that that wasn't falling through the cracks.

DR. HOWELL: Gerry?

DR. VOCKLEY: One of the pieces that has been integral and essential to everything that we have done over the last few years has been the evidence-based review. And I think that the importance of that process really -- it isn't captured in any of the subcommittees. I don't know if it needs to be. But we, I think, can emphasize the changes that that process is undergoing as it relates to rare diseases.

One of the pieces that I'm increasingly frustrated with is when people look at some sort of evidence review -- I mean, and this is going on with PKU. It's going on with a number of things -- is just the point that the studies only have 50 patients in them. Well, 50 patients in a rare disease is a huge number. And I think the committee can do a lot of good by really promoting the process of evaluating

these disorders and then, you know, the various components that are part of the subcommittee's individual charges are what can reflect that and focus on it as they go forward.

And I know we're going to have some evidence -- some more from the Evidence Review Committee later. I would just like to be able to tie some of that back into the formal charges to the subcommittees and, in some way or other, highlight the process as well as the substance of their reports, because even the process of it may well be more important in the long run than any one of the individual reports.

And if we can get people thinking differently about how we formally evaluate these and, at the same time, increase our ability to do this in a scientific fashion, you know, we're going to be light years ahead of where we were even a few years ago. I think we already are light years ahead in terms of the evaluation process.

DR. HOWELL: Thank you very much, Gerry.

Is there further comment?

MALE SPEAKER: Can I raise a new issue?

DR. HOWELL: Of course.

MALE SPEAKER: I think one of the issues that has been integral to the whole discussion of newborn screening for generations have been the ethical, legal, and social issues. We don't have a subcommittee to help address those kinds of issues. But, at the same time, sensitive to the notion that can't keep proliferating subcommittees. And so, just want to raise that set of issues for consideration.

Should it be a separate subcommittee? Might it -- or, alternatively, might there be opportunity to have a relationship with the Bioethics and Legal Working Group of the Translational Network? You know, might that help serve to inform the committee about some of the issues.

Now, those don't tend to be linked to specific screening modalities or conditions, but could potentially assist in that capacity. So I just wanted to raise that set of issues to make sure that it's explicitly on the agenda of the Advisory Committee.

DR. HOWELL: Well, obviously, we've discussed that a lot, with the technology,

particularly with the whole genome sequencing, how big a deal that's going to be. I think that, as you look at the reorganization of the committee, that'll be an issue of whether or not that should be distinct or still embedded, as it has been, and so forth.

Further comments, and so forth?

Thank you very much, Jeff. You're not going to go very far, however.

DR. BOTKIN: No.

DR. HOWELL: So our next section is called the future of the committee. And, as you remember, this committee has reviewed issues related to the residual blood spots. There's been a lot of turmoil in this. And Jeff has recently gotten a grant to look further at this issue. And he's going to present some of the more recent information.

The committee, obviously, has prepared a white paper, which is online, about the use of storage and residual blood spots. And that's now a little behind the times, and so forth. So anyway, Jeff is going to discuss new steps in the newborn consent -- NDS consent conversation.

DR. BOTKIN: Thank you, Dr. Howell.

So we had a two-day meeting in Salt Lake this last week. And this was under the auspices of the Bioethics and Legal Working Group of the Newborn Screening Translational Network, which is funded by the NICHD that Mike had talked about in some detail yesterday.

Certainly, my thanks to Amy Hoffman and Mike for their support for pulling this meeting together and the ACMG, more broadly, for their organizational help.

A number of folks who are here today participated in that meeting with us. Sara was able to attend. Amy Hoffman, certainly, Don Bailey, Nancy Green, Ann Comeau, Beth Tarini, Natasha Bonhomme. And we had about 30 folks who participated in this meeting. And I'll tell you a little bit more specifically about how this topic was framed.

The meeting itself was prompted by a specific NIH project that has been providing the University of Utah with Cathy Swoboda, who's a geneticist and neurologist, as the P.I. on this

project. And it's to do a pilot newborn screening project for spinal muscular atrophy. My piece of that project with Cathy is to look at the ethical and regulatory issues. And so, we've got a couple of activities that we're engaged with in that respect.

We're going to do focus groups with new parents and young individuals about their attitudes, about the permission process for newborn screening pilot. And separately -- although, in a related fashion, the Bioethics and Legal Working Group of the Translational Network is also preparing a survey of state health department IRBs on their attitudes about how to oversee newborn screening pilot research.

So we really had an outstanding group of folks who participated in this meeting. The goal was to reach consensus on some of the key ethical and regulatory issues and the conduct of population-based screening research. The central question was, under certain circumstances, might newborn screening pilot studies qualify for a waiver of traditional informed permission from parents. And by traditional informed permission here, I mean a signed consent form.

The concern traditionally has been that parental permission involving a signed consent form can impair recruitment and the timely completion of population-based research. So here's the ethical conundrum here. We have longstanding and strong respect for parental decision making in clinical care and research. Parents are asked to be decision makers on behalf of their children. Research is voluntary and altruistic.

At the same time, population-based research is of critical importance. This group understands the need for additional data to make decisions about what screening modalities are in the best interest of children. And those population screening projects need to go forward in order to collect those data. So it's certainly in the best interest of children for population-based research to go forward.

But if the consent process itself impairs the feasibility of those population-based research projects, then you've got a conflict between our traditional respect for parental authority and the need to get this type of work done for the welfare of

children. So that's the conundrum.

So we came to a couple of general conclusions here. And I'll explain the rest of the process here in a minute. But let me just articulate a couple of the conclusions from this group, to the extent that we had some general consensus on some of the points.

Clearly, strong support for evidence-based newborn screening and research to support this goal. Everybody believes this is essential to the field.

More specifically, we wanted to define what a pilot study means. There was some debate and difference of opinion, at least, at the beginning. But I think for our purposes, we want to emphasize that we're talking about studies that mimic a newborn screening system. So you've got screening of children, identifiable samples, return of results to kids who screened positive, and then, follow-up.

Although, for our purposes, the research piece of this is the screening and the identification of the kids. Whether they're subsequently enrolled in a treatment protocol or a long-term follow-up protocol

would require separate consent for that phase of a study.

When supporting evidence is incomplete for the introduction of new tests on a state or uniform panel, pilot studies should be conducted under a research paradigm. I think this sounds relatively benign, but I think the notion here is use of state public health emergency authority, for example, is probably not the best way to implement newborn screening tests.

And if we have the data in place and the test is essential for the health and welfare of kids, that sort of authority, of course, makes sense. When you don't have the data, implementing tests in that fashion is less than ideal.

The group outlined circumstances -- oh, folks are probably familiar with the waiver criteria under the federal research regulations. In order to waive traditional informed consent, you need to meet four criteria. The research has to be judged to be no more than minimal risk. There has to be no abridgements of the rights and welfare of the

participants otherwise. The research has to be judge impracticable if traditional informed consent is used. And research participants have to be informed later about the research, when appropriate.

So we walked through each of these criteria in this particular context and drew the following general conclusions. We tried to outline circumstances in which we felt pilot studies might constitute minimal risk and when they might constitute greater than minimal risk.

Criteria here or issues here were the quality of the test itself, analytic validity, and the clinical validity of the test, was there an available treatment that appeared to be beneficial for children, what's the burden of the further diagnostic procedures. If the diagnostic procedures are particularly burdensome and there's a risk that there's a significant number of false positive children who would sustain those burdens of the diagnostic evaluation, then that might well not be considered a minimal risk screening protocol.

We discussed the concept of the rights and

welfare in this context. My personal opinion is that criterion has always been vague and hard to figure out. But, particularly in this particular context, what we discussed was that screening for certain sensitive conditions might make a pilot ineligible for a waiver. So this could be culturally-sensitive, for example.

If a community might feel that a particular screening modality was sensitive, for whatever reasons, then that might not quality in this particular context. Or if there are issues of particular discrimination or stigma that might be associated with screening, that, again, might be a consideration, under this category.

Impracticability -- factors that weighed on impracticability have to do with things like the size of the population that need to be screened. If we're talking about screening 500 people, that's quite a bit different than 400,000.

The SMA protocol that Cathy's designing would engage both Utah and Colorado for a period of three years. So we're talking about 400,000 children.

So the prospects of conducting a formal consent process with 400,000 children over all the birth facilities in two states is substantial.

So it's number of -- so it's size of the population and the number of birth facilities and the number of individuals that might be responsible for obtaining informed consent. And what flows from that, in certain circumstances, is that the birth facilities may be engaged in research and, therefore, have to go through their own IRB approval. And so, California had this experience.

A part of our project was to hear how various pilot projects historically have addressed this issue. And it's, frankly, been all over the map. Some have required written consent process. Others have allowed an opt-out approach. Others have used state authority to mandate initial screening.

A significant conversation focused on the return of results. And not so much -- not at all, actually, the positive results, since that's the point of screening, but the negative results. Is it ethically-necessary, appropriate to return negative

results in this sort of context? What are the risks associated with returning negative results, say, through primary care providers?

What are the benefits to families? And what are the rights involved? Do parents have a right to that information? And what are the implications for the project in general?

It's a huge amount of effort to get those results out in an interpretable fashion. And that may itself impair the ability of a project to be successful. So no real consensus on that particular issue, other than to highlight the importance of it.

Perhaps most important, a really high priority placed on parental education and engagement, regardless of a decision about the permission model. So irrespective of whether you get a signature on a paper or whether it's an opt-out model or exactly how that's designed, significant emphasis on the importance of making sure parents are aware that there's a research protocol going on, to the best of a program ability. And, at a minimum, certainly, they'll have the ability to opt out, which is always

one's prerogative in the research context.

General consensus, I think, that a waiver of traditional informed consent may be appropriate, in some circumstances. I wouldn't say that everybody agreed with that. But I think that the majority, and perhaps significant majority, felt that, in some circumstances, a waiver of traditional informed permission may be appropriate.

And then, an opt-out approach may be appropriate, in some circumstances. Or a waiver of written documentation of consent may be appropriate, in certain circumstances.

Again, under the assumption that there's a meaningful parental education and readily-available mechanisms to opt out. So the opt-out has to be readily available. And I think opt-out requires additional ethics attention, in general.

But I think, as we know, with many programs, you can have an opt-out, but awareness of that is virtually absent, because the ability is buried within a brochure, and they have to go through a phone tree during restricted hours in order to effectuate your

ability to opt out. So we want this to be a readily-available option, if that is felt to be otherwise appropriate.

So those are general conclusions. Our plan is to declare a manuscript for publication with all of the participants in the meeting as authors, with the potential exception of Sara, given her complicated association with federal government.

(Laughter.)

DR. BOTKIN: And so, we hope to have this prepared over the span of the next couple of months or so. And we think this is such an important issue for the conduct of research in this domain that we hope that this paper will have an impact on the field, and particularly IRBs that have the responsibility of overseeing these types of proposals. Thank you.

DR. HOWELL: Well, thank you very much, Jeff.

Fred has comments. Then, Chris.

Fred?

DR. CHEN: Oh, thanks.

Thanks very much for that report. I wonder

about implementation beyond, sort of, publishing the paper and, sort of, what the right avenue might be. And that, certainly, comes in context of another question, which is, what about -- I believe we're still in the comment period for the proposed rulemaking, or the announcement of proposed rulemaking, around the changes to the common rule.

We looked at -- I assume you guys are well-aware that -- are there some changes in that? I know there were specific issues around genetic testing and genetic, sort of, technologies that are there. But is there a possible implementation plan there and another pathway forward for the work of your group in conjunction with the proposed rulemaking?

DR. BOTKIN: Actually, that's a great question, because the announced notice of proposed rulemaking would have significant impact in this domain. And that would prospectively acquired specimens for clinical purposes, if you're going to use them for research purposes, would require a written informed consent process. So that would impact this domain.

I think lots of us are planning on pushing back vigorously against that. It's unlikely to be implemented in the immediate future. Although some folks are saying that the end of the current administration is a goal for getting those changes passed. So they may be accelerated more than the others in the past. But we're acutely aware of those changes and would have significant implications in this domain.

Now, having said that, what they anticipate as an informed consent process in that context is a very simple form with a signature at the clinical interface. So, you know, at least from my personal perspective, that really fulfills traditional values that we want to promote with informed consent. But it is a signature on a piece of paper.

DR. HOWELL: Chris?

DR. KUS: I have some concern in the sense that, if I understand it, the idea is that this is really piloting the screening test and short-term follow-up and not including long-term follow-up. And, I mean, I guess my concern is that kind of perpetuates

the idea -- I believe, newborn screening includes long-term follow-up. And not to have some sense of that in the pilot is concerning.

DR. BOTKIN: Well, that's a great point. And I think each project, of course, will have to be designed around its own specific aims in that regard.

With respect to the SMA project, I think we are thinking about this -- or want to think about it in somewhat separate terms in that one can't presume to get -- for example, if we should determine that, for the SMA project, an opt-out is appropriate at the time of screening, that opt-out would not legitimately carry forward after the identification of affected children and further study of those kids.

And so, at that point, you would need to obtain informed consent for whatever else was going to be happening on a research basis. So for that reason, we're thinking about, in this context, at least, the pilot study being just at the time of diagnosis when you can actually engage those families.

DR. HOWELL: Jeff, could you comment a little bit more specifically about the SMA project,

exactly where that is and its movement forward?

DR. BOTKIN: Well, we're in active discussions with both the state of Utah and Colorado about the feasibility of the protocols. So the study has been funded. But there are a nest of complicated issues in terms of sample handling, this permission issue being a major one up front, and finalizing the testing platform for that.

The laboratorians -- Steve Dobowalski has been active in the development of this platform with -- it's a DNA-based platform. And the current information is that this is a test that's highly sensitive and specific and that the test results give you pretty clear information about the type of SMA the kids will have and the clinical implications of the testing.

So, at least at this point, the claim is that this is a remarkably good test and cheap. So the testing aspect doesn't look like it's going to be a major barrier. At this point, the discussions about the protocol for the screening itself, parental permission issues, transfer of sample questions, et

cetera. But it does seem clear that we -- that Cathy would need basically the whole birth cohort of both states over a three-year period in order to have adequate numbers for subsequent follow-up.

DR. HOWELL: This, of course, is a very interesting problem in that there's no specific treatment available, but a number of exciting things on the horizon. And, of course, it's one of the leading causes of death of infants below one year of age. So it's an important area to pursue.

DR. BOTKIN: Yeah. And I think Cathy would claim two things. One is that if one aggressively implements things like nutrition and balantory support, airway clearance prior to the time of initial weakness, that you can substantially improve the clinical outcome, just from those more general measures.

And she's also hopeful that there's some pharmacologic agents on the scene that may be gene-promoters that may be potentially quite effective in this context. The animal models, apparently, are looking quite promising.

DR. HOWELL: She's correct, I think, clearly, on both of those counts, et cetera.

Mike has a comment.

DR. WATSON: At this point in time, there were representatives of both the Institution of State IRBs (off-mike) at the meeting. They were actually looking for guidance in how to (off-mike) aspects of (off-mike), because they're very non-specific (off-mike) very complex (off-mike). You know, they'd welcome (off-mike) about helping them think about what specific information (off-mike).

DR. BOTKIN: Yeah, I appreciate that. I think that that's quite true. And the federal regulations governing research simply weren't designed with this, sort of, large population-based research in mind. And so, I think folks particularly struggle in this context. And I think there's certain barriers to overcome with health departments that don't traditionally see research as a primary goal.

It may be in some circumstances much easier to simply say, "Informed consent is the way to go." And if that doesn't make your project feasible, then

it's unfortunate. So we want to try to support decision making in that regard.

DR. HOWELL: This is a particularly important prototypic condition that the committee is going to see a lot more in the future, because you're going to have other conditions that you can have an accurate diagnosis and have some benefit that is more medical, and so forth, but still not what we would call a specific treatment. But they're on the horizon, and so forth. So I think that you're going to see those.

DR. BOTKIN: Yeah.

DR. HOWELL: This will be an excellent one to get all the things right as you move along, and so forth.

DR. BOTKIN: And I think related to that, Cathy emphasizes that these kids deteriorate, and they can't be rescued once those nerves -- once that nerve function is gone.

DR. HOWELL: So there's abundant evidence that in SMA Type I, you lose the motor neurons rapidly in the first weeks of life. And she's published that.

So it's a condition that, if you're going to treat it, you have to be on the job very, very early.

We have a cadre of distinguished colleagues here.

Dr. Nancy Green?

DR. GREEN: Good. Thank you.

And thank you, Jeff, for including me in that meeting and providing your leadership.

I wanted to make another point. I think that there was consensus and considerable discussion about in that meeting. And that had to do with the fact that the previous pilots had really been generated from state health departments. You know, we spent a lot of time talking about the California experience. Lisa was involved with that, and Ann's leadership in Massachusetts.

But I think that the group noted that this was somewhat different, because it really was led by an academic group with, you know, federal grants, et cetera. And so, you know, there was considerable discussion about what the interaction was between the academic resources and impetus and leadership and that

which the public health departments, not only brought to the table, but, in fact, you know, was a critical component.

So I think there were, sort of, two items of consensus and, you know, for you to consider for your report that I heard from the meeting. And one was that, regardless of who leads these projects, whether they're, you know, generated from the public health department or from an academic source, that there really needs to be a partnership, because the project itself requires the infrastructure and activities and resources of the public health department, so, really, that there needs to be a partnership in these projects. That's one point.

And then, the other, sort of, that flows from that is that whatever the project is, whatever the pilot is, that it cannot -- that it must support the mission of the public health activities for newborn screening and cannot interfere with the mission for, you know, even, sort of, perception of the public of the mission of public health newborn screening.

DR. HOWELL: Thank you very much.

We have Dr. Ann Comeau.

DR. COMEAU: Thank you.

I wanted to congratulate Jeff on this particular meeting in that the design of the meeting I found particularly beautiful in that it really focused on some of the bioethical issues in a very general terminology. How do we handle projects? And, as the group discussion was maturing, then entered into -- the particular discussion of SMA, which really tested everybody's conclusions that they were drawing as we were going through the exercise.

And I think that there was a lot of back and forth that we're going to have to go back and revisit. Excuse me. I wanted to reemphasize what Nancy just brought up, the idea of the partnership.

And I think the one piece of consensus that we did have was that if it walks like a duck and talks like a duck, if it looks like newborn screening and it's a pilot program, then there is an extra level of consideration that we have to go forward to make sure that the newborn screening program is not undermined

by the research and that the research can benefit the newborn screening program. To that extent, I think we talked a lot about opt-in more so than opt out with various mechanisms.

We talked -- when we got to that level of detail, I think we were, kind of, all over the map on opt-in, opt-out and is it for all projects, or is it for the SMA project. So I think it was a great meeting. Thanks.

DR. HOWELL: Thank you, Ann.

Now we'll hear from one our largest and most active state. And that's Susan Tanksley.

DR. TANKSLEY: Hi. Susan Tanksley. I'm from the Texas Department of State Health Services. And I wanted to share with you the experience of our limited SCID pilot that we've had.

So we began enrolling, or trying to enroll, hospitals and clinics and things into our study months and months and months ago. In October of last year, we finally received our first specimens. Since October, we've received a total of 1,800 consents. So among the about 200,000 or more kids that have been

born in that time frame, we've only received consent to screen 1,800 of those.

It's been a very, very difficult process. And most of the hospitals that consent have been, "Who will do the consent"? So it becomes a very expensive process for the health care facilities.

I don't doubt that the informed consent is important. However, it will limit studies considerably, if Texas is any indication.

DR. HOWELL: Thank you, Susan.

Anybody want to comment on Susan's words?

Jeff?

DR. BOTKIN: I'd like to follow-up on that.

DR. HOWELL: Okay.

DR. BOTKIN: Repeating basically what she said, from another large state. When we tried a consent process, people got missed. People didn't get offered the consent when they wanted it. And that was the big decision -- reason why we made the decision in SCID. We would not have a consent. And we went to IRB. We got a waiver of review, actually.

So, you know, what do you want to say is

worse, a parent's rights being violated, or a kid being damaged? Because we're at the mercy of the hospitals.

DR. HOWELL: The experience in Texas and California are sobering. And they're sobering for two reasons. One, you're personal experience. And the other thing, we're always interested in studies where the people live. And when you talk about Texas and California, it's a substantial portion of the entire country.

DR. BOTKIN: Yeah.

DR. HOWELL: So those are very interesting commentary. Did you all discuss these experiences at your meeting?

DR. BOTKIN: We did not discuss Texas. But Lisa (inaudible) was with us on the phone and presented the California data in some detail. And I will say Ann's (inaudible) there to speak for their experience with the tandem mass experience in Massachusetts that was an opt-in that waived documentation, if I'm correct. But you also had the opportunity to have hospitals all defer to the health

department so that you didn't have to go through individual institutional.

FEMALE SPEAKER: Correct.

DR. BOTKIN: I'm, sort of, (inaudible) speaking for you. But --

FEMALE SPEAKER: It's a success story, to my mind, is the model in Massachusetts of how we engaged parents, gave them education, were able to go through with a pilot program, both for tandem mass spec and for Cystic Fibrosis, and having established that particular mechanism, were able to go forward with the SCID pilot.

Parents and providers feel engaged. Again, it's a waiver of traditional informed consent. But it is an opt-in. And it is -- parents have to be asked. And the only documentation is when parents do not want to participate. And parents get a copy of what it is that they verbally said to the clinical provider who is asking for consent.

Five-minute process, accepted by the hospitals. It works. And we don't have -- we have very few complaints of, "I wasn't asked," or whatever.

And I think a lot of it was because, from the very beginning, our health department IRB and our medical schools' IRB went forward with education of all of the hospitals IRB.

We engaged OHRP and then, brought the hospitals in and said, "We have OHRP agreement for this particular kind of consent. You don't need to go through all of your individual institutional IRBs. This is how it's going to be. It's a state-wide program. We're going forward." And, you know, it's been in place now since 1999.

DR. HOWELL: Don has a comment, and then, Ned.

DR. BAILEY: So I just wanted to say I was able to attend the meeting and really appreciate the invitation to do that. That was a great discussion.

You know, I think this is an incredibly important series of topics that this committee will need to address in some more systematic way. And I, certainly, agree with Jeff's comments earlier that we need to think about whether we want a separate subcommittee, do we want to link with the MYCAS, but

some official designation of those responsibilities for this committee, I think's, very important.

It's, clearly, something where we have this big intersection of ethics and data and the need to know information. And so, the data we've already heard today we've got this big range from, what, you know, 2 or 3 percent of the people consenting in Texas to our Fragile X project.

We're getting about 67 percent. In Massachusetts, we're getting over 90 percent. So there's an incredible range of what happens when you ask for consent and in the ways that you ask for consent.

And so -- and these could be a synthesis of data around, you know, what are we learning when we do do consent processes. And then, this committee, I think, has a responsibility to make some recommendations going forward.

DR. HOWELL: And, Ned?

DR. CALONGE: So I just want the committee -- and after the comments -- just continue to recognize that states are actually idiosyncratic in their

approach to these issues. So coming from, you know, the state, you know, New Hampshire's motto is, "Live Free or Die." And Colorado's is, "Live Free and Die."

(Laughter.)

DR. CALONGE: The fact that only a couple of people said I wasn't asked, to me, just strikes fear to my heart, because they know who their legislator is. And it ends in a bill that harms public health. And I just spent eight years defending a lot of those activities. So I would just tell you that the state solution won't work for every state. And even, states that look like they should be the same, like Colorado and Wyoming, are vastly different. So Wyoming allows no philosophical exemptions for vaccines. And Colorado prides itself on having philosophical exemptions for vaccines. So just, as we go forward, recognize that gathering data, using it carefully, and understanding that the public health term, "whacko," is a real, you know, legitimate term.

(Laughter.)

DR. CALONGE: Just recognize that those set up interesting challenges.

DR. HOWELL: Alan?

DR. FLEISCHMAN: Jeff, this sounds like an extraordinarily important academic exercise that you've done and that it, certainly, be published. And I would argue that this committee could convene OHRP, along with the organizations of health commissioners and territorial leaders like NACHO, AASTO, NACHO, and those kinds of organizations, in a discussion of relevant issues so that all health leaders across the country would understand the range of variation.

This would help, as individual state leaders come to their legislators to hear what Massachusetts and Texas and Colorado are experiencing. So I would think that we could do that.

I would doubt that merely having this committee make recommendations about good practice is actually going to make change in this regard, although, that might be a good thing. But I think we would need to do the educational activity, cross-discipline, cross-policy, and academic world.

DR. HOWELL: Becky?

DR. BUCKLEY: I think that the influence of

this committee is under-estimated, because I think that one thing I learned from the past four years is the importance of (inaudible). Because there were so many states several years ago that weren't screening but for just this limited number of things.

Now, because of the recommendations of this committee, even though it's just a recommendation, they don't have to do what this committee says. But they followed suit.

And I think if this committee came forward with a stance on performing these preliminary studies, which brings up the question of whether we should even remove the word, "pilot," from the study and call it something else like, "limited study," or, "initial study," or something like that that would take the research connotation out of it to get some of these things implemented.

After hearing what happened in Texas, I think that that's really unacceptable. I think that we have to be able to move forward. And if this committee were to come forward with a stance that you're recommending, then I think that it would have a

lot of influence.

DR. HOWELL: I think, Jeff, the comments that you've heard underline the importance of what you're doing. I think it's going to be critical.

Let me also remind you that this committee has prepared a white paper that a summary of which is published, of course. But the entire document, as you recall, has been referred by the Secretary to the Interagency Coordinating Committee, which is the group of representatives from all the federal agencies. And they are charged with studying that paper and getting back.

So that may -- there might also be some useful information coming back from that Interagency Coordinating Committee for you to consider. But I think that it's critical that we figure out how to do this. But it's also key that the states -- the really big states that are big geographically and big population-wise -- seem to have had the biggest problems. And so, we'll need to look at that.

It's one thing to have a small state with a small population. And then, you have a huge state

with a very diverse population. It's going to be very different.

I think Ned hit the nail on the head that if ever you've seen one state, you've seen one state. But let's remember, as your committee goes forward, to focus on the states where the people are. And so, because that's critical.

Are there further -- there are a lot -- we could talk about this for a long time. Is there anything else critical?

Mike, do you have a critical comment?

DR. WATSON: (Off-mike) Medicaid program (off-mike).

(Laughter.)

DR. WATSON: (Off-mike.)

DR. HOWELL: Chris is going to have the final word. Otherwise, we might not get coffee.

DR. KUS: Well, I guess the question comes up -- and we had the discussion about whether there should be another subcommittee or that kind of thing. And I think this falls into that idea. So I think we should make sure we talk about that.

DR. HOWELL: I think that, clearly, will be on the agenda as you go forward. But I think that convening -- Alan's comment also is very prudent about convening the decision makers. And that might work with Mike's thing, too.

Thank you very much, Jeff. You've got a lot of work to do. And we're delighted that you're so energetic and ready to go.

The Evidence Review Group, as you know -- we've heard about them already -- has really established a wonderful tradition for evidence review in rare disease. This group, as you know, has been centered under Jim Perrin's leadership at Mass General with Jim and his group. And this year, however, the group is moving to Duke, and my old home town, of course.

And Dr. Alex Kemper will be taking over this. And so, Alex is going to tell us about moving the evidence process forward. And some of us will consider moving from Mass General to Duke going forward, because some may --

DR. KEMPER: Yeah, I have to say, go Blue

Devils.

Sorry about that, Dr. Bailey.

So hopefully -- there it goes. Great.

Good morning, everyone. So yesterday, we reviewed the past history of the External Evidence Review Group and the products developed. What I'd like to do this morning is talk about our plans for the future and to get your input and advice about how to continue to make this process even better.

So I'm going to be talking generally about what our plans are. And then, Dr. Lisa Prosser, who's at the University of Michigan, will be talking about using modeling to further extend what we've done. So I'm going to touch on that just real briefly.

Again, I'd like to acknowledge the great group of people that I have the pleasure of working with within the work group, but also acknowledge the special help that we've gotten from Dr. Copeland, from Lisa Vasquez, and Alaina Harris, from Dr. Calonge, who always comes up with those really good ideas to make us think deeper about what we're doing, and Dr. Scott Grosse at the CDC, who's been very informative around

some of the economic issues that we've struggled with.

So I think it's helpful to take a step back and think about what the core principles are that we have as we do these reviews. So we want them to be comprehensive. I know Dr. Vockley, a little bit ago, was concerned, for example, about a review that was going on, not done by us, around PKU where they were restricting to studies that had 50 subjects or more.

I have not looked at that, so I can't comment on that directly. But I can tell you that we really want to be as comprehensive as we can be and try to leave no stone unturned. As we prepare these reports, we do our best to be unbiased. We want to be transparent in the way that the information is presented. And we want to be fair in how the material's presented so that we can inform your decision making.

So, as Dr. Perrin summarized yesterday, we've had a number of challenges in developing these reports. Most of these challenges are not going to be surprising to you. But I think that it's helpful to just go back and enumerate what those are.

So we've really struggled with inconsistent case definitions across reports. So when you look at a particular study of condition, it's hard to know sometimes whether or not they're really talking about the same thing or if they do have a good case definition in the report, sometimes it's hard to combine the information.

There is variable duration of follow-up across the reports. So some reports follow individuals for very short periods of time, and others, for long periods of time. Again, that's not surprising.

There is variations in the outcomes that are reported. And, related to that, proxy outcome measures are common. So instead of information about the health outcomes that we really are interested in at the end of the day, it can be changes in enzyme level and that sort of thing. And so, you know, it's sometimes a struggle to go from that to the real health outcomes in terms of improvements of quality of life.

There's significant knowledge that's in case

reports and case series, and, especially in this rare disease area, we don't want to exclude those. But the traditional evidence process isn't really built for these single case reports. And so, that's one area where I think we've been fairly innovative. And we can talk later, if you'd like, about our plans going into the future about this.

Individual cases can appear in multiple reports, so that as you look at case -- individual case reports and then, merge into a case series or even in the long-term -- the longer-term studies. Sometimes it's unclear if these are really the same people or unique individuals.

And then, finally, something that we struggle with is the harms of screening and the harms of treatment seem underreported, just oftentimes not there in the literature. So in terms of improving the process, there are a number of venues that we've taken.

One is that we had a one-day meeting back in April with experts in evidence evaluation, including individuals who worked with the U.S. Preventive

Services Task Force and HIQ, and other large systematic review efforts. And that was convened in April of 2011.

The Institute of Medicine released standards for the conduct of high-quality systematic evidence reviews. It's actually a fairly long and comprehensive and well-directed document. If anybody's really interested, the Web site is listed.

And then, we've looked at the HRQ Methods Guide for effectiveness and comparative effectiveness reviews, which is revised on a fairly regular basis. And I've listed the URL for the most recent revision, which was August 2011.

So in terms of incorporating new processes and making the system better, there are a couple of domains that I want to talk about. The first is refining the development of the work plan, including issues related to case definition, the analytic framework, and the key question development process. Next is related to improving the process of data abstraction. And that ties, again, to completeness and transparency.

And one of the issues, I think, that we need to plan into the process is allowing for future updates as new evidence becomes available. It's very clear in all these conditions that there's very rapid advances. And so, I think that, you know, we need to think about the evidence reviews like a loaf of bread. There needs to be a fresh buy or a sell by date.

(Laughter.)

DR. KEMPER: And, unlike bread that I normally buy, there needs to be an easy way to update the process. I can't carry the analogy on any further on the spot. If I'd prepared better.

I'll talk some about data synthesis and presentation, including further standardization of the report. Dr. Prosser is going to talk about adding quantitative synthesis to the process through modeling.

And, you know, Dr. Bailey made some very interesting comments yesterday about the presentation and guidance that we can give. And I'm going to add some comments later. And maybe Dr. Bailey can expand on it to help us with our thinking.

And then, last things is a separate issue, but I think we ought to discuss here, which is assisting the committee with the collection of missing data, things that come up a lot, like workforce or general infrastructure issues. So in terms of refining the process of the work plan, thus far, all projects that we've done, all the reports that we've developed for you all have used a similar analytic framework. I put the one up there for congenital heart disease. But they're all fairly similar.

And we used the analytic framework to develop the key questions that we're going to use in the process of the report. And then, we developed case definitions from the nomination form.

Now, more recently, we've been working with experts to really tighten up the case definition. But I think that there's some things that we could do better in the future.

First of all, I think that we ought to tailor the analytic framework right up front to make it more clear what we're doing. So, for example, the time horizon -- and when I talk about the time

horizon, I'm talking about how long do we want to follow people out for the benefits of screening.

Are we going to look at what happens in the first few years of life? Or is this a -- you know, are we trying to really look at things that happen much later in life? I think this time horizon issue has really become important in the conversations that we've had around screening for hyperbilirubinemia or kernicterus.

Another thing that we have to think about up front is the comparator. So, as we do these reports, are we comparing to newborn screening, to what's usually happening in clinical care?

So, for example, with the bilirubin report, you know, there are a fair amount. I don't know the numbers. But there are a fair number of nurseries where children are already screening, getting screened for bilirubin at the time of discharge versus no screening at all. And I think that how we make those decisions impacts how the report looks. And then, I think that we need to make sure that we are very specific up front about the kind of outcomes that

we're looking at.

Now, I talked a moment ago about the case definition development and how important it is. And we've been using an outside expert panel to help us refine it. I think that was crucially important around the critical congenital heart disease issue, just because it was such a wide range of conditions. But I think, in general, we need to rely on experts.

And then, we need to make sure that the analytic framework is specifically addressed to these issues, including spelling out the key questions in gory detail, having a preliminary, but well-defined search strategy, which we will continue to develop in partnership with our medical librarians and looking at a wide array of databases, including MEDLINE, EMBASE, COCHRAN.

One of the places that I've actually begun now to find some information, interesting information, for other domains has been in clinicaltrials.gov, which is a registry of trials. And then, finally, proceeding to specific meetings or other potential places as the particular topic come up. We'll have to

refine that better.

We need to be clear about the expected rules for study design inclusion. And I have written up here, which will probably be everything. Again, these are rare conditions, and we can't be too restrictive on study design. And then, what we've done before and will continue to do is a preliminary list of experts that were interested.

Now, one of the things that I would like input from you all, when we're done, is issues about the transition from the work plan to beginning the evidence. I think that, if we develop these more formal and well-described work plans, as we do with the other ARC reports that we develop for the EPC, making sure that we get peer review from those experts, I have a technical panel here. But sometimes, these people are also referred to as key informants, people that are knowledgeable about the area.

I've written up here a public comment period. So it's common in the evidence-based reports that we develop for ARC. And it's now actually in the

Institute of Medicine guidelines around systematic reviews -- is that there should be a period of -- that these work plans should be open for public comment.

Now, of course, just because, you know, somebody, you know, says something during the public comment period, we don't have to change the work group work. But I do think that you can gain some interesting information and just be -- you know, we need to keep -- if we went this way, we would need to, you know, be careful to keep track of the comments and our responses to them.

And then, the other thing that I've spoken to some people in here about is the role of liaisons from the Advisory Committee to the External Evidence Review Work Group, just to make sure that the product that we plan to develop meets with what the Advisory Committee would like to get at the end of the day. You know, the challenge here, of course -- and, you know, some people have raised this as an issue -- is that we need to make sure that the Evidence Review Group, you know, remains external. We don't want to be overly influenced by any of these individuals.

But I do think, personally, that we could benefit from having that liaison between what we're -- between us and the full Advisory Committee. I think that that also might have positive downstream effects, because these reports that we develop are long and often complicated, just by nature of the beast. And I think that, by having that kind of interaction, I think that the reports themselves might be very well -- or at least I should say better understood at the time that they are presented to the Advisory Committee.

So moving on to the next topic, is related to improving data extraction. So the development of the evidence tables can be challenging, because they study heterogeneity, and, especially as we include more and more case studies and, you know, these case reports, that kind of thing.

And the other thing is traditionally, this data extraction requires multiple rounds of data extraction, looking at articles over and over and over again as you better understand things, especially in these complicated areas. And that can introduce

error.

And then, the other thing, as I said before, it's important to maintain the tables in a way that allows for easy updating. And the traditional way that we've been doing it so far, in either Excel or Word, leads to a process where it's difficult to maintain the tables and it's difficult to come back at some point in the future to reevaluate what was done in the process of updating things.

So one of the things that we've moved to, in the evidence reports that we develop for ARC, is using a particular software program called Distiller. And if anybody's interested, they can go to the Web site, systematic-review.net. And they have a demo on there as well. It's really nice, because it's Web-based.

It tracks all the reports, all the articles that we find and also facilitates reviews into forms that you can develop. So we can develop, you know, the items that we want to extract from these reports and have it automatically populate evidence tables that you can also slice and dice in a million different ways, especially if you want to do things

like meta-analysis.

You know, we should only be so lucky to have enough data to do meta-analysis. But in case that comes up.

The other thing that's nice is it develops a wide range of reports about things like the reliability between different reviewers. It keeps track of reasons for exclusion, helps with quality scoring, and, again, the evidence tables, as I talked about.

And it improves the efficiency and, I do believe, the accuracy of the process. So this is something that we're going to be moving to.

In terms of the data synthesis and the presentation, I think that, as we develop more well-explicated key questions and we use this software for developing the evidence tables, we're just going to be able to provide more detail. And it's also going to allow us to expand the grading and evaluation of individual studies and the body of evidence as a whole for each of the key questions.

And so, as before, issues that we're

interested in is the risk of bias in any particular study, the consistency, both within the study, if it involves more than one subject, but also, very importantly, the consistency across studies, issues of precision -- so how tight are our point estimates. Again, oftentimes, our point estimates are broad, but I think that it's important for us to be able to look at this issue of precision.

The directness -- and that gets to the issue of how well does any particular study, or the body of evidence as a whole, address each individual key question. And then, the issues of reporting bias -- remember, before, I said that oftentimes, information about harms and that kind of thing are not fair. By developing these more rigorous evidence tables, we'll be able to manipulate them in a way, I think, to better get a sense of reporting bias across a number of different domains.

Dr. Prosser, in just a few minutes, is going to be talking about decision modeling. And just to, sort of, whet your appetite for what Dr. Prosser is going to say, this decision modeling is a way to

provide a quantitative assessment of the findings.

They can be linked directly to the analytic framework. It's a nice way to complement the narrative summary and evidence tables. And it can address areas of uncertainty to help inform the decision making process.

And then, as Dr. Bailey, I think, talked about before, it can also help to identify important areas for new research. So if you found that there's one particular thing that the decision really weighed on, you can target investments in future studies to really, you know, improve the precision around whatever that particular question is.

You know, I actually read this very interesting line about modeling last night -- is that, you know, these models are really simplifications of what's out there. I don't want you to think that every nuance is going to be in here. But the idea of this modeling is it really captures the key components.

And the line that I read that I thought was, kind of, clever is, "It's the lie that lets you see

the truth." So I think you'll see that more as Dr. Prosser talks.

So, as with the work plan, I think that, as we develop the initial report, there is, again, this opportunity for further peer review. Again, that fits with the recommendations from the Institute of Medicine around how these things are conducted, which could include a public comment period and then, again, review by the liaisons from the Advisory Committee.

And I'm going to emphasize, again, this need to protect the evidence review from external pressure. Again, we want to be transparent and fair and all those good things that I talked about before.

You know, I'm going to go back and just talk about -- you know, I think there is room for discussion, too, about the types of reports. So, you know, so far, we've generated the big, full systematic reviews that have helped to inform the decision making here. But there is also opportunity to develop other products like, you know, what Dr. Bailey was eluding to, and also a shorter summary that could be more accessible to the general public as well.

And that's something that we started doing with other reports that we've generated from the EPCs for our ARC-funded work. And, again, that would be, you know, a decision for you all to make.

Now, finally, the last thing I'd like to talk about is this issue of missing data. So there are always gaps of significant interest to the Advisory Committee. These things are, you know, difficult to find in the published literature. And they're just not reliably available in the greater literature: things like workforce and infrastructure and economic data.

Now, most of us also consider ourselves to be health services researchers in addition to evidence reviewologists. There's probably a better term for that. I'll defer to Dr. Calonge, who probably knows.

But I think that, as part of these reports, we can develop strategies to collect this information. Of, if that's something that, you know, depending upon what the scope of work is, that's something that you'd want us to be more involved in, you know, we'd be happy to talk about that as well. And, again, you

know, those next steps really depend upon the particular condition and what's needed and that kind of thing.

So our next steps are to work with members of the Advisory Committee to formalize the processes that I just talked about. I think I threw out a lot of things for the Advisory Committee to grapple over.

And, again, I don't expect, in the next few minutes, for that all to be resolved. But I do think that we need to come to, you know, some conclusions around those issues.

I should mention that the review that's being led by Dr. Perrin at MGA around hyperbilirubinemia is coming to a conclusion. But it's going to include new decision modeling. It's being led by Dr. Prosser. And I, certainly, learned a tremendous amount from watching her walk through these very complicated issues.

And, of course, I want to remind everyone that, of course, we look forward to more nominated conditions. So we're here for you. And I think -- yep, that's it. I'd like to --

DR. HOWELL: Thank you very much, Alex.

Just a brief comment from Alan?

DR. FLEISCHMAN: Alex, would you put up the slide on the three issues in data that you're recommending? That one.

DR. KEMPER: That one? Okay.

DR. FLEISCHMAN: Yeah. I would counsel the committee that, while Alex wants to move the work for the committee to be closer to the kinds of things she's doing for the ARC projects, I would counsel precisely the opposite direction.

This is a federal Advisory Committee that you and Jim have done spectacular work in being external work group for. I think you should not have public comment. I think you should not have liaisons of members of the Advisory Committee to relate to, because I think that that precisely changes the role of the federal Advisory Committee's relationship to this external work group.

And I would be happy to discuss that at some length with the committee and with you. And it doesn't decrease my admiration for the superb work

that you've done in the past and will do in the future. I think the process should not reflect your advice to an agency as compared to an advice to this federal Advisory Committee.

DR. DOUGHERTY: Just to clarify that the U.S. Preventive Services Task Force is not a federal agency. But it's an independent task force, much like this committee, that is staffed by the agency. So there's not that much difference. And Ned may want to make more --

DR. HOWELL: Well, this committee, of course, is an established federal Advisory Committee.

DR. DOUGHERTY: So is the U.S. Preventive Services Task Force.

DR. HOWELL: Well, okay.

DR. DOUGHERTY: So -- well, it doesn't -- it's a little different.

DR. CALONGE: Some of us believe it's different in large ways. The designation of a FAC fact carries with it a lot of benefits and a lot of constraints. And I think that not being a FAC is an advantage in a lot of ways to the task force and a

disadvantage in others.

And there was a move, of course, in the ACA to make it a FAC, that because of where that was introduced didn't end up in the final bill. So it's a very interesting issue that would bore most people in the room.

But I did want to talk about Alan's comments. So I think the issue about the Advisory Committee is one that I didn't quite think about. I do have concerns that the total separation of the committee membership from the evidence review leads to some disconnects when the evidence review is presented and the committee works through the process of translating the synthesized evidence into a recommendation. And so, I understand your concerns.

And I think continuing to look for a way to make sure that committee membership is involved enough so that we don't have that disconnect is an important issue. So I see both sides.

And, you know, sharing the -- or being on the evidence review calls -- which, thank you for inviting me, and I felt committed to that -- I think

helped anchor the work of the Synthesis Committee to make sure that the product that comes out meets the needs of the Advisory Committee so that all the i's are dotted and the t's are crossed.

And so, thinking about how to make sure we have that linkage while avoiding the potential influence or bias that could be introduced by membership or involvement with the committee is just something we'd have to work through. Both EGAP and the USPSTF have members on those groups that -- and, actually, in the community guide as well -- have members on the Evidence Review Groups that serve in a Technical Advisory Panel, or the TAP, role and provides that linkage. And so, figuring out a way to do that without introducing influence or bias that's untoward is, I think, a critical issue.

DR. HOWELL: Joe?

DR. BOCCHINI: I was going to bring this up in my discussion as well about how the work group should be formed to address nominated subjects, because I think my experience on ACIP has been very similar, that the work group is in part formed by

membership, members of the ACIP as well as, then, experts in the area, appropriate liaisons, that may be interested in the subject and then, individuals who bring evidence who are external to CDC and may be even internal with CDC.

And I felt that that really, really significantly informs the committee or the ACIP, because, as the evidence review takes place or the evidence becomes available, the liaisons or the individuals on the committee can inform the entire committee of the progress, get feedback. The evidence people get the feedback as well. And it really keeps the committee much more engaged in the discussion.

So when the time comes for making a recommendation, actually, the subcommittee, or the Evidence Review Committee, really works with the members of the committee to bring forward recommendations that, then, are reviewed by the committee and then, either modified or changed before a vote occurs. So I think it's a process we ought to consider, because I think it may inform the process much better as you go along.

DR. HOWELL: Alan?

DR. FLEISCHMAN: The processes that we've dealt with over the last seven years are extraordinarily important clinically and in public health and have a political underpinning. And the advocacy communities have played a role, both in the desire to more forward varying disorders into nomination as well as in the effect of the public comment period.

That's very good. It's very important. And it's very real. And I would just be thoughtful, as an outsider to the committee, that we have, around the committee membership, people with varying expertise, very different than some of the very focused kinds of experts that sit on some of the other kinds of committees. And they bring a very important aspect to the discussions at this committee, very important. And that's part of the federal Advisory Committee goal.

If there were experts -- and I would never be among them -- who are evidence-based experts or -- what was the other term you used?

DR. KEMPER: Any evidenceologists.

DR. FLEISCHMAN: Any evidenceologists.

(Laughter.)

DR. FLEISCHMAN: I would not be among those. The question would be whether people would defer to those experts who were, you know, more knowledgeable and liaisons. So they really were in that process. And I think the messiness of having to teach those of us who aren't evidenceologists about this process is actually a good thing in this committee.

So I just -- you know, I understand what the goal that you're trying to accomplish is. But I just caution that that may actually have a negative impact.

DR. HOWELL: Dr. Homer has a comment.

DR. HOMER: Yes, thank you.

Just in past roles as Chair of the Committee on Quality Improvement at the American Academy of Pediatrics, where we had evidence panels, and then, as a member of the U.S. Preventive Service Task Force, I do think having a liaison between the committee which needs to use the information to make recommendations and the evidence groups, simply in terms of framing

the questions, but fully, then, standing back for the actual execution for the review, is very helpful.

Because, one, we have -- at the Committee on Quality Improvement at the AAP, we did have the experience of receiving the report, which did not necessarily address the questions we needed most addressed. So it was really in framing those questions that was most helpful.

Similarly, I do think, precisely because of the important role of the advocacy community for this committee's work, that having the opportunity for the public to comment on the questions, which is, again, similar to what's being done in the comparative effectiveness process now that it's been established for the groups, is, I think, very appropriate and has the potential to allow greater buy-in from those communities when the final report comes out, not in the process itself of evidence review, formulation of synthesis. That's a technical task.

But formulating the questions, I think, is very important. Thank you.

DR. HOWELL: Thank you.

Ned?

DR. CALONGE: So just to follow-up on those comments, so I think, Alan, one of the real important things is some ground rules for the role of a committee member on that. And I would hope that Jim and Alex and Alex and Lisa would say that, you know, as I join those calls, once they got into is this good evidence or not evidence or those, that's where I saw my role ended, and I wasn't there to influence the work. So that was a ground rule, is really providing what Dr. Homer was talking about.

I think the challenge is that, then, Alex needs to realize that it's natural for us, as experts, to try to cross over that line every now and then. And the way it worked with the task force is that evidence folks would call up the Chair and say, "You've got to reign this person in, because they're overstepping their bounds." And the Chair has to step up and do that.

So there are ways to protect against bias influence of membership. So I wanted to say just that.

DR. KEMPER: Sure. And if I could just expand on that, that's why I think it's really important, too, that we have, like, a written document that outlines all these steps and how we're going to do things.

I don't think it -- I mean, it can't be as big as the ARC manual. And nor would we want to repeat most of that stuff. But I think that having a process that's written down that everyone can look at and know, you know, if we do do this liaison thing, or there is a public comment period, that we would know what the expectations are for how that's used.

Again, most of the -- I probably actually would never have come up on my own with this idea of a public comment period, either during the development of the questions or afterwards, have the IOM report not come out in the process of all this, which recommended it. So I think that we just need to make a decision one way or another. But I'm fine with what the committee recommends.

DR. CALONGE: Right. And my only -- and so, I'm not going to speak for or against. I think

transparency is always important. And it actually helps the acceptability of your work moving forward.

The only thing about public comment period is you have to resource it.

DR. KEMPER: Right. So that's, I know, a big problem.

DR. CALONGE: And I think you need to realize that once you allow people to make comments, they will. And you have to somehow address them. So, as we put in a comment period for the USPSTF, we quickly realized that probably a blind e-mail box wasn't a good idea. And we're actually going to have to read those comments, synthesize them, address them, and -- what are you laughing at, Jeff? I thought it was a great idea. But --

(Laughter.)

DR. CALONGE: -- it didn't seem transparent or respectful. So actually figuring out how to deal with the comments, synthesize them, respond to them in a substantial way without allowing them to bias science of the review is just (inaudible). And that's exactly what we did as we posted the key questions and

the analytic framework and then allowed folks to comment on those.

DR. HOWELL: Alex, thank you very much.

Carole, one very brief comment, because we're about ready to leave.

DR. GREENE: Perhaps a naïve comment. Some of the need for input seems to be related to developing the question. Perhaps I don't understand. But I thought we have a very strict format where we know what the questions are for each review.

DR. KEMPER: Well, let me just go back. So we do have this analytic framework. I didn't list the key questions. But each of the key questions develops directly from this.

So, you know, does the -- you know, is there direct evidence that the screening test leads to a better outcome? But even within those, those questions need to be carefully crafted so that we know what time horizon we're looking at, what particular outcomes are we looking for. You know, we just really need a roadmap to make sure that we capture the evidence appropriately.

And, you know, I think internally we've done a good job of coming up with the questions. And, certainly, we've gotten, you know, helpful feedback about the questions as we've gone into the process. I just think that we need to be explicit about how those questions are developed, because, you know, as, kind of, Dr. Homer eluded to, if you're off a little bit by the questions, then you'll end up off in the (inaudible).

DR. HOWELL: Thank you very much, Alex.

We're going to take a break. And we will return at 11:20, et cetera.

And we will hear from you and Lisa after the break.

DR. KEMPER: Thank you.

DR. HOWELL: And everything has to be a bit shorter.

(Break.)

DR. HOWELL: -- Lisa Prosser are going to start with their duo, et cetera.

But, Alex, are you going to speak first, or is Lisa going to?

DR. PROSSER: I'll start going until we put up the correct presentation here. It's the next one, Evidence Evaluation and Methods Work Group.

FEMALE SPEAKER: (Off-mike.)

DR. PROSSER: Prosser.

DR. HOWELL: Looks promising. Here you go.

DR. PROSSER: Ah-ha, great, perfect. Terrific. Thank you. Great.

So, as Dr. Kemper mentioned earlier this morning, there have been a lot of limitations in reviewing the actual evidence for assessing the values of adding new conditions to the panel. So I'm going to start talking just a little bit about some of the limitations of evidence review with respect to the Methods Work Group meeting that we had in April.

I'll give a brief introduction to decision analysis and then go into a case study in which we applied a decision analysis modeling approach to newborn screening for MCADD and then, talk about how we plan to apply this for hyperbilirubinemia. And I know that the decision analysis is very familiar to some of you and not familiar at all to some of you.

I encourage you to, please, jump in with questions along the way. This can be an interactive presentation. There will also be time at the end to have some discussion and questions as well.

So the Methods Working Group that was convened in April was charged with considering new evidence review methods that we could bring to the table here to supplement what we've been doing in the Evidence Review Group. And, in particular, if you consider modeling to assist in evidence synthesis and generation so that we could take the sparse data that we often have for conditions being considered for addition to the panel and use decision modeling as a method for evidence synthesis to provide additional information to the committee for consideration.

And we defined it at that meeting that modeling would be an appropriate approach to incorporate into the evidence review process here and that we would apply this to hyperbilirubinemia as a case study. So this application to hyperbilirubinemia is expected to create a process or a framework that we can use for evaluating conditions moving forward.

And one comment there, just -- there were a number of representatives at that meeting that have been involved with evidence review in different formats at the U.S. Preventive Services Task Force, at ARC, from other decision making bodies. And the recognition there was very clear that the way that decision modeling has been used in other contracts is different from how it's going to be used here, that, in general, decision analysis modeling -- and I'll talk about this a little bit more in the MCADD case study -- is used as a backbone or a structure for developing cost-effectiveness analyses. But here, we're using that backbone, the decision analysis model, to project health outcomes as a stand-alone and are not planning to move at this point into the arena of cost-effectiveness analysis.

So decision analysis is just a systematic approach to decision making under conditions of uncertainty and provides a framework for evaluating all the alternatives that are available. So in this case, it would be universal screening versus not screening or, for some conditions, potentially it

might be -- another alternative might be targeted screening for certain conditions.

And so, it requires explicit consideration of each aspect of the decision problem. So defining the full set of alternatives, identifying choices regarding the timing of implementation, specifying the uncertainties involved. So if there are data that we don't have or downstream outcomes that are uncertain, that we specify that up front so that we know where the areas of uncertainty are. Assigning relative values to the full set of possible outcomes, and then, using all this information to identify which alternative is projected to result in the maximum benefit, as well as characterizing the uncertainty associated with that projection.

So what we expect to get from the process here is not one answer, but a range of potential outcomes. So we won't be able to say, you know, this type of screening will result -- or screening for hyperbilirubinemia will save X number of lives or prevent X number of cases of CBE. But what we'll be able to do is put a range around that so that there is

some information about what the level of projected outcomes are relative to no screening, or, in this case, relative to current practice.

The advantages of modeling is that we can take what data we do have, and we can evaluate both existing and untested alternatives. So we can simulate head-to-head comparisons.

So if we were talking about a situation which we have -- we're looking at comparing two drugs, the drug A and drug B, we might have randomized clinical trial data in which drug A has been compared to placebo, drug B has been compared to placebo. We can take all those data, put them into a decision analysis model. And then, we compare those three alternatives, drug A, drug B, and placebo, so that we can then get the relative value of drug A and drug B.

It requires an explicit definition of the assumptions, which is particularly important in the case of newborn screening in that it provides a documentation and transparency in the decision making process that the committee -- and then, once it goes to the public, is available in terms of providing

information, not just on what evidence was reviewed, but what potentially other additional assumptions were made with respect to long-term effectiveness, long-term outcomes for which we have no data, but that did feed back into the policy decision.

As Dr. Kemper mentioned earlier, we can use this, once we have a model up and running, to identify which parameters are really driving the model. And so, that will be a place to identify and target for future research.

And, with all cases of decision analysis modeling, one of the primary benefits is that we can take data from, say, a randomized clinical trial that only lasted three or five years and extent that into the future so that we can project what the long-term data would be, and, in this case, over a lifetime, for a newborn that's been screened at birth.

What we don't have here -- and we'll talk about this during this presentation -- is that we don't have randomized clinical data. So we'll be making those projections, based on what available data we have, supplemented by expert opinion.

So decision analysis modeling can provide insight into comparative effectiveness. And I use that term because here we're not going to be using the decision analysis modeling to look at the cost effectiveness of different screening options, but to project health outcomes. And that's really one of the key marks of comparative effectiveness research, is understanding what long-term health outcomes are. Whereas here, we typically only have short-term health outcomes.

So it's going to be particularly important for child's health policy by providing supports for projecting long-term outcomes. And I think we'll see that more, not just here looking at newborn screening, but at other issues around child health interventions, where we're trying to project long-term health outcomes and understand what the long-term results are.

So, in general, cost-effectiveness results and the accompanying decision analysis models that have been used to develop those data are being used increasingly. And one particular place that that's

happened here in the States is ACIP, the Advisory Committee for Immunization Practices, where the consideration of economic information is one of the stated areas of evidence that they consider formally in their decision making process.

Now, other places here in the States we know that that hasn't been the case. So I think that it's open to the committee and further deliberations as to what role cost effectiveness will play here in the committee. There have certainly been a lot of questions around cost. And we have been reviewing the evidence, if there are published papers, to include that in the evidence review.

When we go forward with the decision analysis modeling approach, we will have the opportunity there to potentially incorporate costs into that decision analysis model and project cost-effectiveness information. But that will take another level of data collection beyond what we're doing here for the decision analysis modeling.

So the general approach here is to incorporate modeling into the evidence review process

by using simple models to project health outcomes. And we're not planning to go to cost-effectiveness analysis yet, although that will be possible in the longer term. So the initial goal is to use a model to project health benefits and potential harm.

So before I go into the case study, let me just pause for a moment. Are there any questions or comments about modeling so far? Okay, great.

So I'm going to launch into a case study that gives an example of how we've used decision analysis modeling in the past. So this was a study that we started back in the early 2000s. So some of the data that you see here will not be relevant today.

As Dr. Kemper mentioned, you know, everything we do here in newborn screening is moving so quickly, it really has an expiration date. So some of this could have been updated more recently. But it gives an example of, you know, how we can use these models to project long-term outcomes.

So this was a decision analysis model that was created to look at the expansion of newborn screening programs when tandem mass spec was

introduced. And the question, as everyone here, I'm sure, knows, was that the incremental test costs were extremely low. But at the time, the total costs of follow-up and screening were not particularly well-characterized.

And there was potentially this higher incidence at that time. Now we know what that looks like in practice with newborn screening. So we wanted to use a decision analysis model, both to estimate the costs, not just the incremental test costs, but the costs of follow-up and screening as well as the costs -- the long-term costs of treatment for MCADD.

I'm not going to go through this slide in any detail, except to say that, you know, the condition met the criteria that it was a condition that could be screened for and that early identification and treatment resulted in prevention of negative health outcomes over the long term and that the incidence here is the rate that we were working with that, you know, seven or eight years ago, before there was lifetime screening here in the States.

So this slide shows a schematic of a

decision analytic model used to estimate projected health outcomes for newborn screening for MCADD. So this is a very simplified model here. We have three different types of inputs into the model.

We have costs. We have probabilities for each of the different outcomes along the way. And we have health date values. So in this model, we are projecting economic outcomes as well.

So we put all these inputs into the model. And then, we can project both health outcomes, short-term, screening outcomes, the number of false positives, how many kids required follow-up, both clinical outcomes, the number of cases identified, number of hospitalizations, both under a no-screening option and screening, so how many hospitalizations were averted, how many deaths were averted, under-screening versus no screening as well as the economic outcomes.

So we could look at the costs. The total cost of screening, including both incremental test costs as well as costs of further follow-up until resolution of a presumed diagnosis or a true positive

as well as qualities.

I won't talk much here about quality-adjusted life here, except to say that that is an economic end point for translating clinical outcomes into a common metric. A quality-adjusted life here can be thought of as roughly equivalent to a year in perfect health. And so, that was one of the other economic outcomes that we were looking at in the MCADD analysis.

Now, you know, many people look at these models and just think it's a black box, that what happens in there is not transparent. And the intent here is to make sure that this is a completely transparent process.

So I'm going to go through the newborn screening MCADD model in a little bit more detail and then, move into the example for hyperbilirubinemia. But again, you know, the overall goal and intent here is to make sure that this process is as transparent as possible, that there is understanding and agreement in terms of what assumptions, what outcomes, the inputs that we're using for the decision analysis model to

generate additional data for the committee.

So within the newborn screening simulation model, there are two sub-models, one that simulates a hypothetical cohort of newborns going through newborn screening and an identical cohort that goes through another sub-model in which they don't experience screening, but they're identified by a clinical identification.

So this slide here shows a slide schematic of the newborn screening program sub-model. So the newborn would undergo a screening test. There would be either a normal result with no further follow-up, some probability of an inadequate sample, or they might repeat test for some other reason.

Another probability is that there's an out-of-range value, and they would require a repeat sample until they're either referred to a pediatrician at a metabolic center or they were resolved, in the first part of the screening sub-model, by the end of the first year. And one important thing is that we have to identify timing for all of the points that are included in the decision tree of the decision analysis

model.

Either result is a false positive, presumed diagnosis, or true positive. And then, newborns that were identified with MCADD in the model, then moved into the lifetime MCADD sub-model of screening.

Now, so each of these arrows represents probability that it was either developed by reviewing the literature or with assistance from an expert panel. And that's important to keep in mind.

So for this model, this is a probabilistic model. And each of these arrows was defined by a probability distribution. So there was a most likely value and then, a range of distributions defined by a confidence intervals so that when we ran the model, it wasn't based just on one value, but that we were pulling from that distribution so that we could create confidence intervals around all the projected health outcomes.

In this model, it was a cost census model, so each of these health dates was evaluated with a cost. And, again, there was a range in terms of the costs that were included in the model as well as the

health date value. Here we've ranked all of the health outcomes using health utilities used to drive quality. So they were all rated on a scale from zero to one.

So newborns that (inaudible) the newborn screening sub-model that were identified as having MCADD then were simulated through the rest of their lifetime. And this part of the model was relatively simple.

They could either -- in each year of life, they could either remain normal. They could have, say, some probability of intellectual disability or developmental delay. Or they could die, either from MCADD or from another -- from any other disorder.

They also faced a probability of a short-term hospitalization each year. So we tracked these throughout the lifetime of the model so that we're able to compare the newborns screened hypothetical cohort to the unscreened cohort in terms of hospitalizations as well.

So this slide shows a sub-set of some of the projected outcomes from the model. So in the second

column, clinical identification, there is a hypothetical cohort of 100,000 kids. And we identified in their 5.88 children with MCADD. The number in parenthesis is the confidence interval around -- or, sorry, the standard error around that projected estimate. Of course, there aren't any false positive screens on the clinical identification side.

Here we're also projecting costs and quality-adjusted life here in order to calculate the cost effectiveness of screening versus clinical identification. So, in the screening arm here, we projected an additional number of cases with MCADD to reflect what had been available at the time in terms of pilot data from Massachusetts and from other countries.

The model projected that there would be 20 false positive kids -- 20 kids that were identified that would end up having false positives. And that's something that we could vary and look at with sensitivity analysis.

The costs -- here this is the total cost for the screening arm. And we're also able to track that

and to decompose that into the costs associated with testing, the costs associated with short-term follow-up, and the costs associated with long-term treatment. But that's not shown here. Again, also with the projected cost data, there are also confidence intervals associated with those that we can understand the uncertainty around those numbers.

To calculate the cost-effectiveness ratio, or the costs and numbers of quality-adjusted life years that were gained from screening versus clinical identification, that calculation was about $21,000 per quality. So MCADD -- screening for MCADD was not cost-saving, but would be considered cost-effective by many metrics.

There's a lot of debate about exactly where that threshold is. How do you decide if something's cost-effective or not? And that varies by different characteristics and may be something that the committee will consider here along the way.

There is emerging evidence, just as a side note, that the threshold is probably different for preventive programs than for identified treatments.

And so, that's a thing that could be considered along the way.

But so our primary end points of this model is the cost-effectiveness ratio. So base case, $21,000 per quality-adjusted life year gained. But what's really important here is to be able to look at some of the projected long-term outcomes.

So what we're able to do with this model is we're able to project, throughout the life course. So for the 100,000 cohort of hypothetical newborns, we can see, over time, what the cumulative number of deaths are, over time, so what the incremental deaths averted at each time point is as well as the number of cases that ended up with having intellectual disability.

One of the very interesting things from this model is that, in our earlier runs, we found that the number of hospitalizations was actually higher under screening than under no screening. And so, at first, we were concerned about that, because our initial hypothesis was that youth screening would be preventing negative health outcomes.

But what was happening -- and we were able to see that by looking more closely at the projected outcomes in the model -- is that, as we're saving kids from dying, that they're then at risk for hospitalizations. So the number of hospitalizations was actually higher under the screening option. But still, the cost effectiveness looked favorable.

Then, in terms of thinking about what this can potentially provide for the committee here is really in terms of sensitivity analysis. So when we varied the different inputs into the model, what does that do in terms of changing the outcomes that we're looking at?

So here the base case -- and I'm going to use cost-effectiveness ratio here, because that was the primary end point for this model. But for hyperbilirubinemia, we'll be talking about specific health outcomes.

So if we changed the cost of the initial screen and varied it all the way up to $50, which is about seven or eight times what we had assumed in the initial base case analysis, it really changes the cost

effectiveness. So that was one of the few parameters that we found that the analysis was very sensitive to.

So most of the other parameters that we varied in the model had very little effect on the outcome of cost-effectiveness ratios and really varied, you know, within a few thousand dollars from the initial result, which we would view as being essentially unchanged, but very robust to changes to the input parameters. So, for example, when we changed -- when we used either higher event rates, so probability of hospitalization, probability of dying due to MCADD -- when we varied those from the top of the confidence interval to the bottom of the confidence interval, the range of change in the cost-effectiveness ratio was only $18,000 to $32,000, which is still very similar cost-effectiveness ratio. And, again, when we changed the specificity of the test, there was very little difference in the cost-effectiveness ratio.

So this will really be the key part of what we can do when we take the evidence that's available in the literature so far and to use it as inputs into

a model supplemented by expert opinion to create some projected health outcomes, but really to create those ranges around the projected health outcomes. So for MCADD, we are able to project the screening tests and follow-up results, short-term outcomes, projected number of kids with the condition, cases of developmental delay, hospitalizations, and deaths. We're also able to project costs, both in the short-term and over the long-term, as well as quality-adjusted life years.

And, in general, the results were sensitive to just cause. But at that time, there was a big question around, you know, what would happen if the false positive rate was not what it was originally anticipated to be, if it were much higher. And it turned out that that didn't really change the cost-effectiveness ratio at all.

So we're now thinking about applying this to hyperbilirubinemia. So the plan here is to create a simple decision analysis model to use the evidence that we have and to use the model as a way to synthesize this evidence into tangible health

outcomes, both short-term and long-term.

We're part-way along this process so far. And when we think about putting this into a model, there are a number of inputs that we really have very little or no data on. And what we'll be doing is working with the expert panel.

We've already had one conference call with them in which we have reviewed the structure of the model. The next conference call or two will be to supplement the data that we have to develop assumptions around the missing data that we need to actually run the model. And then, we'll be able to project short and long-term health outcomes.

So for hyperbilirubinemia, there will be a screening sub-model. And then, the comparison will be the clinical assessment sub-model, which will reflect current practice. And this is a pretty simplified -- so this is a simple model here.

It's much simpler than even what we have right now as a draft model. It'll probably be a little bit more complex than this. But the intent is to be as transparent as possible and make sure that

each of these steps is documented and vetted by the expert panel as well as with input from the committee, if there is a liaison, depending how that process proceeds.

But what's important here is that we'll be working through a different process than the way that models have been used for, say, the U.S. Preventive Services Task Force or for ACIP, where those models have been built on data from randomized clinical trials, from large cohort studies, from retrospective databases. And there, the validation of the models has hinged on matching to actual data that's available and then, projecting beyond that.

Whereas, here, it's a different decision modeling approach that's really geared towards a method for evidence synthesis. So it's an alternative to meta-analysis, because we don't have the evidence base that's needed here to do any kind of formal meta-analysis. So this can be viewed as an alternative way to synthesize the evidence compared to an meta-analysis approach.

So for hyperbilirubinemia, an important part

of the process of modeling will be to process what's happening right now practice, because that will be the comparator for the analysis. So this is where there is considerable variation across the country. And, again, there are not very good data on what proportion of kids are being tested and with what screening approach.

And so, what we'll have here is not just possible options or a range for each of the parameters in the model. But we'll actually have different scenarios so that we can look at, you know, if X percent of kids are currently undergoing screening. And we can vary that range from, you know, 0 to 100 percent. And we can look at different scenarios to provide that information. That'll be an important part of this assessment.

So just one last comment here. So one of the things that we've started talking about and that will also be a very important part of this model is to talk about how we define the cohort, what sub-groups are included in the cohort, that the data will differ, depending on the age of the newborn. And so, we'll

probably have a couple of different analyses based on whether we're talking about healthy, full-term baby or we're talking about children with other characteristics. And we'll have to stratify the model by sub-groups.

The other piece that has not been integrated yet, but is that there also needs to be very specific timing for each of these branches in the model. And that will be incorporated here.

So the intent is to be able to project health outcomes, both screening outcomes, short-term outcomes, long-term outcomes, comparing clinical assessment to universal screening. And what we'll be able to provide is, kind of, a base case estimate as well as a range over which those estimates are likely to vary.

We're not planning, at this point, to go into cost-effectiveness analysis. One of the other challenges for newborn screening conditions is, not just is there very little evidence on effectiveness of treatments or incidence rates, but there's also very little data out there on the economic side.

And we also don't have the same ability to use existing data for these conditions, because they're so rare, as we do for something like asthma, diabetes, or multiple sclerosis, where it's relatively easy to take a retrospective claims database and go in and estimate costs for different types of treatment or annual costs for a condition. That we tend not to have that data for conditions that are being considered for newborn screening.

And we also don't have the ability to go into these retrospective databases to do that as well. So if we want to move towards evaluating the cost effectiveness, that's something that would likely require primary data collection.

So in terms of anticipated findings, the intent is to be able to project health outcomes and the associated uncertainty for the health outcomes, as they're defined. We have a list now that's being augmented in our discussions with the expert panel. We'll be able to identify the key parameters, so which are the ones that are really driving the analysis, and also to provide improved transparency for assumptions

on health benefits and potential risks of screening and treatment.

So, at this point, I'm going to open it up for questions, discussion, comments.

DR. HOWELL: Jeff?

DR. BOTKIN: Yeah, thank you. Very interesting.

And I had a specific question about the MCADD modeling and how you deal with circumstances in which you have a spectrum of disease.

DR. PROSSER: Yeah.

DR. BOTKIN: So you have kids who are true positives identified by screening, but may never have been identified clinically. In other words, they have -- and I don't know what current thinking is on MCADD, whether that's a significant percentage of that population. But it's not a false positive.

DR. PROSSER: Yeah.

DR. BOTKIN: But it's also not really a true positive, either. So what sort of assumptions were made about that phenomena?

DR. PROSSER: Right. So that's a really

nice example of where modeling can provide useful information, because what we did is we included those kids in the model. And then, we were able to vary our assumptions around what happened to them. So we were able to assume that either they were identified and would never have had any symptoms in the absence of screening. But they received treatment, but really received no benefit. So they were just added costs in the model.

Or we could also include them in the model as having symptomatic and had that would not have been identified through clinical identification for whatever reason. Maybe they died very early on, and it was misclassified.

And so, by being able to vary that, it didn't make any difference in terms of the cost-effectiveness results. But we were able to vary that assumption. So we were able to include that in the model.

DR. HOWELL: Gerry?

DR. VOCKLEY: Thank you.

I have some questions about the MCADD

assumptions that I think are probably best left to offline, because it seems to me that, based on the historic literature, there are probably some costs that aren't being captured.

DR. PROSSER: Yeah.

DR. VOCKLEY: But I think the more important question or comment is that, you know, I think you have a very good opportunity here to go back and look at some of the better-characterized screening disorders right now and say, "Okay, what do we know, based on 10 or 20 years worth of experience for particular diseases that fall into different categories"? And the cynic would say, "MCADD's a bad example, because if you don't find it, you drop dead, and you don't cost the system anything." So, you know, it's cost effective not to screen.

DR. PROSSER: Not cost effective.

DR. VOCKLEY: It's not cost effective to screen.

DR. PROSSER: Okay.

DR. VOCKLEY: I said it in a double-negative there. And so, if you could pull out data on

disorders where there are more chronic clinical effects, you could really, sort of, validate your model going forward for something like hyperbilirubinemia, where the effect is not death, but disability.

DR. PROSSER: Yes.

DR. VOCKLEY: And really show how well it fits with a couple of real-world models and validate it pretty nicely for going forward. So I think you've got some great opportunities here.

DR. PROSSER: That's a good point. And I'd like to address this question around cost-saving versus cost-effective.

So, you know, if we're looking at a situation in which there's immediate death, we don't necessarily assume that that's going to be cost-saving. What we're really interested, when we're doing cost-saving analysis, is looking at the relative value of that. And so, we're never looking just at costs, but at what the health is that is being purchased for that.

So, you know, we're purchasing life years by

investing in a technology that saves lives. So just to -- as a side note, that your cost saving does not equal cost effective. That, you know, most health interventions are not cost-saving. But we still choose to invest in them.

But what we want to know is whether they provide the value that we're looking for, if they're cost effective or not. But we're not looking at just minimizing costs, because that's only half of the equation. We want to know what we're getting for that investment.

DR. CHEN: Yes. You mentioned the well-known issue of time variability in terms of risk for hyperbilirubinemia. And so, how, actually, do you envision that, going into the, sort of, risk modeling in the decision analysis?

DR. PROSSER: So what we will probably be doing is identifying specific time points for the base case analysis. And then, we can vary those.

DR. CHEN: Okay.

DR. PROSSER: So assuming that all kids are screened at 6 hours or 12 hours or 24 hours, and then,

we can vary that and see how it changes the results.

DR. CHEN: Uh-huh. And I'll just ask the other. There's a significant racial/ethnic variable as well in hyperbilirubinemia that will also need to be --

DR. PROSSER: Right. Right. And that goes to my comment about that. We'll have to stratify the cohort, because there are a lot of other variables that go in there. Yeah.

DR. HOWELL: Dr. Homer?

DR. HOMER: I just mention -- you may have covered this, and I might have just missed it. But on the hyperbilirubinemia case, since what we're screening for is hyperbilirubinemia and the outcome we're interested in is, obviously, encephalopathy, developmental delay --

DR. PROSSER: Right.

DR. HOMER: And the linkage between those two remains enigmatic. So how are you going to model the uncertainty around that linkage? Because that's always been the bug-a-boo when we've done the evidence reviews around that topic.

DR. PROSSER: So that's where we'll make an assumption about what that translation is, you know, how good of a marker it is for ABE and then, CBE. And we'll have to vary that. And there may be a lot of variability around that particular assumption.

DR. KEMPER: So the purpose of this modeling is not to replace the full report. But it's additive. And it's going to point out, I think, specifically, in this case, where the important gaps are.

Because, you're right. There are really precious few data around the relationship between hyperbilirubinemia and acute bilirubin encephalopathy and kernicterus. I think we can make reasonable guesses and put boundaries around what those are to get a sense of what's going on. But it's important to remember that this model -- you know, none of this modeling stuff is replacing what's happening with the evidence reports. It's just another way of looking at it. And I think back to issues when we were looking at critical congenital heart disease, how nice it would have been to have this kind of modeling, because of the questions that come up around, you k now, how

many babies are you really going to find, what's going to be the false positive rate, what's going to be the long-term benefits of doing that.

You know, we have all that material in the full report. But it's not as clear as it would have been with this kind of modeling. So they go together, kind of, hand-in-glove.

DR. HOWELL: Lisa, thank you very much.

DR. PROSSER: Thank you.

DR. HOWELL: And we'll look forward to seeing your wisdom.

We are now going to move to committee-related work, preparing for the transition. And Joe Bocchini, who is the incoming committee Chair, will preside over this discussion.

DR. BOCCHINI: Well, first, I want to thank all for the opportunity to take on the task of running this committee. I think that, as I look around, with the expertise around this table and in the gallery there in the field of genetics and the newborn screening and at the accomplishments that Dr. Howell and Michelle Puryear made in this limited period of

time, I think it's a daunting task to follow them. And I'm assuming that anybody who is involved with newborn screening would look at this opportunity and be very nervous about doing it. So I'm assuming that what the HRSA did was said, "Well, let's give it to the infectious disease guy."

(Laughter.)

DR. BOCCHINI: Maybe he doesn't understand enough to know what dilemma he's (inaudible).

(Laughter.)

FEMALE SPEAKER: That was the Secretary's choice.

DR. BOCCHINI: So I believe with the strength of the committee and with what Rod and Michelle did to get it organized and have it run, that this will be a successful transition. So I, certainly, think that we could make it work.

My task today was to give some ideas about where the committee is and where we need to go. And I think that it's been prefaced very nicely by the work that's been done by the subcommittees and by the prior presentations of others, who have really, you know,

laid out some of the issues that are before the committee and some of the things that we really need to think about as we go forward.

So, actually, what I did was very similar to what some of the other presenters did. And that is I went back to the initiation of the establishment of this committee and looked at the charter and the duties. I want to just quickly review some of those and then, see how that led to some of the things that I'm going to then bring forward to the committee.

As you learned earlier, or were reminded earlier, this committee was chartered in 2003 with Section 1111 of the Public Health Services Act. And the charter was updated in the Newborn Screening Saves Lives Act of 2008. It was in the reauthorization of the Public Health Service Act that year.

But what it did was extended the operation of this committee for a five-year period beginning in April of 2008. And so, reauthorization of this committee is actually required in 2013.

The objective and scope of activities of this committee has been mentioned before, but I'll

just review it. The committee provides advice to the Secretary about aspects of newborn and childhood screening and technical information for the development of policies and priorities that will enhance the ability of the state and local health agencies to provide for newborn and child screening, counseling, health care services for newborns, and children having or at risk for heritable disorders.

And I think that in the submission of the report to Congress this year, it was mentioned in the committee's report that the focus has been primarily on newborn screening, because that was the area where the greatest impact could have been, but not that we were limited to newborn screening. And I think some of these issues have come up in discussion before about advancing the work of this committee to other areas. And I think that, clearly, it's within the major objective of the committee and scope of its activities to do so.

The duties were three-fold: to establish the bylaws, to specify the committee's operation procedures. And it's very clear that that's been

done. And the work of the Evidence Review Committee and others, clearly, show that the committee's very aggressive in looking at the ways it should look at information and the way it should operate. And, clearly, we're reviewing that as we're going along.

Review and report regularly on newborn and childhood screening practices, and recommend improvements in the national newborn and childhood screening programs. And, clearly, that's what the committee has done.

There are a number of activities that are also -- were placed in the Public Health Service -- or reauthorization Act in 2008 that have an impact and complement the work of this committee. Section 1112 established the clearinghouse for newborn screening, 1113, the program for laboratory quality, which we've heard about at this -- earlier in this meeting, 1114, establish the Interagency Coordinating Committee on Newborn and Child Screening, and 1116, establish the Hunter Kelly Newborn Screening Research Program at NICHD.

And all of those we've heard about during

this meeting. And, clearly, they're moving ahead and developing things that, clearly, will have an impact on what this committee does and inform the committee and the committee, in turn, provide advice for those projects.

Section 1109 was originally in the Children's Health Act of 2000. And it established the grant programs that exist to improve the ability of states to provide newborn and child screening for heritable disorders. And this committee provides advice and recommendations to the Secretary concerning those grants and projects, which are awarded -- or funded under this section and the technical information for the development of policies and priorities for the administration of these grants under that section.

Now, there are a number of specific duties that are outlined in the Newborn Screening Act of 2008 that further provide an outline to what the committee's duties are. One was to make systemic, evidence-based, and peer-reviewed recommendations that include the heritable disorders that have the

potential to significantly impact public health, for which all newborns should be screened, including secondary conditions that may be identified as a result of laboratory methods used for screening.

And, clearly, this is where the committee has been remarkably successful in advancing a standardized uniform panel and now has made additional recommendations, which have been improved for additions to that universal panel.

Another duty was to develop a model decision matrix for newborn screening expansion, including an evaluation of the potential public health impact of such expansion, and periodically evaluate and update the recommended uniform screening panel as appropriate, based on such a decision matrix. And I think it's very clear that the decision matrix has been made for newborn screening expansion. We're modifying or looking at ways to strengthen the evidence on which that's based.

But I highlighted these two areas, because I think these are areas that I think we've had some discussion about, but, clearly, are things that we

potentially could focus more on, which would be the public health impact for the individual expansion. That's been discussed in some detail already.

And then, the issue about going back and reevaluating and updating what we've done, I think, is really important. I think most policies are subject to revision.

The American Academy of Pediatrics -- every policy that's made has a five-year life span. At the end of that five-year life span, it's either revised, retired, or reaffirmed. And I think that that's -- other agencies -- I know AAFP has a similar policy, and CDC.

The ACIP has a similar policy about revising documents over a period of time. And this committee needs to consider reviewing and then, updating or modifying things, based on either a time period as well as based on new data.

Now, other duties include considering ways to ensure that all states attain the capacity to screen for conditions chosen. And in some way, that helps to inform how to provide grants through Section

1109, also provide recommendations, advice, or information as may be necessary to enhance, expand, or improve the ability of the Secretary to reduce the mortality or morbidity from heritable disorders, which may include -- and I think this is some of the -- these are some of the things that we came up today, and, certainly, came up in each of the subcommittees.

Follow-up activities, including making rapid diagnosis in short-term and those that ascertain long-term case management outcomes, and appropriate access to services -- this, certainly, speaks to the report on one of the committees.

Implementation -- that became a big issue in two of the subcommittees for us to think about. And I think, clearly, it's under the purview of this committee to look at that and to make recommendations concerning that for monitoring evaluation for newborn screening activities, including diagnosis, screening, follow-up, and treatment activities, and then, diagnostic and other technology used in screening.

Additional things are availability and reporting of testing for conditions for which there's

no existing treatment and conditions not included in the recommended uniform screening panel that are treatable with FDA-approved products or other safe treatments as determined by scientific evidence and peer review. And this, certainly, could lead us to some of the things that Ned raised about the possibility of looking at things that might not be considered for universal screening, but might be targeted for specific things or specific individuals.

And then, developing minimal standards and related policies and procedures used by state newborn screening programs such as language, terminology, standardizing case definitions, et cetera.

The committee also has a duty to recommend quality assurance oversight and evaluation of screening -- the state screening programs, ensuring that tests, technologies used meet established standards. And this, certainly, was brought up in the Laboratory Evaluations Committee.

And public and provider awareness and education, certainly, has been an ongoing effort by this committee, and the subcommittee there has made

numerous contributions. And then, looking at costs and effectiveness of newborn screening and medical valuation systems and intervention programs conducted by state-based programs.

And I think that's, clearly, something that the committee will need to address. That's, certainly, become very important in a number of areas and, clearly, for recommendations that we make, I think cost effectiveness is now going to have to be an important part of each of the decisions that the committee makes.

The committee, also under its charter, has the responsibility for identification of, causes of public health impacts of, and risk factors for heritable disorders and the coordination of surveillance activities, including standardized data collection, reporting, harmonization of lab definitions for heritable disorders, testing results, and confirmatory testing and verification of positive results. And, again, that was spoke to directly by the Laboratory Group.

The committee has a number of reporting

requirements. After three years of existence, it needed to publish a report to Congress, and subsequent to that, is responsible for an annual report on peer-reviewed newborn screening guidelines, including follow-up and treatment. This committee reviewed and contributed to that report that was submitted this year -- submitted to Congress, the Secretary, and the ICC as well as to state departments of health.

Now, in terms of subcommittees, the Advisory Committee has three standing subcommittees. We've heard from the three of them: Follow-Up and Treatment, Education and Training, Laboratory Standards and Procedures.

And, at Sara's request, the committees did consider their current status and the future. And I think we had some very good suggestions from each of the three committees on how they should interact, better way to interact for the Chairs, and then, going forward, either modification of title and issues that are looked up at each committee, and then, perhaps even establishment of an Implementation Committee. And I think those are things that Sara and I will have

to look at and start to consider whether -- how we can fit those recommendations in in a smooth way and have the meeting continue in such an effective way by adding those parameters.

Current working groups -- we have the (off-mike) and then, (off-mike) and specific topic-related groups (off-mike) and evaluation methods. And these are working through their processes. And, obviously, additional working groups will be needed, some of which may have been, sort of, the seeds planted today for the development of subsequent committees and committee assignments.

So here are some of the thoughts that I had about what are the current needs that require being addressed or to be considered. And one of the things, based on the transition of membership, we have no members now in the Nominations and Prioritization Working Group. So we'll have to repopulate that group. So we'll have to assign members to that group.

We need to review the structure and function of each of the current standing work groups. I think that's already a process that's been started. And

then, we need to prepare for the reauthorization in 2013.

And I think that, by review of legislation and our charter, we need to determine whether our standard operating procedures and all of our committee activities match those, the duties that are outlined in the charter. And if not, we'll look at ways that we can do that so we could meet our requirements for 2013.

I think we have an excellent matrix for -- and we're modifying it for development of working through nominations. But I think that the public health impact that I was talking about earlier -- I think we need to have a formal matrix for evaluation of public health impact. Some of them have already been outlined in previous discussions.

Benefits are important. Cost effectiveness, as we said -- I think that, as we look towards modeling, I think, in addition to modeling health outcomes, we need to begin to look at modeling cost effectiveness. And that may mean the need to incorporate health economists into the process so that

that can be done.

We need to look at technical aspects, laboratory capacity, provider capacity. So we need to know how states can include or implement the things that we're talking about. And, sort of, to frame that, I took two things from the Secretary's letter to Dr. Howell on the critical congenital heart disease to show that the Secretary's interested in this committee doing those as well.

This is a paragraph from -- or a sentence from one of her paragraphs. "In addition, I'm requesting that the committee collaborate with HRSA to complete a thorough evaluation of the potential public health impact of universal screening for CCHD, as required by the authorizing statute, Section 1111." So she thinks that this is our responsibility. And so, I think this is something we need to address. And I think it fits with what we're doing.

In addition, later in the letter, she indicates, "Specifically, it would be beneficial to states, health care facilities, and individual clinicians to have the Advisory Committee and other

public health experts partner with HRSA to provide information about a number of issues, including, but not limited to, the following: what will be the impact on state health departments, including staffing needs to implement this program?"

"What are the roles of the state health departments? What capacity is present to ensure that all babies are screened and the results are communicated to providers, including assuring that those not screened at birth receive a screen?"

I'm sure some of this is directed to the fact that this is point of care testing and not being done in a state laboratory. But I think it's, sort of, a model for us for us to consider these kinds of issues when we look at adding things to the newborn screening, whether they be point of care or whether they be in the laboratory or whether they be new technologies to modify what's being done.

So I think the other thing that came up that I think relates to these issues was follow-up on policy decisions; implementation issues; surveillance issues, since that, clearly, is in our purview;

patient outcome data; and looking at the effects of the decisions that have been made in terms of diagnosis, short and long-term case management outcomes, and whether there's appropriate access to services for the patients that are identified. And then, overall evaluation of program -- I've already discussed the possibility of planned policy reviews. I think that would be important.

And, certainly, our annual report gives an opportunity to do that. But, in addition, going back to the states with specific recommendations, based on what's happened as a result of the initiation of policies, would be very important.

And we've already talked in some detail about this. I think this was a great opportunity to review the structure and function of our working groups. But also, it's an opportunity for us to look at how we structure a working group for individual nominated disorders that we accept for review.

We've had some discussion about that and how that should proceed. And I think that might be something that the committee looks at in detail.

What's the makeup of those committees? What should be the standard operating procedures? What's our interactions with the Evidence Review Team? What's a work product that we would like the working group to bring forward?

And what's the format of that? And how should the interaction be with the committee as the data's evaluated? And how does the committee become informed about the issues so that, at the time of presentation, an appropriate discussion and then, decision made for a vote? So I think that's a process that we need to look at.

And then, an additional thing -- and I think Jeff's report on the meeting that was held in Utah is potentially an example of this. That there are groups outside of the committee that do things that may enhance the work of the committee. And, in many cases, they come to the committee with those details. And, in some, they may even ask for support from the committee.

And so, I think the committee needs to consider what should be the process of review of those

products. Is it such a thing so that, for Jeff's group, could it be that the committee would then either endorse that or support it or even approve that as part of the SOP of our committee and then, maybe potentially disseminate that. So I think that it might be important for us to start thinking about how we can enhance the role of the committee or help others who are working in a similar field by being involved in the development of those products or at least supporting or endorsing them.

So that's my summary, after looking at what the rules were and considerations of what's been going on in my tenure on the committee. And I think that the success of this committee is, clearly, based upon the people who are around this table.

I think we have five excellent new members who will join this table next time. And so, I think going forward, we have the expertise to continue at the rate that Rod has set. And I hope we can do that, because I think that's where the benefit is for the women and children of this country. So I'll stop there and see if there are any questions.

DR. HOWELL: Thank you very much, Joe.

Ned?

DR. CALONGE: (Off-mike.) Thank you, Rod.

Joe, that was fantastic, quite a great summary. And I will tell you, it's been interesting to sit next to Joe Bocchini and watch him actually capture the concepts as they flew by from committee members and then, integrate them, both in terms of things you'd already been thinking of and things you heard. That was really fantastic.

My question has to do with the reauthorization. And is there a specific process? Or, I mean, I can't believe there's, like, a form to fill out. But, I mean, really, to the degree of identifying those processes that need to occur and dedicating, you know, the work of your other members to help you get that done, because 2013 will be here before you know it.

DR. HOWELL: Right.

Sara, can you comment on that?

DR. COPELAND: Yes. I'll just -- am I on?

DR. HOWELL: No.

DR. COPELAND: No? Our Office of Legislation is already aware. I've already put it on the agenda for -- it's called an A-19 process. And we are starting it --

(Laughter.)

DR. COPELAND: Part of it -- but part of it is definitely making sure that our charter is in line with the legislation and the duties and making sure that there's as little controversy as possible. Otherwise, we run the risk of running -- it being, like, (inaudible) genetics and health -- GHS, so losing our authority to do this. So I want to make sure that we've dotted all of our i's and crossed all of our t's.

DR. HOWELL: Jeff?

DR. BOTKIN: I guess I, kind of, have a broad question about the charter and even our name. I mean, the heritable condition phrase is in there. But that hasn't limited us from looking at congenital heart disease, which is congenital, but not heritable, and hyperbilirubinemia, that only some causes of which would be heritable.

So are we satisfied with that state of affairs? I mean, can we move on to infectious diseases and things of that sort if they're proposed for analysis? Or do we, sort of, perhaps need to rethink the charter in that respect? Or is that thin ice?

DR. BOCCHINI: Well, I think we've already done that. So I think -- I would think, and I would hope that congenital infection would be under the purview of this committee, if and when we have an opportunity to make a specific diagnosis. It's a common problem with serious sequelae.

There is a potential for emerging treatments for CMV, the most common one. And toxiplasma we already have therapy for. So I would hope it would be under the purview of the committee. I think we've gone beyond heritable. So for congenital heart disease, as you said, we've --

DR. HOWELL: We've had considerable discussion offline about CMV already. And that will continue to come up. And we participated in a meeting at the CDC some years ago about the possibility of

newborn screening for CMV, obviously, because of its relationship to severe hearing loss.

Gerry?

DR. VOCKLEY: Rod, do you see that as a problem with the charter?

DR. HOWELL: I don't see -- you know, the name of the committee changed between the first and the second authorization, because during our first iteration, we had and genetic. And downtown dropped genetic, and we ended up with heritable and no genetic in that mix.

DR. COPELAND: It's going to depend on the OGC's interpretation of the legislation, because our charter has to reflect what's in the legislation. So ultimately, it's going to be a legal legislative issue.

DR. HOWELL: I'm sure many people will pour over that.

Gerry?

DR. VOCKLEY: Well, I do think there's some risk in mission creep. Not that there aren't other important issues that affect newborns and the health

and well-being, in general, of children and maternal health. But there are other groups that those are -- that oversee some of those processes. So we have a legislative mandate.

We have a unique opportunity to take on a group of disorders that traditionally has had no other home and no other advocates. So I would hate for us to -- I would hate for the committee to lose that focus with looking at other conditions that don't, at least, have a significant heritable component.

Yes, bilirubin is already a little bit of a deviation. I would argue that congenital heart disease still falls in the category, because we recognize it as a multi-factorial disorder. So there is an heritable component to is. So I think we're still okay there. I think as soon as we step across the line and lose the heritable component, we are risk to losing the focus on heritable disease.

DR. HOWELL: I'll make a quick comment. And that is that also it would seem, however, highly appropriate if you're considering to screen all newborns for a given condition using dried blood

spots. That that would be so much within the purview of what this committee has considered.

And CMV, I think, would still fall into that. That's a personal opinion. I'm a big CMV advocate, as you can tell.

You know, Joe, I think that was a great discussion. And it seems to me that we have one small agenda item left that is scheduled to take 30 minutes. And I can't imagine it'll take 30 minutes. And I would think that it would be prudent for us to try to get that agenda item before lunch.

Would the group -- rather than to have lunch and then, come back for a few minutes, and so forth? Because this next thing is entitled, "Passing the Gavel." And since we don't have a gavel, it shouldn't take long.

(Laughter.)

DR. HOWELL: And no one even bothered thinking gavel today. But it would seem to me -- I would like to make just a few comments. And then, the folks who have toiled in the trenches will get some elegant certificate, I'm told, from Madam Secretary.

But I would like to comment briefly. We've talked for days now about this committee and what it's done. But it's been my wonderful privilege to serve as Chair of this committee since its inception.

And the committee came upon -- was formed at a time when there was rapidly-developing technology in the area of mass spectrometry so that we really were able to work with other people to see the really dramatic expansion of newborn screening. And that's really been a very exciting time.

The other thing is that the committee has had just outstanding membership. I mean, we've had people with diverse talents, and so forth, all along.

There a few people I would like to mention by name, and so forth, knowing that I'll miss a lot of people. But Dwayne Alexander, the former Director of NICHD, was very important in helping to get this committee underway. And he was always extremely supportive of the activities of the committee and what it was doing and trying to link research programs at NICHD into areas of area. And I think Dwayne did a great job.

And Alan Guttmacher, his successor, continues to be highly supportive and interested. And, again, the research programs evolving from NICHD are very important, as are the programs at CDC. But Dr. Tina Urv is currently toiling away at the NIH to try to oversee a portfolio of situations that really relate heavily to this committee. And she will continue to do well.

I personally would like to also thank Dean Pascal Goldschmidt at the University of Miami, who is my boss and has been extremely generous in two ways: number one, paying me, which is always helpful.

(Laughter.)

DR. HOWELL: But also, being totally fluid and flexible about the work that we do in the committee and viewing the importance of the genetics -- population genetics.

We need to, again, talk about Michelle, who really worked so hard during the inception of the committee until very recently. And the committee would not be where it is today without Michelle there on the firing line.

And recently, we've had Alaina Harris and Sara Copeland moving into that place. And Carrie Diener has been there running the shop in the meantime.

We must comment about the American College of Medical Genetics and Mike Watson, who sits on the committee, because the HRSA contract that the college oversaw, and so forth, was really the groundwork of this committee. And I'd like to acknowledge Mike and the team at ACMG.

And then, the advocacy groups -- there are many who are represented in this room. And you all know who you are. But I specifically would like to single out the March of Dimes. It's been persistent in supporting our activities and working downtown to help educate the Congress about what the committee is doing.

And we have never seen more dramatic evidence of the advocacy community than we saw in the past month with the critical heart disease study, because, fundamentally, the education that was carried out downtown really changed the course of action

there. And so, I think that's just invaluable.

And we have to talk about Marina Weiss, who has been one of the folks running the show down there. And, again, Jennifer Howse, who is a member of the committee.

But anyway, it's been my privilege.

And if I had a gavel, I'd be pleased to pass it to you.

But I'm sure that Joe will do a wonderful job. And I will be observing close at hand, because I'm going to stay involved in newborn screening.

And I'll be checking up on you regularly.

(Laughter.)

DR. HOWELL: And if you do something I don't like, you'll hear from folks who work downtown under that big dome, and so forth, et cetera.

(Laughter.)

DR. HOWELL: And Sara is going to have a few words, we hope, kind words, from HRSA.

MS. LINDE-FEUCHT: Thank you, Dr. Howell. I just wanted to say, on behalf of HRSA and HRSA's Administrator, Dr. Mary Wakefield, and also, I think I

can say safely, on behalf of Dr. Peter Van Dyke, who has retired from our Maternal Child Health Bureau, just a great, big thank you to you, Dr. Howell, and to the other committee members who are rotating off. The work you have done is tremendous. And, obviously, we rely on your expertise and your thoughtful consideration of all these issues. So, on their behalf, I just wanted to say thank you.

And that thank you will have to suffice for now, because we don't actually have the physical certificates to hand out to the out-going members. So, like any good government, you know, project, it's probably in the mail. So --

DR. HOWELL: Outstanding. So everybody knows who's leaving. And so, we'll thank everybody. And your certificate will be in the mail, I gather. Okay.

DR. BOCCHINI: If there is no other comments, we will move to adjourn.

FEMALE SPEAKER: And you still get lunch, if you're a committee member.

(Whereupon, at 12:35 p.m., this session of the Advisory Committee adjourned.)