24th Meeting of The Secretary's

Advisory Committee on

Heritable Disorders in Newborns and Children

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DR. HOWELL: We have a very, very busy agenda. And before we get into the agenda, I would like to make a couple of comments. And that is that yesterday, I had the privilege of introducing three new distinguished members of this committee. And I commented at that time that folks who are nominated and appointed to the committee by the Secretary have in common that they are all people of great accomplishments, so that we're accustomed to having members of this committee receive a variety of recognitions for their outstanding service.

But I wanted to point out one tremendously outstanding accomplishment that one of our members had happen very recently. And that is that the most important scientific recognition that a person can get in the United States currently is election to the National Academy of Sciences. It's a very special recognition. Very few people achieve that. And I want to congratulate Rebecca Buckley for her election to the National Academy of Sciences.

(Applause.)

DR. HOWELL: And I might --

DR. BUCKLEY: It was an honor, a very great honor.

DR. HOWELL: It was a great honor. And, of course, that's highly irrelevant to our discussion later in the day because those

extraordinary accomplishments centered around immune deficiencies that will be a center of our discussion later in the morning.

And so, Becky, congratulations. Being a pediatrician, I'm confident that your accomplishments all go back to the fact that you got a very good start in life; right?

(Laughter.)

DR. BUCKLEY: Dr. Howell (inaudible) were house officers together -- taught me everything that I know.

(Laughter.)

DR. HOWELL: Yesterday, we had an opportunity to have three subcommittees meet. And we're going to start off the morning by having reports of those. And we're going to start off with the Subcommittee on Laboratory Standards and Procedures, Jerry Vockley.

DR. VOCKLEY: Before I start, relative to my presentation or the session yesterday, in my quest to build bridges, I inadvertently crossed the FDA inappropriately with the NIH and introduced Anne Pariser as Anne Parisi.

So, Melissa and Anne, I don't think you're here. I'm sorry.

DR. PARISI: It's not the first time.

DR. VOCKLEY: Yeah, well. The Laboratory Standards and Procedures Subcommittee -- I have to keep looking at the slide because I

never remember the name -- has the following members, including our committee members, organizational reps. and some very active additional members. On the committee for the first time this meeting was Fred Lorey, who, of course, also just joined the larger committee.

We had some very interesting presentations and requests for some additional assistance from the subcommittee. The agenda here -- we heard from the Massachusetts program on their attempts to use additional, essentially -- I'll call it having fun with math, refining MS:MS interpretation. Then Steve Dobrowolski from the Utah group giving us an update on some of the work that they're doing on spinal muscular atrophy screening. Our good friend, Jelili from APHL, discussing an ongoing -- no, I'm sorry. This one is a new effort to build some definitions for quality measures going forward for database capture.

And then, from the National Library of Medicine, this is the ongoing effort looking at ways of better defining the language that is used to exchange information. In this case, in particular, we're talking about the language used for reporting newborn screening.

So in regards to the MS:MS project, this is funded -- from Massachusetts. This is funded through HRSA. And so, we were delighted to have a report from them on the project. And the goal of this project was both to improve the predictive ability of the data that comes

out of newborn screening and as a result of that, be able to better communicate risks related to it. So instead of saying that your C14:1 is high, using VLCAD as an example, they presented data, which, as I said, this is kind of a fun with math -- looking in a more rigorous way at all of the metabolytes and trying to define other consistent patterns that, in and of themselves, were not as specific as the C14:1 is to VLCAD, but in combination with C14:1, makes a difference.

So, for example, there are a couple of calculations that involved taking, not just ratios of two numbers, but adding a couple together, multiplying by something else and dividing by something else. So it ended up being -- the ratios that they -- or the metrics that they identified looked quite promising. And, for example, in VLCAD where they had a handful of known true positives and some that had not been substantiated and were felt to be, either non-specific or, perhaps even carriers. And they have really good discrimination in those two groups.

So they will be continuing to work on that. And they've expanded their project now to pick up the state labs from New York, Wisconsin and Connecticut. That choice was made because they're looking at two programs that use derivatized samples and two that use underivatized samples for their screening purposes.

So I think -- and this is a little analogous to what the region

four has done with some of their worksheets. And it really is designed to pull more information out of the testing that's already been done, as opposed to immediately going to, say, a second tier test or follow-up.

From Steve Dobrowolski, we had a report on molecular screening for spinal muscular atrophy. And this is an NICHD-funded effort that is designed to really try to develop a better screening for this disorder. For those of you not familiar with it, it's a complicated locus. There is the SMN1 and the SMN2 genes. They can be present in multidive. It's a tandem duplication. They can be present in multiple configurations. And it's SMN1 deletions that are pathologic, but SMN2 status that is predictive of severity.

And so, Steve showed a very nice data on a multiplex PCR-based DNA melting technique to look, not only identify the SMN1 status, but in the same screening reaction, had the ability to define the SMN2 status. And then, just for fun, as he puts it, they threw in TRECs. So they had a nice -- for SCID. So they had a nice multiplex assay that still had room to pick up maybe one or two other disorders that he was considering adding to it. So quite a nice, I think, advancement going forward. And we'll see if this falls out to be the best screening technique. They'll be comparing it with some others that are on the horizon.

We end up doing a lot of IT overlap when we have an IT

group or sub-group or whatever we call it that works outside the -- or as part of this committee. We end up overlapping quite a bit with some of what they do. And in this case, the APHL has an ongoing interest and effort in identifying the key quality measures that are followed by state screening programs. And so, they have been asked by -- and I forget who now. Sorry -- to develop essentially an expanded or an edited group of quality measures to capture laboratory systems for long-term follow-up. They've already been working on the immediate needs of newborn screening and short-term follow-up. And now they're going to try to put something together for a longer-term follow-up. This was a very, very short timeline. They've, sort of, just got this request in the last month or two. And they've been asked to have a report ready by July. And so, that will be a quick turnaround. It does involve the National Library of Medicine and overlaps, to some extent, then, a little bit with the final presentation that we had.

Coming to that final presentation, then, we heard of the ongoing efforts to update the LOINC language, reporting language panel relative to newborn screening. As an example -- or a report, we had heard last time about the efforts to develop new language to report out on hemoglobin, which is a fairly complicated issue because of all of the different variants and the way the labs capture the data. And so, they

showed us the new language that will be used -- or that they propose to use for that.

But we spent much of the session focusing on, really, the questions and answers that they should capture relative to newborn screening interpretation going forward. And as a specific request -- and I'm going to bring this to the full committee -- they have asked that our subcommittee help them with developing the structure and standard names for new codes for new conditions and tests going forward. And that because of the overlap with what is a screening test and then ultimately the diagnostic test for these disorders, they would like to include the reporting -- the language that's going to be necessary for reporting out the diagnostic tests as well.

So in addition to all of the information of this report, we have an official request by the National Library of Medicine for the subcommittee to help out with this effort. So I guess I have to bring that to the committee and ask for permission to do that.

That's the end of the report. So --

DR. HOWELL: Okay, thank you, Jerry. It was your group's opinion, as I recall yesterday, that this is something that you would be perfectly willing to try to look at these names. And it was in the purview of your committee, and so forth. Is that correct?

DR. VOCKLEY: It seems like we're doing it already informally. So formalizing it, at least for initial trial period, seems reasonable to me, yes.

DR. HOWELL: I doubt that we need a formal vote on that. But I would just like to inform the committee that this group is doing that. And if anyone has any concerns about that, share them with Jerry. Is there anybody that would have -- I see no problem with doing that. I think it'd be important to advise the committee, which you have done.

DR. VOCKLEY: Perfect. Thank you.

DR. HOWELL: Thanks.

One thing I will comment, and that is that, as you know, we had a Health Information Technology Workgroup that has since decided its work was done. And Sharon Terry, who's co-chair of that, we expect to arrive later today. And I'll ask her to comment about that when she comes, and so forth. We've received a letter about that.

Thank you very much for that very good report, and so forth.

And now move to the Subcommittee on Education and Training that's co-chaired by Tracy Trotter and Don Bailey. And apparently, Tracy is the spokesperson.

DR. TROTTER: Thank you.

Yes. I would first of all like to welcome our new co-

chairman, Don Bailey. This was his first meeting. And we had a, I think, very productive meeting. We did not have fun with math.

(Laughter.)

DR. TROTTER: I am delighted to point out. So these are our subcommittee members. And all but one of those folks were there in attendance. And we had another dozen interested folks who were also helpful for us.

We were updated in the broad spectrum of educational training programs that are going on at our various and sundry offices, first being the Newborn Screening Clearinghouse. Natasha brought us up to date on where they are. The beta Web site, the nbsclearinghouse.org, has been up for some time, as you know and will continue through the summer with the goal of going to the live launch of babysfirsttest.org, which will be the real Web site in September of this year.

And we talked a lot about a number of things that have been added, including more sophisticated user guides, more condition-specific information from various -- that are linked to various databases, some of which are noted here, some of which are not. They have had an ongoing blog post with the Immune Deficiency Foundation to, sort of, bring the SCID screening information up to date. And the babysfirsttest development is going very well. They have brought in a company named

Blenderbox, which is a company that routinely does educational non-profit-type of Web sites. And these are just some of the statistics from the last three months during this time.

They're not really publicizing this in any way, other than, sort of, word of mouth among those of us in this room, probably. But they're still getting a fair number of visits without making any efforts to do that.

And both the Materials Workgroup and the Public Education Workgroup has met by telephone five or six times, depending which one you're talking about. And that will continue through the summer.

The challenge awards that I mentioned in January, which are designed to engage as a community and bridge the clearinghouse with existing programs, had four awardees for six-month projects that were announced on April 1st out of a number of excellent applications that I had the opportunity to see some of. The March of Dimes, NYMAC, the Hawaii Department of Health and APHL were all awarded grants, which probably in September we'll be able to hear something about how those are going.

And they have embarked on, between the Genetic Alliance and the Newborn Screening Clearinghouse, a program on identifying quality indicators. And these four groups are working together to see how we actually can identify those in the area of newborn screening and quantify quality improvement. That report also will probably be available

by September.

Other folks who updated us -- the Family History for Prenatal Providers, which is a tablet-based, computer-based family history program. We had an update from Alaina Harris, who's a staff person for them. And they're moving along. And hopefully, by September, they'll actually be in their testing mode and we'll be able to take a look at that.

We had a special presentation by Brian Pike from the Southeast region on the educational -- some of the educational and training aspects of their region and some interesting programs, especially in the area of nutrition for metabolic diseases and training for such thing. You have heard in the past about the Genetics in Primary Care Institute that RFP went out in January, I believe. It has been reviewed. There is, at this point, no identified funding. And because of that, there's not an announcement of an awardee. But we anticipate to be able to do that within a reasonable time.

Colleen updated us from her group. And the representatives from ACMG, Barry Thompson, was there talking about the foundation's summer genetics scholar program, which is, I think, a very exciting program for medical students who have completed their first year of medical school, spend a time with a -- in a genetic situation in a focused way for some period of time during their summer. And, to me, it serves

two great purposes, from an educational standpoint. One is, hopefully, increasing the number of medical geneticists that come out of the pipeline down the road, which obviously, is a significant shortage right now and is going to be worse.

And the other is, at the very least, introducing young medical students to this exciting field early on so that, as they go on to do other things, whatever their specialty or sub-specialty is, they will be tuned in, more genetically literate and, I think, much more able to handle the information as it comes out.

We had two presentations from groups that are independently working on newborn screening in general. Kelly Leight's group, called called Preserving the Future of Newborn Screening, updated us on their development of educational materials as did Jill and Cate on Saving Babies Through Screening Foundation, through their video, which we look forward to having a look at by our next meeting.

Our usual updates from our representatives from the major primary care groups, Tim Geleske from the American Academy of Pediatrics and Fred Chen from Family Physicians and Allen Hogge from ACOG update us on that. The numerous things, actually, that are going on, as you might imagine, in those groups that relate to our educational efforts was well-received.

So that's just our -- that was for Michele. She likes to get the law in there at least once. So we've got to.

(Laughter.)

DR. TROTTER: So the national newborn screening awareness campaign, which is something that you all as a committee approved, is moving forward with last time, is launching into phase one. There was a little delay when the government shut down, or nearly, but launching phase one. So we are now looking at the lay of the land, as it were, what's out there now, what do we need to identify, what gaps need to be filled and what audiences want to hear. And at the end of that first phase, then we'll try to get appropriate stakeholders together to then hopefully create a plan. From that point, I would think, bring that back to you to see if you think this is a reasonable idea to go forward or not.

And that was most of our meeting. Any questions, concerns, complaints?

DR. HOWELL: Thank you very much, Tracy.

We'll now go for the Subcommittee on Follow-up and Treatment, Coleen Boyle and Jeff Botkin. And Jeff is going to be the spokesperson?

DR. BOTKIN: Yes, I'm going to be presenting this morning. And my apologies for not having any PowerPoints, for those of you who

are visual learners.

(Laughter.)

DR. BOTKIN: Our subcommittee welcomed Robert Austrander. He's a family practitioner from New York, Robert in the audience there. He's going to be an articulate and helpful contributor to our subcommittee.

So most of our discussion was focused on the issue that we spent some time with yesterday, which is hospital-based newborn screening. So I want to outline the substance of our conversation at the subcommittee meeting and potentially get feedback, if that's appropriate.

So we're building on a discussion the subcommittee had by telephone over a number of months, at this meeting yesterday and then at the subcommittee meeting. So I think everybody recognizes that there are significant new issues to be addressed in screening that goes beyond blood spot screening. So how best to address those new issues, of course, is the key question.

Our group is interested in maintaining a focus on newborns as the population of interest for this discussion. I think, clear from the background authorizing legislation for this committee that this committee's mandate is not restricted to newborns. Nevertheless, we felt important not to bite off more than we could chew and that newborn focus would be

appropriate. And certainly, issues that arise within the nursery environment will be a little bit easier to address rather than the broader set of issues relevant to infants and children and the various places in which they might receive screening.

So our focus then, we anticipate, being newborn screening broadly construed and leave it for additional discussion at some future time about older of infants and children. Now, our recommendation at this point, or our initial plan is to pursue a white paper for this effort to develop these ideas in the context of a white paper rather than through developing a conference. And I think we had initial discussions over the last several months that a conference might be the best way to invite stakeholders and to further explore these ideas. The conclusion yesterday that a white paper would be a more appropriate and efficient way to develop these ideas.

We have a tentative first part of the title for the white paper, "Reframing Newborn Screening." And there's a colon, because all titles have to have a colon. But the concept, of course, is straightforward here, reframing newborn screening to be a term that refers to this broader set of activities beyond blood spot screening and expanding the types of interventions that have been familiar with the hearing screening efforts.

So the point would be to address the issues that make

hospital-based screening different than blood spot screening. We would be addressing standards for screening in some of the things that Nancy outlined for us yesterday in terms of the nature of the test, the urgency of the intervention, equity issues, all being important to look at standards for what would qualify in this particular context. And particularly, we're interested in the roles and responsibilities from the various stakeholders. And I think that's going to be, perhaps, the hardest nut to crack in this domain, who's responsible for what, once we move beyond the more familiar domain of blood spot screening.

So the white paper would identify and outline these issues. And we anticipate the white paper making recommendations. And that's unclear how specific those recommendations would be. But I think the concept here is we need to outline what the issues are and then, at least take tentative steps toward drawing some conclusions about some of the key issues.

So stakeholders, of course, are essential. And there's a whole host of stakeholders that have been identified here. There's public health, the hospitals, third-party payers, including Medicaid, primary care providers and their official organizations like the AAP and the AAFP, nurses, the public, more broadly. Preventive Services Task Force and the Joint Commission have been identified all as key stakeholders that we

want to engage in this effort.

We've identified at this point a core writing group that will be responsible for initial drafts and for engaging those stakeholders. I don't think we anticipate that we're going to have a long list of co-authors representing each of the stakeholders, but rather have a smaller group of authors who will engage the stakeholders and make sure those folks are informed and supportive of the direction of this paper.

Additional discussion this morning about whether the Webinar might be an appropriate tool to help in this process. I don't think, from my perspective, been quite enough discussion about this yet to understand whether that Webinar would be a mechanism to gain input or more of a mechanism to publish initial or draft content in order to get feedback from that larger community. But that's certainly on the table then about a mechanism that we can reach out.

So that's my summary of that particular element.

Coleen, I don't know whether you had anything to add, or other committee members, subcommittee members?

DR. HOWELL: It sounds like a very good idea to me personally. Now, we should hear some thoughts from the committee about that. And so, did you discuss a timeframe?

DR. BOTKIN: I don't believe we have.

DR. HOWELL: It's a very silent group this morning.

DR. BOTKIN: Need some more coffee here.

FEMALE SPEAKER: (Inaudible).

FEMALE SPEAKER: I was going to say a draft.

FEMALE SPEAKER: Okay.

FEMALE SPEAKER: Okay.

(Laughter.)

DR. HOWELL: I think the content of this is so important that it really should move along, I mean, bearing on our discussion yesterday, and so forth. So, I think that if the group could conceive of having at least a draft by the next meeting, that would be helpful, I think, and so forth.

I would assume that all the silence around the table would mean that folks are comfortable with your committee moving ahead on that. I don't think we need a formal vote on that.

DR. BOYLE: Let me just say I would say we have a draft that we'd share with our subcommittee, not a draft ready for the full committee. So it's going to take a while in terms of vetting. And really, I mean, I view the Webinar as an opportunity and a process to get input to this, to reaching out to the partners and the audiences that we felt weren't represented around the table and in our subcommittee yesterday.

DR. HOWELL: Sounds like a good idea. So great, we'll look

forward to hearing great activity in this area.

DR. BOTKIN: Great. Thank you.

So other agenda activities yesterday -- Amy Brower gave us an update on the National Coordinating Center, HRSA data set efforts looking at public health measures for long-term follow-up. And, as folks may recall, it's uniform data sets for follow-up of children with the full range of conditions identified through newborn screening. And this is a really important and complicated effort that sounds like folks are making good progress on to try to develop uniformity to enhance data collection in this arena.

I had a medical foods update from two perspectives. Susan Barry gave us some additional information about a draft paper that's moving forward. This is a regional collaborative survey effort. And then Christian Brown gave us a quick update on federal legislation regarding medical foods. And legislation is currently pending at both the Senate and House at this point.

Al Zuckerman also gave us a very thorough update on a variety of HIT activities that are ongoing relevant to newborn screening.

So our thanks to all of our subcommittee members for their contributions.

And anything additional?

DR. BOYLE: And one more issue was that the white paper that Brad Thorell had developed linking newborn screening-related results to vital record information to help facilitate follow-up and evaluation -- we have had subsequent conversations with NAPSIS. And, as you may recall, the former executive director of NAPSIS was -- and the board -- were supportive of that concept. But I can't remember what his name was. Garland Land, I think, was leaving in December. So we wanted to wait until the new director is in, whose name is -- I don't remember her name, either. I apologize.

But anyway, she feels that the board is still very supportive. And we are going to get NCHS and NAPSIS together on a phone call. And we will definitely report back to you in September. And hopefully, we'll have moved along with that issue by that time.

DR. HOWELL: With regard to the medical foods, this committee obviously has had a considerable interest in that and sent a letter to the Secretary, who, quite properly, pointed out that this was -- she thought that's a good idea, but was not necessarily in her purview. Is there anything you report on the legislation, other than the fact that it has apparently some additional sponsors? Is that correct? Is there evidence that this is moving along? Or is it fairly stuck? Were there any comments about that?

DR. BOYLE: I don't if Christine -- thanks, Christine.

MS. BROWN: Hi. I can give you an update on that. Christine Brown, from the National PKU Alliance. It's moving. It's moving slowly. There is a good possibility that it may be attached as an amendment to a Senate bill. We'll know more about that when we meet with Senator Kerry's office in about two weeks.

In addition to that, we're still looking at other ways to advocate the inclusion of medical foods as essential health care benefits under the ACA. A number of geneticists and dieticians have been testifying or providing comment at the IOM meetings that are happening throughout the country. And the Department of Labor survey was recently sent to HHS, which was the other piece on determining essential health care benefits. And that piece was obviously a little disappointing. I mean, that's the survey that looked at, you know, health care plans across the country and what they currently cover.

And, for example, in that survey alone, they found that only 27 percent of health plans cover diabetic care management. So if they're only covering 20 percent of diabetic care management, are they going to even look at really, you know, coverage in terms of lab fees, you know, dietetic visits, et cetera, for inborn errors of metabolism? So it's going to continue to be an uphill battle. But, I mean, we have a coalition of, you

know, 40, 45 organizations that are working together on the legislation.

DR. HOWELL: Well, the medical foods issue is important. And I think this committee is very supportive of that program. And hopefully, members can individually do what they can to make that move along.

MS. BROWN: I would hope so. Thank you.

DR. HOWELL: Thank you very much.

Jeff, other activities from your committee yesterday?

DR. BOTKIN: No, thank you.

DR. HOWELL: It sounds like you had a busy and productive day. Thank you very much, and so forth.

We now are going to hear about the EEM Work Group meeting from Ned Calonge. And Ned is in the mile-high city.

And, Ned, I'm told you're on the phone.

DR. CALONGE: I am. Can you hear me, Rod?

DR. HOWELL: Yes, we can. Welcome to our meeting.

DR. CALONGE: Actually, I'm in the Pacific Northwest in Kelso, Washington. So I wish I could be there with you.

DR. HOWELL: And I hope you're inside. I'm sure it's raining there. I don't know. But --

(Laughter.)

DR. CALONGE: If it's not, it will be.

(Laughter.)

DR. CALONGE: So I'd like to report on the meeting that we had on April 13th in Bethesda. And if you think about that day, that would be the week immediately following the potential close-down. And so, we were very excited and felt that it'd be successful just by the fact that we got to have a meeting at all.

I want to recognize that there were a number of committee members and members of our evidence group that participated. Dr. Bocchini and Dr. Dougherty from the committee attended, from our HRSA staff, Dr.

Puryear and, of course, Dr. Copeland, a number of staff from the Evidence Center, including Dr. Perrin, Dr. Greene, Dr. Kimber, all participated, Dr. Crofter as well. And I can't go without recognizing that Alex Zapp made sure we all got there and were courteous to one another when we talked.

In addition, there were a number of experts in different parts of the evidence-based medicine world who came together to try to help shape some additional thinking around our own evidence-based methods and how we translate things into recommendations for the Secretary. We heard presentations on the EGAT process from Dr. Steve Toish, from the

great process from Dr. Shuneman, from the community guide process from Dr. Jonathan Fielding and U.S. Preventive Services Task Force from David Grossman. And then, finally, we heard comments from Dr. Diane Petey regarding the use of modeling to inform the policy and David Atkins, who had experienced both at Grady and USPSTF helped me string things all together.

I'd like to share the concept of what we brought forward and what we hope to translate into additional recommendations for the committee to consider, moving forward. The first point I would like to make is that we were urged to consider the place of other study designs in our evidence-based methodology. And actually, beyond the traditional observational study designs, there were recommendations on how we could use case theory to represent the kind of case control study that could move our information forward.

I think the important thing to remember when we consider additional study designs is that their (inaudible) validity through sources of bias that we just need to keep in mind and think about the directionality of the bias and be honest with ourselves about whether or not the bias overcomes the utility of the data in making decisions. So the case theory was a real important area and we were pointed to some new work by some epidemiologists, Dr. Cummings (inaudible) at the University of

Washington, in how to consider these issues.

I think the other recommendation was time theory analysis, which may be less relevant to newborn screening, but at the same time, thinking about casting a broader net with how to gather information to inform our work, going forward, was critical.

The second area was the fact that we needed to keep in mind that we have a number of national experiments going forward. Specifically, we're pointing to the issue that some states, based on local decision making and policy settings, launch into screening for new conditions before other states. And what that provides us with is ongoing information in the form of an actual experiment that could really help move our work forward and better inform the committee as well as the other states about the utility of these screening approaches.

The issue, though, that that brings up is that keeping track and developing registries that allow for longitudinal assessment is simply critical to using these national experiments to better fill in the evidence gaps around screening for certain conditions. And so, an urge to the committee and the smart people in the room there in Washington about how we could make registries come alive and contain sufficient information to provide us with case theories and comparative data, moving forward, is just something that it's an opportunity we are currently lacking

in most settings. And we will never gather the data we need to make decisions on very rare conditions if we can't figure out a way to follow these cases over time.

The third major theme that came out of the discussion had to do with the use of modeling to help inform decision making. I'm going to quote Dr. Bocchini, who, earlier in the presentation, said, "Models don't make decisions. People do." And the point she's trying to make is that these models don't contain the answers within them. But what they do is reframe or reconstitute the data in ways that can help us wrestle with the issues that face us in making decisions around our newborn screening and what conditions to add.

So modeling can give you -- I guess one of the ways to look at it is there's uncertainty involved in looking at conditions where the data are insufficient. And what modeling can do is help us understand the limits of those uncertainties. One way to put it is how wrong could we possibly be. Or, you know, how much benefit could we do if we reached every kid who screened positive? And at the same time, knowing the limits of the testing, what are the harms that would be associated with, specifically, false-positives, but also false-negatives, moving forward?

And modeling that happened at a high level, conceptual level that were simple to build, that resulted in decision analysis or for things we

call outcome tables, you know, what happens if you screen 100,000 or 1 million children and you look at all the potential outcomes that could occur? Those simple models should help inform the committee, moving forward. We believe that the evidence group under Jim can have that level of expertise and those models can also help us inform -- I'm sorry, help inform us in our mission of trying to understand the potential cost/benefit of the tests -- or the conditions we're studying.

Sensitivity analysis is important in building models so you understand how good your model is. And then just recognize that the model doesn't answer the question. It simply helps inform the committee about where the uncertainty is and helps us make a decision.

I guess the last issues I would bring forward have to do around uncertainty and how we communicate that to all the stakeholders in newborn screening and then what we do in decision making, moving forward. So if the evidence is insufficient and we believe the evidence is going to remain insufficient for some time, we have uncertainty around the net effect, the net benefit associated with newborn screening for a condition. So communicating that to our stakeholders, including other clinicians, parents and advocates, scientists and researchers, will be critical to our success and to the reception of the recommendations of the committee, moving forward.

We did talk a little bit about the subject, I know, you guys had brought up yesterday, which do we need other categories for our conditions than the four we currently have. And I think the two things we talked about and that I think the committee will need to discuss and make decisions about, moving forward, was one is the concept that Medicare has a coverage with evidence development.

And those of you who were involved with the decision making framework early on know that we had considered a category called the provisional category, where we would add a condition with the understanding that we were going to collect specific evaluative data, moving forward, both some time in the future, as we filled in the evidence gaps, we could rereview the condition and make a better decision about whether to keep it on as a permanent condition in the core panel or whether or not the evidence now accumulated to the point where we could take it off.

So this is like the concept in Medicare of coverage with evidence development that embraces adding a coverage to a specific medical therapy or managed strategy with the dedication of collecting data, moving forward and then reevaluating the type of the coverage that continues. So this concept of a provisional addition of a condition is something, again, I would like the committee to wrestle with at some point.

And the last modification or consideration for modification of our result is that does every condition we look at need to end in a recommendation from the committee to add the condition as a uniform screening test for all births. Inherent in the idea was that there may be conditions for which the evidence is insufficient or the system that would need to evolve to capture the screening data is sufficiently different or onerous, compared to our newborn blood screening, that we make the recommendation to the Secretary not to add the condition as something that should be part of the core panel for all infants born in the United States, but that there might be other recommendations that say a hospital should embrace this screening test as a best practice or we turn the condition back to the clinician and medical staff of those institutions to figure out how to get implementation and how to implement recommendations for which we believe there's potential benefit, but the evidence doesn't support.

We don't reach that bar of saying, boy, we are certain this is going to take children with longer or healthier, and therefore, need to be added as a condition, to be done at every birth. So these two issues about the potential adding of conditions provisionally and then other recommendations other than a uniform screening approach are the things the committee talked about.

But I apologize that this was a diatribe with no slides.

Michele, I guess you could fire me, if you needed to. But these are the discussions we had. And I'd really like to hear the thoughts of others that could inform Dr. Perrin, the Evidence Review Group and the rest of the committee, going forward.

DR. HOWELL: Thank you very much, Ned.

Denise, you were there, as was Joe. And could you add your comments?

DR. DOUGHERTY: I thought it was an excellent meeting. And I liked the way Ned summarized it. So I don't have anything to add. I think the decision modeling is a terrific idea and will be very informative to the committee.

DR. HOWELL: The two specific recommendations that he had?

DR. DOUGHERTY: Which were? Sorry.

DR. CALONGE: No, no, the -- Rod, I think she was talking about doing decision modeling.

DR. HOWELL: Okay. Okay.

Joe?

DR. BOCCHINI: Yeah, I, too, thought that it was really an excellent meeting. There were a number of individuals there who have

made significant contributions to development of evidence review and how to approach it in a transparent way. And I think they gave us some very good suggestions, as Ned pointed out, how to take limited data and use it to our best advantage and then, in reference to the severity of the problem that's being evaluated, how to then modify our approach, based on a potential outcome for the individuals with the limited data that we have.

And I think that the modeling recommendation was really good. I think it gave us a -- gives us a good opportunity to look forward and then make decisions in a more rationale way. So I think overall it was really an excellent meeting.

DR. HOWELL: Coleen?

DR. BOYLE: So I had a question for Ned and others who were in attendance. So that I guess I'm intrigued, again, by this idea of acceptance with provision. But it seems to circle back to what you had originally proposed or identified as -- in your number two, which is the number of the natural experiments and taking opportunity there and somehow urging whatever rollout occurs under that -- you know, if we were to go forward with a provisional recommendation, to capture that data so that, in fact, we can continue to build on that evidence base.

I just feel like, you know, I think we tried to do that in the context of the CCHD recommendation. But I don't know if when you

discussed the acceptance with provision you thought about the implications there and how, you know, we needed to somehow move forward in a very deliberative way about getting additional information.

DR. CALONGE: Well, Coleen, we didn't really talk about that as specifically as, I think, you are. I think, you know, what's easy to say that everyone in the room -- there was a palpable sense that this was something we had to figure out how to do, otherwise we'd kind of continue operating in the dark with hopes that we were doing the right thing. But I don't think anyone overlooked the fact that (inaudible) actually the policy implications of trying to do it are completely different.

It was interesting that there are groups of ethical experts who are looking into the use of information to support public health issues that are also wrestling with information in the comparative effectiveness world and in genetic screening -- genetic testing world as well and trying to figure out whether or not the exemptions for public health that are associated with HIPAA could also translate to broader areas involving informed consent and linkage of information and (inaudible) identified ways, moving forward.

And it was fascinating to hear that, from a legal standpoint, there are ethical groups that have decided that if it's a public health issue, it fits under their 5(12) exemptions -- I'm sorry, Section 5(k) exemptions

and therefore, don't require informed consent. The problem there -- and I know there's a number of newborn screening spot retention folks in the room -- is that there's a difference between legal interpretation and public acceptability. And so, trying to figure out how to change the dialogue around the importance of gathering these kind of data in terms of how they help the population and changing that dialogue just to have a better sense of the benefit of how linking those data could be helpful to kids in the future is a dialogue that I think somehow needs to be embraced and policies arise around them.

But I don't think there's any easy way to do it. And until that happens, I think we are probably most squarely in the world of figuring out how to do this with better and proper research methodology.

DR. HOWELL: Any further comments from Joe, Denise? Joe?

DR. BOCCHINI: I was just going to say, for the provisional, that would be something that you would want to use very rarely. I think that that -- one of the things that we did talk about -- and, Ned, you might be able to expand on this -- is that if you make a recommendation in a provisional way and people adopt it, then bringing it back or taking it out because of new data would be something we really don't want to have happen. So you'd have to be pretty certain that you're likely to be correct

before you went forward with something provisional.

And I know ACIP has had some issues with provisional recommendations, and it's now rethinking that term. And maybe rather than provisional, you look at pilot studies or things like that in limited areas to try and get the data that you need rather than go provisional.

DR. HOWELL: I think that's a very good point because stopping something is extremely difficult, unless it was clearly a pilot study, et cetera.

Jeff?

DR. BOTKIN: Well, I appreciate that comment. I guess I'm supportive of some sort of provisional approach, given the fact that if we tend to have either an up or down vote on promising conditions, it seems to me a negative vote can significantly inhibit the development of that test for a number of years. On the other hand, a positive vote may suggest that the data is sufficient for a firm conclusion.

So the question to me is how do you leverage the larger research system to move forward on what you think are promising conditions. And it seems to me, that's sort of provisional, as we did to a certain extent with congenital heart disease to say, very promising, but yet, there's some gaps. So how do we leverage the system to get those gaps filled in a timely way, it seems to me, to be the challenge.

DR. HOWELL: And we'll discuss that further today with SCID because it's the prime example of the fact that there were additional data that we wanted and that was specifically included in our recommendation, et cetera.

Jerry?

DR. VOCKLEY: It might be a moot point because not everything that's submitted to the committee goes to the Evidence Review Group. But we do also want to be careful that we don't, sort of, provide a back door into getting more funding for a condition by getting it to the committee and saying, oh, well, all we have to do is get them to say no buts. And it raises the priority. So that's just a -- like I say, if it gets to the -- we do a preliminary screen, so we probably aren't going to run into that. But it is theoretically possible.

DR. HOWELL: Ned, it seems that there's considerable support for some of the thoughts that came out of your group, and so forth. Did you discuss the mechanism of going forward with those thoughts as far as was it suggested that this go back to our Evidence Group, that we constituted to look at these issues, and come back to the committee with recommendations? Is that what you all were thinking?

DR. CALONGE: Well, that's certainly what I was thinking. I'm hoping Michele is sitting next to you nodding her head.

(Laughter.)

DR. HOWELL: Well, I'm sitting right next to her. And if we need to, I can nod her head.

(Laughter.)

DR. HOWELL: But the bottom line is it would seem prudent, with these very important thoughts, we need to have a mechanism to move forward. And I would think that we would want to communicate this to Dr. Perrin and to his group to see if they can come forward, have some discussions and come forward with specific recommendations about this decision.

Michele?

DR. PERRIN: Dr. Howell, this is Dr. Perrin. If I could just --

DR. HOWELL: Oh, hi, Jim.

DR. PERRIN: If I could just make a quick comment, which is that's exactly what we, and especially Alex Cantor, are thinking of doing, which is developing a manual of procedures relating to how we do evidence reviews, really, much based on the discussion that we had with this committee. And I think we very much look forward to bringing this back to that group of consultants and advisers for their advice on how to make this even stronger. But, you know, we really want to develop fairly clear procedures on how we're going to move forward.

DR. HOWELL: Coleen?

DR. BOYLE: So that addresses, I think, some of the methodologic issues that were brought up, you know, other study designs, natural experiments, the modeling. But it doesn't really -- I mean, the uncertainty part of it -- but it doesn't really address the issue of a committee decision. So how is that going to be brought back to us in terms of the work group?

DR. HOWELL: I would assume that these recommendations would come back to the committee.

DR. BOYLE: From the work group?

DR. HOWELL: Yes, absolutely. That would be my thought. It clearly would be a committee decision. But I would assume that this group would be getting some material together and making recommendations and suggestions to the committee.

DR. CALONGE: So, Rod, this is Ned. Could I interject there for a moment?

DR. HOWELL: Sure.

DR. CALONGE: So I think what Coleen is actually pointing out is that there are a couple of fronts to move forward on. And one is evidence modeling issue and how this fits in. And that's something that's clearly within the purview of Jim Perrin and his group. The issue of other

products of the committee, I think, is actually less the purview of the Evidence Group. Although, if Jim wants to take that on, that's great.

We did have a separate Recommendation Process Committee that actually published the paper and adopted our process, kind of, went away. But traditionally, this would be committee members working more specifically on that process and decision making and going forward.

And, Michele, I don't know if you've thought about this, but, like, reconstituting or thinking about how the committee should consider these other issues that have less to do with evidence review, modeling and presenting information to the committee and more with what the committee does with that information, maybe something we have to think about again.

DR. HOWELL: Okay. I think that there's much head-nodding, which you can't see. I think that that would seem to make a great deal of sense to me and around the table.

Is there any -- so the point is that we will expect to see some material coming back from the Evidence Group. We'll try to get Michele and her team to reassemble this other group to look at some of the way that this committee handles evidence once it comes back.

Is there further discussion?

Thank you very much.

We have Chris.

DR. KUS: Yeah, just, Ned, could you expand? You talked about provisional, and you talked about pilot, the pros and cons of that kind of possibility. I think we talked a little bit about the provisional being hard to stop. But what about pilot? Any more discussion on that?

DR. CALONGE: Well, I think the pilot approach is actually, as you've heard, it's a superior approach. I guess one of the things that you have to implement it. So what we have so far from a pilot standpoint is the fact that there is -- the variability is based in terms of considering adding screening for conditions not on the core status. So even though the intent of the (inaudible) Committee was to try to, you know, get away from that variability from state to state. You know, since there is 50 general assemblies, there is going to be 50 different viewpoints on what should be added to the list.

And figuring out how to, in a structured way, take advantage of early adoption and (inaudible) decision or policy making from a state-to-state basis, I think, will be important. Plus, if we see an area where we think pilots might actually move the decision forward, having a process or a way to try to advise or incite states to implement pilot screening programs in those conditions -- figuring out how to do that with the

different states now available are all considerations, I think, we have to spend some time on. It's what you would expect from a highly functioning, nationwide newborn screening program, which, of course, it's one I believe we all aspire to.

DR. HOWELL: Thank you very much.

We're going to later hear from Dr. Brower about a pilot program which I think has been exemplary and exciting, and so forth. So we'll hear about that later.

But I think that we've had an adequate discussion of this. We're, fortunately, very ahead of the game. But if we look at the things that we have to include later, if we go to one of those, our break is going to be extraordinarily late. And so, what I'm going to ask us to do is to take a very brief break and return here at a quarter of 10. And we'll hear about the evidence review of the bilirubin issue and then proceed ahead.

Thank you very much, Ned and Jim.

(Break.).