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SECRETARY'S ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

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Friday, January 28, 2011

Renaissance Dupont Circle Hotel

1143 New Hampshire Avenue, N.W.

Washington, D.C.

The meeting was convened at 8:31 a.m., R. RODNEY HOWELL, M.D., Chairperson, presiding.

PARTICIPANTS

MEMBERS PRESENT:

RODNEY HOWELL, M.D., Chairperson, presiding
JOSEPH A. BOCCHINI, JR., M.D.
TRACY M. TROTTER, M.D., F.A.A.P.
GERALD VOCKLEY, M.D., Ph.D.

MEMBERS PARTICIPATING ELECTRONICALLY:

JEFFREY BOTKIN, M.D., M.P.H.
REBECCA H. BUCKLEY, M.D.
BRUCE NEDROW CALONGE, M.D., M.P.H.
KWAKU OHENE-FREMPONG, M.D.

PARTICIPANTS (Continued)

EX OFFICIO MEMBERS PRESENT:

COLEEN BOYLE, Ph.D., M.S.
KELLIE B. KELM, Ph.D.
EX OFFICIO MEMBERS PARTICIPATING ELECTRONICALLY:
DENISE DOUGHERTY, Ph.D.
EXECUTIVE SECRETARY:
MICHELE A. LLOYD-PURYEAR, M.D., Ph.D.
ORGANIZATION REPRESENTATIVES PRESENT:
American College of Medical Genetics:
MICHAEL S. WATSON, Ph.D., FACMG
Association of State and Territorial Health Officials:
CHRISTOPHER KUS, M.D., M.P.H.
Child Neurology Society:
BENNETT LAVENSTEIN, M.D.
Department of Defense:
THERESA HART, M.D.
Genetic Alliance:
SHARON F. TERRY, M.A.
March of Dimes:
ALAN R. FLEISCHMAN, M.D.

PARTICIPANTS (Continued)
ORGANIZATION REPRESENTATIVES PARTICIPATING ELECTRONICALLY:
American Academy of Family Physicians:

FREDERICK M. CHEN, M.D., MPH, FAAFP
American Academy of Pediatrics:
TIMOTHY A. GELESKE, M.D., FAAP
American College of Obstetricians and Gynecologists:
WILLIAM A. HOGGE, M.D.
Society for Inherited Metabolic Disorders:
BARBARA K. BURTON, M.D.

P R O C E E D I N G S

(8:31 a.m.)

CHAIRPERSON HOWELL: Ladies and gentlemen, let's do find our seat. We're going to be very, very aggressive on our time frame today because there might be a bit more snow this afternoon. The roads are still not completely open and we've got a lot of people that have flights, and because of the cancellations in the recent days the airports are going to be busy. So we're going to be very, very timely in getting our work done, and we've got a lot of good things to deal with today.

Now, Michele, do you have the list?

DR. LLOYD-PURYEAR: Sure. Jeff Botkin.

DR. BOTKIN: Present.

DR. LLOYD-PURYEAR: Rebecca Buckley.

DR. BUCKLEY: Present.
DR. LLOYD-PURYEAR: Ned Calonge.
(No response.)
Kaf, are you up? Can you talk?
VOICE: Not yet.
DR. LLOYD-PURYEAR: Okay.
Denise Dougherty's on. Alan Guttmacher is ill.
DR. DOUGHERTY: I'm here.
DR. LLOYD-PURYEAR: Yes, I said you were on.
DR. DOUGHERTY: Okay, thanks.
DR. LLOYD-PURYEAR: I said Alan is ill.
Freddy Chen.
DR. CHEN: I'm here.
DR. LLOYD-PURYEAR: Tim Geleske.
(No response.)
Mike Watson's not here. Bill Hogge.
DR. HOGGE: Here. Alan, actually.
DR. LLOYD-PURYEAR: Oh, it's Alan? Oh, okay. William Alan.
I'm just looking at names of people who aren't here. Alan Fleischman's here, Barbara Burton's here. Okay.
CHAIRPERSON HOWELL: Thank you very much.
We had some very active subcommittee and workgroups yesterday, and we're going to start with those

reports. We'll start with Gerry Vockley, who is the Subcommittee on Laboratory Standards and Procedures. Gerry.

SUBCOMMITTEE REPORTS:

SUBCOMMITTEE ON LABORATORY STANDARDS AND PROCEDURES

DR. VOCKLEY: Thank you. I don't understand what the issue with the snow is. I've got my reservations for I-70 already.

CHAIRPERSON HOWELL: That's good.

(Laughter.)

(Slide.)

DR. VOCKLEY: I think we had a meeting last night or yesterday afternoon of the Laboratory Standards and Procedures Subcommittee. I think I wrote what we did on the slides, but I'm not 100 percent sure. We'll find out.

Here are our members, which did not translate well from my Mac to the PC. But we have quite a distinguished and expert group, and it was really one of our more interesting meetings. It had to be to keep me awake.

We heard three presentations: first from Dieter Matern at the Mayo Clinic. We had asked him to present a comparison of some newborn screening technologies looking at lysosomal storage disease, and in true fashion far exceeded our request.

We then had a discussion of in vitro diagnostic

devices, which in the case -- which in our context translates into laboratory-developed tests. We had Dr. Gutierrez from the FDA and Bill Slamek from Perkin Elmer speaking there, our Laboratory of Medicine colleagues updating us on messaging relative to the medical record and newborn screening.

So with the newborn screening initiatives, as I said, we had asked the Mayo lab to update us on a study that they're preparing to do with looking at various technologies available to screen for lysosomal storage diseases. Because of some overlap in the technology, Dr. Matern included some work that they were doing on Wilson disease, x-linked adrenoleukodystrophy and Friedrich's ataxia.

Going through some of the major considerations of what I'll call now non what's become standard metabolite-based screening, there are some issues that raise in that kind of testing, as well as considering the additive effect of adding additional tests to the screen. So for example, if you have one test, even with exceptionally good predictive value and false negative rates, as you add 10, 20, 30, eventually you get up, even with perfectly acceptable and even fabulous laboratory performance, to a range where the level of follow-up becomes a significant drain on the system.

So we have to keep that in mind as we're moving forward and continuing to add to the panel, that it is not

just adding one more test, and if everything else had a low false positive rate and this has a low false positive rate we're not doing anything more to the system. We are. We're stressing it additionally.

This sort of overlaps with the real reason for doing the comparative study, and that is if you don't do the comparative studies and you don't know which test is best, then ultimately you have labs doing different procedures for different kinds of testing, and some may be better than others and it adds to the follow-up load.

However, I will say that, even with a growing menu of tests, the numbers that Dr. Matern presented out of the Minnesota program for their screening results were truly impressive. I mean, they basically were getting positive predictive values where one out of two or one out of three babies or test results were something real, which is quite phenomenal given the number of tests that are going on.

The platform options that they are looking at for their comparative study are antigen-based technologies -- in particular, they're using a Luminex platform -- metabolite-based enzyme assays. So it's looking at a metabolite, but it's the product of an enzyme reaction specifically rather than looking in a non-directed way as we do, for example, with an A-cell carnitine profile. And then a digital

microfluidic-based enzyme assay which she described as being a lab bench on a chip. They were using a system from Advanced Liquid Logic. And then comparing this to whatever the standard traditional enzyme assay was for the field.

(Slide.)

I lifted this directly from his presentation. It was the only -- it's the only real data slide I wanted to share. It's not a data slide; a comparative slide, just to show you some of the key issues related to evaluating the platforms. That is, can you do them in a multiplex fashion, how complex is it for the lab to actually run that test, are the performance metrics suitable to high throughput, and of course, since this test is being done at Mayo or the study was being done at Mayo, he wanted to emphasize that they were in fact all available at Mayo.

So they will be comparing enzyme assays in the context of the lysosomal storage diseases, a fluorometry-based assay that's been the standard in the field, multiplex enzyme assay -- this is the Michael Gelb and Ron Scott technology with mass spec -- Popwood's platform using luminex for LSD enzyme assays, and then this digital microfluidics.

They don't have any results for us yet. It has been a challenge for them to get it up and running. But they now have all the platforms in place, and hopefully in the

coming year we should have some additional -- some first-look data from them.

(Slide.)

The technical challenges that are arising or that will arise out of whatever evaluation they make is that we really have to continue to consider that multitasking is in some way, shape, or form going to be necessary; that because of this issue with the additive effect of increasing numbers of tests, that the consideration of second-tier testing to decrease the false positive rate becomes potentially more important.

There was some discussion about the need for consent, not only for multiple tests, but for test development, and then disease-based standards for both quality control and test development.

(Slide.)

Switching gears and moving to the discussion keyed by Dr. Gutierrez and Mr. Slamek, Dr. Gutierrez first pointed out that laboratory-developed tests fall into the device oversight infrastructure for the FDA, so that's the connection there. In the context of newborn screening, the test is a device. So FDA can look at both safety and efficacy, and they have three levels of oversight that they can bundle things into.

The way they make the decision as to how rigorous to be with that oversight is really tied to the perceived risk. So, interestingly, newborn screening is really viewed as a low-risk procedure in the FDA terminology, not because of anything to do with the technology itself, but the fact that there are such elaborate follow-up mechanisms in place to deal with any information that comes out of the testing.

In that regard, he graciously acknowledged the work of this committee as evidence that the FDA could cite to say this is in fact low risk. people are watching this very carefully.

(Slide.)

One of the other pieces that came out of the discussion was that this next generation of testing that we're talking about is really the interpretation -- that's the wrong word because that's got a formal definition in the sort of testing world, but the ability to understand and parse out the key pieces of data from this testing becomes much more an issue than the actual test itself.

The example that came out was whole exome sequencing. The technology is there. You can get the whole exome sequencing on an individual. We pulled up on line, Dr. Howell pulled up on line, an ad to do it for a thousand bucks.

Interpreting that is way beyond our capacity right now, and certainly in the screening mode it's not even close. But that really is going to become an issue of how to handle the data almost more than what the tests or technology is.

Then ultimately it was recognized that, as with most things, there are significant gaps in what we know and what we can do relative to rare diseases. But rare diseases are driving the field in a lot of ways with this group of technologies.

So that was a very interesting discussion, and Sara and I, Dr. Copeland and I, are going to be putting together a short -- some sort of short statement that we can just send on to the FDA encouraging them to consider, continue to consider, the ramifications of this kind of testing relative to rare disease. Sara, I'm going to count on you because I just don't remember very much about what came out of that, what we said we were going to do. But that's okay.

(Slide.)

I think I covered most of this: low-risk -- yes, so I said all that off the previous slide.

(Slide.)

So the last slide is just a quick update from Clem McDonald's working group that talked about messaging relative

to newborn screening. We were informed that HLS7 messaging is in fact in final stages of testing in Kentucky and is scheduled to go live within the next month or two, and that they're making significant progress in a variety of other states; that based on the latest NLM review, that the HLS7 messaging in fact fully complies with the guidance that has come out for that. So they've really made quite nice progress.

They continue to look at proposals for how the reports -- what needs to -- what information needs to be transferred relative to newborn screening and LOINC nomenclature. There was a little bit of discussion in particular about the hemoglobinopathies. So they are making good progress and I don't think there is much else that -- anything really new that the subcommittee needs to comment on about that.

(Slide.)

This is the final slide. LOINC codes now available for SCID, lysosomal storage diseases, and they're looking into the additional or defining the additional card variables that need to be captured. These are the fields that they now have available: the date of the last transfusion, whether or not the patient was on a specialized formula, whether or not the parents refused for some piece of

the testing, the birth hospital, and post-discharge provider and practice information.

So that is it.

CHAIRPERSON HOWELL: Sara, you had a comment?

DR. COPELAND: Yes. I just thought it was really important to note that Piero -- Dieter Matern's project is funded by NICHD through the Newborn Screening Saves Lives Act legislation. So it's a contract to Mayo to develop new newborn screening technologies, etcetera. I thought that was an important point to make sure we got.

CHAIRPERSON HOWELL: I think that it is going to be extremely valuable to see the head-to-head comparisons of these technologies all run in the same place, because that will be I think extremely informative.

Are there any other questions or comments of Gerry or Sara about this meeting?

(No response.)

So we'll expect to see a document that you're coming up with, that should be sent to the FDA about the level of risk in the newborn screening arena. Okay, great.

We're going to now hear from Tracy Trotter from the Subcommittee on Education and Training.

SUBCOMMITTEE ON EDUCATION AND TRAINING

DR. TROTTER: Thank you. First I would like to thank and send good thoughts to my co-chair, Jana Monaco, who could not be here today because her son is at National Children's having a surgical procedure done and she needs to be with him. And this was her last meeting. But we think of you, Jana.

(Slide.)

I want to thank everyone from yesterday. We had a packed-house meeting and a packed agenda that took all of our time and then some. I think we -- I think a lot of things are moving forward that are exciting. Here are the people who are formally on the subcommittee at this time.

(Slide.)

So our first report was from Natasha regarding the newborn screening clearinghouse, where things -- for those of you who know how Natasha and Sharon do things, things move fast around there, and they are. The beta web site is now active with the URL as shown, nbsclearinghouse.org. We'll talk a little bit about what that might be different fairly soon.

There's a user guide available both in a pdf and web page. Condition-specific information is now available in

a number of different ways. There are blog posts going on from each of the regional collaboratives. The concept of a name for the web site I think has now come down to be "Baby's First Test," which had been talked about before. They have put out an RFP for web site development, babyfirsttest.org, and received 11 proposals from some very significantly impressive firms who have done things like this in the past.

Internal review brought that to three proposals, and the final decision, if you get caught in the snowstorm you'll hear about it because it's going to be next week. It will be right here.

(Slide.)

They also announced the first newborn screening clearinghouse challenge awards. These awards are to engage the community and to bridge the clearinghouse with existing programs, what's out there in terms of outreach, engagement, educational efforts, and how can they use those more efficiently. The RFP was available yesterday and is due on March 1st. The projects are approximately six-ish months in nature, and there is up to, not guaranteed to but up to, $25,000 per project.

So it's an exciting kickoff that will, they hope, impact between four and eight groups that will be awarded those grants.

(Slide.)

We had then presentations from a number of our members who are -- I'm happy to say we have at least eight or nine members of our subcommittee who are working on very significant and exciting projects that they brought to us, just so we are up to date on what they're doing. Emily Edelman from NCHPEG updated us on the family history for prenatal providers program. That's a tablet-based history program. We were as a group very excited about it. It is clearly for most of us in clinical medicine the kind of thing that we need to have happen if things are going to go forward and allow us to deal with large amounts of data and getting more information from people efficiently and using it efficiently.

That project's going very quickly now and we will have some information probably in the spring about their first testing; we understand a demonstration in May at our meeting.

(Slide.)

I'll come back to the Genetics Primary Care Institute later. Brad Thompson joined us, who is the father of a 21-year-old daughter who has special health care needs, who updated us on something called the Hali Project. Hali is his daughter. The project is very interesting and unique and

we were all very excited to hear him describe.

Basically, he trains or his group trains parents to be ombudsmen, if you will, for children with special health care needs and work in primary care offices, literally spend a half a day in a pediatrician's office or other primary care, interfacing with the families of children with special health care needs and helping them with basically all the non-medical issues, but issues that need for them to get things done -- organizing follow-up appointments with subspecialists, understanding how the system works, knowing what community resources there are, dealing with many of the emotional needs and expectations of families.

This is something worth your attention if you have an opportunity to learn more about this. I believe it's thehaliproject.org?

VOICE: dot-org.

DR. TROTTER: Thank you, dot-org.

We were all taken very much by this.

Natasha also gave us a quick update on the HIT work group and the congenital conditions program, one of which you're going to hear more about from elsewhere.

Then we went back to our roots of what we're supposed to be doing. It says that, according to S. 1858, that we shall give information and advice in dealing with

public and provider awareness and education. As I'm sure you all remember vividly from my last presentation, but I will not quiz you about it, our subcommittee brought forward a proposal, a rough proposal, that Coleen Boyle I believe was the genesis of, that this may be a good time, an appropriate time for a national newborn screening awareness campaign.

Those of us that have been involved in newborn screening, or in my case actually I'm just a person who ends up utilizing it -- I'm the end user of it -- have had probably one of the, if not the, most successful public health programs ever in the United States, going along under the radar, without sort of very much information one way or the other, which has been fine until now.

Now, in the era of 97 channels available to you and they all need to talk about something, positive information needs to I think lead this forward. A more well informed public makes better decisions, and this was felt to be a good time to approach this project, much like autism was approached with a CDC project recently, much like the folic acid project from the March of Dimes.

So we asked Angela Colson, who is in the CDC Communications Group, to put together a proposal, which should be passed out to committee members at this point. It really talked about a four-phase, professionally run national

awareness program. I'm going to talk a little bit about phase one this morning because our request to the committee is that you agree that this is something that we should -- the committee should go forward with, and if so Dr. Howell will decide how that's going to happen.

(Slide.)

So phase one would be called planning and strategy development, which has two phases. One is, which you see on the slide, a media environmental scan, which is really just saying what's out there, who are the stakeholders, what are they doing in this area. Lots of things are being done, as you all well know, and many of you are doing them. They maybe not always in a coordinated fashion and maybe we could be stronger by doing it together and being more consistent.

To understand what the current message is, both good and bad, and to identify information gaps.

Maybe one of the most important things is to define specific audiences. As a number of people who have been through these kinds of campaigns mentioned to us, you actually cannot be everything to everyone, and to do so you probably lose what you're after.

The second part of phase one would be a facilitated strategy summit. "Facilitated" I think is defined as having somebody who doesn't have a dog in the

fight trying to control the rest of us. That summit would review the analysis, solidify the goals that hopefully came out of the environmental scan, and more specifically define priorities and target audiences.

To round it out, the second phase would be developing and pretesting. The third phase would be implementing and the fourth page and critical phase we think is assessing effectiveness and making refinements. Almost every project that goes well needs tweaking down the line, and if one doesn't think of that ahead of time it's not going to work.

(Slide.)

So our recommendation to the committee as a whole is that we move forward with such an awareness campaign, and that these four components be part of that. We broke these out above and beyond what we've already talked about because we felt they were important linchpins to it.

One is to identify, somewhere in phase one, identify a very specific audience group so that we drive the strategy of what we do and how we do it. Two is to clarify a message that we thought initially needs to be broad and simple. Too much information tends to make people's ears not work. Have both qualitative and quantitative objective outcome measurements in place from the beginning, so that we

can in fact tweak these things as time goes on, and have a realistic outline of phases two through four with budget numbers. People do need to know what we're getting into, of what the results might be at the end of phase one, that we are not going to get into, I realize that, but I think we do need to at least have a clean view of what we're up to.

(Slide.)

I'll come back to that at the end to ask for your vote on that.

The last area was something that's been in the works for a while, as you all know. This also comes from our mandate, which is to raise the number of primary care providers who are competent and confident in providing basic information. The Genetics and Primary Care Training Institute -- the RFP, if you haven't finished it you really shouldn't be here today because it's due the 31st. The proposals will be reviewed in March and I hope that at our May meeting we'll have an initial startup report from whatever group has taken this on.

So at this point, I guess I would like to make a motion that we move forward to a phase one evaluation of a newborn, national newborn screening awareness program under the auspice of the Secretary's Advisory Committee.

CHAIRPERSON HOWELL: Tracy has made a

recommendation. Can we have a second to the recommendation?

DR. BOCCHINI: Second.

CHAIRPERSON HOWELL: Joe has seconded it. Let's entertain some discussion. One is, I would like you to spend a little bit of time describing in a little more detail what's in the phase one that we're getting ready to vote on, exactly what that would entail, with some numbers.

DR. TROTTER: What kind of numbers would you like, Rod?

CHAIRPERSON HOWELL: Well, I've got some numbers here. Are those the numbers you're talking about?

DR. TROTTER: Oh, you mean dollars?

CHAIRPERSON HOWELL: Yes. Are there other numbers?

DR. TROTTER: Not important ones.

So everybody has one of these handouts except me, actually. Gerry, let me have your handout.

CHAIRPERSON HOWELL: One is coming quickly.

DR. TROTTER: So we'll start with the numbers. The estimation from -- I think this comes from Angie and Coleen's work on previous projects at CDC, is that correct? Yes. $65,000 to complete phase one. We have no, nor do I have any capacity to give you, numbers for two, three, and four, but I think professional communication groups, this is

a pretty -- as I understand, a pretty straightforward program in terms of how they would do it, so we should be able to find that.

CHAIRPERSON HOWELL: So the phase one that we're talking about would be to select the contractor and do the environmental -- that person would do the environmental and media scan, the stakeholder assessment.

DR. TROTTER: Correct.

CHAIRPERSON HOWELL: And conduct a partner strategy summit, and then submit a report of outcomes for the 24th meeting of this committee. Is that correct?

DR. TROTTER: That would be our goal.

CHAIRPERSON HOWELL: Are there further comments or discussions about this? Coleen, you've given a lot of thought to this and apparently have participated in some of the background.

DR. BOYLE: I guess I would ask -- would you like to say, because you worked with Angie on the development of this.

DR. TROTTER: I forgot to, and I apologize, to thank the planning group that was appointed by Rod and Michele between our last meeting and now, who helped us work on this and focus on getting this ready for our meeting today, with some conference calls. It was very, very

helpful, with people, obviously, from outside the committee who had had experience in this. That's made a big difference in how we approached it.

MS. HARRIS: I will just echo what Dr. Trotter was saying. Then the other thing that we got from Angie was just pulling together this contractor that's doing the overall environmental scan and really getting a clear picture of what's out there, I think the important thing being the person without a dog in the fight, if you will, that can give us a clear picture.

Coleen, what else did you want to touch on?

DR. BOYLE: Well, I haven't been working with the committee, so I'm at a little bit of a distance in reviewing the proposal. But I guess I'll just react based on coming to a couple of these committee briefings planning strategies. Obviously, Tracy has done a wonderful job telling us about all of the activities that are currently ongoing, and obviously there's a long history in terms of education and communication on newborn screening.

So I think the rationale behind the first phase of this is to really get a good sense of that and not to sort of reinvent the wheel, as you were saying, as well as bring all the stakeholders together, so that information is consolidated, refined, and that provides us with the

appropriate platform for trying to move forward in terms of communication, to really understand what the needs are and how those resonate with the community.

So I think this is the baseline to set the stage for phase two, three, and four, and also maybe get a better sense of what's our likelihood of succeeding, and this is really the right way to go. So those are all the questions that would be answered through this process.

DR. TROTTER: I should mention that one of our speakers today, presentations today, regarding parental attitudes on newborn screening, if you look at that data you'll see what we're talking about in terms of missing, we're missing some targets that we should be hitting. We've realized, at least I have in the last three years as chair of this committee, that there are really a wonderful amount of really good things happening out there with a lot of groups. We just don't quite have a consistent way to put that together, and this might be the way to do that.

CHAIRPERSON HOWELL: Are there further questions or comments? Sharon.

MS. TERRY: I really appreciate this and think it's time. I think we're going to have to be really careful on the choice of a contractor because of the complexity of the landscape they're scanning. There are certainly very

vocal voices and we experienced some of those in Utah a couple days ago when we were there for a blood spot meeting.

There's also, though, the stuff like what will come out in Dave's data, that is different than that data. So there's almost a two-pronged kind of sensibility, because one is very important. The vocal people are able to do great damage and in the meanwhile the uneducated public is who we know they are to be.

The other part I'd say is I think if we do get to phase two, three, and four, I think in general government and nonprofits do a poor job compared to commercial entities, obviously, for advertising and for doing "Got Milk" campaigns and that kind of thing. So I think again we're going to have to be very hard-nosed about what we decide to do, how we decide to do it, and also how focused that's going to have to be to be real and not just another nice kind of small program.

I even fault Genetic Alliance as bad at distribution because it's very, very expensive. Marketing is expensive. Probably the one exception would be March of Dimes and some of their campaigns because they are well-known and very widely assimilated or consumed, and so we probably want to make sure that we pay attention to some of the things that March of Dimes has done.

CHAIRPERSON HOWELL: Chris.

DR. KUS: Tracy, is the contractor looking at a one-time campaign or has your group talked about or will the contractor deal with the issue that this would be an ongoing effort because people age and there's going to be a new group?

DR. TROTTER: The discussion of sustainability came up both this time and last time. So it's one of the questions that needs to be answered, is what would -- once we have identified things, if phase one goes well we're going to have, I think, the information in front of us that allows us to give a real answer to that. I think it probably has to be sustainable to be worthwhile. But there may be ways to do that that are not clear to me right now.

CHAIRPERSON HOWELL: Alan, you had a comment?

DR. FLEISCHMAN: Yes. I would agree with Sharon's perception here. This is a big bite, but I think $65,000 is a small amount of money in order to create the strategy. And then we get the chance to see whether that makes sense, as Coleen is saying.

I'm pleased that the senior vice president for communications and marketing at the March of Dimes, who was responsible for the folic acid campaign and is responsible for the prematurity campaign, has volunteered to be on this

committee. He has a tremendous knowledge base about some of the effective aspects of this.

CHAIRPERSON HOWELL: Coleen.

DR. BOYLE: That's wonderful news, Alan.

I wanted to respond back to Chris, and I think we had this discussion before. The more I think about it, I think the more appropriate -- and again, I think the environmental scan in phase two is very, very necessary, because some of what I feel like I'm thinking sometimes is folklore.

But if we think back to the work that we've done in autism, seven, eight years ago -- and I think I said this to the committee before -- I think parents and providers' expectations around child development, very early child development, was really focused on growth milestones. I think through the efforts, the combined efforts of our group, others working in this area, private providers, advocacy groups, we've been able to change that, that culture and that expectation, so now parents are much more receptive, much more focused on social and emotional development of children, and so are providers.

Similarly, I think that's where we want to -- this is my feeling. We want to move parents to expect this, and it's not a feared package, some unknown. To me, that's what

a campaign does. Its message changes as that assimilation advances.

DR. TROTTER: That's sort of why the consensus was we start with a broad positive, simple statement that creates an expectation that this is a fabulously good program for your child and it's going to happen. Then the nuances could come in terms of drilling down to further information.

CHAIRPERSON HOWELL: Is there further discussion?

(No response.)

I've heard nothing except positive support for this and some suggestions that would enrich the program. We've had a motion and a second. Those favoring the motion, please raise your hand.

(A show of hands.)

On the telephone, those favoring?

VOICE: Aye.

VOICE: Aye.

DR. FREMPONG: Can you hear me on Skype?

MS. HARRIS: Dr. Frempong, we can hear you.

CHAIRPERSON HOWELL: Barely, but we heard you.

DR. FREMPONG: Aye.

CHAIRPERSON HOWELL: Any nays?

(No response.)

Is there a nay on the phone?

(No response.)

Unanimous. So we'll proceed with that, and our esteemed treasurer to my right says that there is money in the till to do that.

You had other -- did you have anything else?

(Slide.)

DR. TROTTER: No. Otis says thank you.

CHAIRPERSON HOWELL: Thank you very much.

We now are going to go to Coleen's committee, which is the Subcommittee on Follow-Up and Treatment, and it's Coleen and Jeffrey Botkin. I assume that Coleen is going to present and Jeff is in the background to comment.

SUBCOMMITTEE ON FOLLOW-UP AND TREATMENT

DR. BOYLE: Well, good morning, everyone, and thank you. Jeff, hopefully you're on the line as well?

DR. BOTKIN: I am here, thanks.

DR. BOYLE: Wonderful. It would be lovely to have you in person, but I know the challenges.

(Slide.)

As the other subcommittees reported, we also had I think a very productive meeting yesterday, a very thoughtful and productive meeting. Thank you all of you who

participated, those on line as well as those in person.

(Slide.)

I just outline for you in this slide here sort of the three topic areas that we -- the first two of which we got updates on, and then the third, which we spent the majority of our discussion on. I'll similarly focus mostly on that.

So, briefly, for the medical foods, you know this has been a longstanding effort of our subcommittee. We've had numerous letters to the Secretary about the urgency of the issue and regarding insurance coverage for medical foods. We know that with the Affordable Care Act there is an opportunity and a need to reinforce that message, and I know that that's continuing to happen. Thanks to the work of this committee and subcommittee for that.

We did get legislative updates from Christine Brown and we heard that Senator Kerry is going to re-introduce the bill that was introduced in the last Congress, so we're encouraged by that issue as well.

We know that -- you all know that we've been doing a survey with four -- excuse me -- three of the regional collaboratives to get a better sense of the impact of medical foods on families.

Sue Berry, who's still here, hopefully -- there

she is, way in the back; I see the hands -- gave us an update. Apparently there is a draft manuscript that we had a brief discussion about. We're going to be seeing that draft hopefully in the subcommittee soon. It's right now with the regional collaboratives for their input.

We did have a brief discussion about whether or not that manuscript would come out as committee work or actually just we would end up focusing more on putting it out as a manuscript as part of the regional collaborative effort, and we probably lean more towards the latter than the former.

You know that probably a year ago we, the subcommittee, took on the issue or spent a subcommittee session to look at short-term follow-up issues, and from that discussion we were trying to see whether or not there were any sort of no-brainer issues that we felt should be addressed in regard to trying to firm up the short-term follow-up for newborn screening. The one that we highlighted was the ability to link newborn screening results with vital records in real time, so that we would be able to close that loop and provide more assurance from a public health perspective that newborn screening was occurring.

Brad Therrell, I was very grateful, took on this issue and developed a white paper that I believe the committee saw maybe last time. Did we ever bring it to the

committee, Brad's white paper?

DR. LLOYD-PURYEAR: What?

DR. BOYLE: Brad's white paper.

DR. LLOYD-PURYEAR: No.

DR. BOYLE: No. So we never got it here yet.

So there are a number of recommendations in the white paper, but one of the recommendations is to include on the birth certificate vital records form or electronic form a field for a newborn screening number. We're still working out the details of that. We want to make sure that we have all of the principal players, both NAPHSIS and NCHS, on board with that recommendation and really receptive to helping the committee move that forward.

The leadership of NAPHSIS has changed hands as of the end of December. The prior leadership was supportive of the idea. So we're going to revisit that once the new leadership is in place. Also, we've had some preliminary conversations with NCHS as well, and the message back to the subcommittee was that it's really in the states' purview to make this happen.

Sort of anecdotally, I don't know if Brad is still here. He mentioned that one state -- there's Brad back there -- one state -- do you remember what great state it was, Brad?

DR. THERRELL: Wisconsin.

DR. BOYLE: Wisconsin, the great state of Wisconsin, which I know is represented here, actually has already included the field, anticipating the guidance from the committee, has already included the field within their vital records electronic information. So that's encouraging, and that's really what we want to see happen.

So hopefully next time in May we'll be able to report back to you.

(Slide.)

So the last issue, which is again the issue we spent the most time on, and I think it was a wonderful discussion, this was brought up primarily because of the vote by the committee last session and some of the concern that I heard expressed around the table and by others, obviously after the vote by the committee to include critical congenital heart disease as part of the recommended panel.

That was sort of the -- the fact that this represented a really different paradigm relative to newborn blood spot screening and how the system currently works in terms of the public health assurance and short-term and follow-up -- excuse me -- short-term and long-term follow-up aspects of newborn screening.

I know Jane several times, yesterday as well as

last time, asked the question of whether or not this really needed to be within the mandated -- recommended; I know it's not mandated -- recommended screening panel or whether or not this is really sort of the professional recommendations and really should be viewed outside that recommended newborn screening panel. So we had a very nice discussion.

Over the last months since our last meeting in September, Jeff Botkin, Alex Kemper, and Michele and I and a few others were trying to actually put, and we came up with a series of questions, that we thought needed to be addressed in trying to understand sort of the juxtaposition between blood spot screening and hearing screening, which is obviously an issue that's been going on for quite some time, and some of these new conditions that are coming before the committee.

So in our introduction yesterday Michele gave us an overview of some of the perspectives that came out from the meeting held two weeks ago for critical congenital heart disease. I think you're going to hear a little bit more about that from somebody later, maybe next after me, so I won't talk too much more about that.

Then we had Sylvia Au, who presented not just her thoughts, but she told us that basically she was giving voice

to a lot of concerns within the state health department -- I see some heads shaking back there -- but sort of the state health perspective. So she walked us through some of the challenges in terms of the administration of this, the impact that these conditions would have in terms of the administration, of policy, and the financing.

We heard very loud and clear from her that states, as we all know, states are very strapped right now in terms of their ability to be able to manage what's already in their purview, particularly with the addition of SCID, challenges with CF, challenges that remain with Eddi, and that to make some of these conditions successful within the public health mandate and purview that it really did take additional resources to make that happen.

(Slide.)

So I'm going to walk through fairly quickly some of the ideas that we tossed around. I don't want to say that this represents all of the ideas because I think it was really a very good discussion. But I do want to say that where I was trying to get the discussion was to think within the context of this committee and what this committee needs in order to help move this issue forward. So that was really where I was trying to get our subcommittee to move yesterday.

So just very briefly, as I already summarized,

this is really a new paradigm in many ways and it's how we interface professional standards with public health programs, and does that interface change depending on the condition and the attributes of that condition. So that's really the crux of the question and that's I think what we're going to try to dive a little deeper on and give some more thought to.

We know, and I think Chris Kus mentioned this yesterday -- he held up his copy, his very little copy, of "Bright Futures."

DR. KUS: Cliff's Notes, that's the Cliff's Notes.

DR. BOYLE: Cliff's Notes, the Cliff's Notes of it, my style, of "Bright Futures."

There are many professional guidelines for systematic care of children within the context of well child care. So how did the conditions that are coming before the committee -- the one we heard about yesterday, hyperbilirubinemia; critical congenital heart disease -- how do they differ from other universal practices that are recommended for good well child care, including developmental screening -- we know that within the context of autism and other developmental disabilities -- vision screening, and there's a whole host of I would consider them professional mandates.

There is a need, with these new conditions, I

think, to think about clarity around who's responsible for what. So the roles, responsibilities, resources, and I guess the liability would be the other one I left off of here, that are required, and I put "for non-traditional newborn screening," meaning non-blood spot-related newborn screening; and how these may vary from condition to condition. I don't think we just have category A and category B. It really might be much more fluid than that.

There's I think a real diverse opinion about the roles and responsibilities for public health. Many felt that there really might be a very limited role, limited in terms of perhaps liaison and education around these issues, about surveillance and evaluation. Then others I think felt that public health might have a greater responsibility in terms of tracking and assuring the short-term and long-term follow-up, and that this may vary from state to state in terms of how states roll this out.

(Slide.)

Other issues was the issue of incorporating recommended screening panel -- and I think Bob Bowman brought this up to us, and how she read to us the state mandates for Indiana, which sort of took my breath away. So that once a condition is included in the newborn screening panel, there the state is beholden to do many services. Bob can share

with you what is required there.

I think that as a committee, I think we need to think very carefully about the implications of what this recommended panel means in terms of perhaps its translation to state health departments.

We also heard that there needed to be clarity of definitions. We've been starting to call this point of service screening and perhaps that doesn't necessarily capture what we're talking about well, and before we sort of put that into stone or carve it into stone I think we need to think through carefully what we're talking about in the context.

Michele brought up the fact that the committee is charged not just with newborn screening, but really screening during childhood, and how does that fit within this context. So again that's another issue to think about.

I think I already said that: Perhaps there's no one right way. That's what we heard, and it really depends on the states, the condition, and other factors.

(Slide.)

So, getting back to what's the implication of all this for the committee, that's really what we're trying to address here. Obviously, there's many, many questions. Some of these will be discussed at a state level, some of them

will be discussed outside of this room because they're really not the sort of purview of this committee. But I think what we were trying to get to yesterday was how our subcommittee perhaps can be most helpful to the full committee in terms of wrestling with some of these issues.

Marie Mann actually suggested -- I don't know if Marie is here; I'm having a hard time seeing anybody, but Marie's pretty short. So hi, Marie. Marie suggested that we perhaps revisit the ACMG, the 2005, '06 report -- I don't remember when it was published, but there were a number -- the criteria for newborn screening were revised per that report, and perhaps we should go back to that and see how those criteria resonate with the conditions that the committee is currently considering and how perhaps they might be revised.

Jeff Botkin suggested that perhaps -- Jeff, I hope I don't plagiarize what your suggestion was -- that perhaps we think about a two or multitiered sort of recommendation coming from this panel: one that, again depending on these criteria -- for example, if we think of the criteria perhaps around traditional blood spot screening and critical congenital heart disease, and perhaps hyperbilirubinemia as well, there is the issue of urgency and equity, and there may be other criteria actually that fit within that framework as

well.

But that's really where the whole public health assurance and responsibility falls. Maybe some of the other conditions that we might be considering perhaps don't fall within that context, so maybe we can be thinking at the committee level of multiple, I don't know, tiers of recommendations, and that, depending on where that recommendation falls, that might give a better sense of defining the roles and responsibilities.

So I'm trying not to make this too complicated, but that was sort of the general thought from, at least the conclusion from yesterday's discussion, and I hope I'm communicating it well. Jeff and others, you can come behind me.

So anyway, thankfully -- and again, this is just at the beginning of our work here, but I think we did really move the bar. We moved along quickly yesterday. I was actually very pleased with it. But Nancy Green and Marie Mann actually took the leadership, in a little bit of an arm-twisting way, to actually try to take some of those thoughts and start to put them in -- they originally framed it as a matrix, but it's a little bit more linear right now, but it may actually evolve into thinking through a matrix.

I'm not going to spend a lot of time on this, but

I just want to let you know sort of where we're going with this. So Nancy very bravely spent part of her night last night trying to put this, to give some thought to the attributes of point of care. I think this is just the newborn screening piece of it, versus just child screening piece of it.

We don't need to read this, but I do want to tell you that this is where the subcommittee is heading and to think through both the attributes of this as well as thinking about some of -- in going back to the ACMG report, thinking about what the key attributes in terms of the condition, the screening test, the diagnostic test and process, the system attributes, which are not listed here, and perhaps other things as well that might again help the committee make recommendations about perhaps where a condition falls and again whether we have this discussion about a tiered recommendation approach.

So that's it. So, Jeff or others that were engaged in the conversation, do you want to add anything to that?

DR. BOTKIN: This is Jeff. No, I think that was an excellent summary, and I think that we've made enough progress here that I'm quite hopeful that we'll be able to provide the committee with some guided points for further

discussion about this. So I was very pleased with the discussion yesterday.

DR. BOYLE: Thanks, Jeff. I think where we're trying to get to is to have a session in May, at the May meeting, where we are able to have more of an informed discussion and bring in perhaps some thoughtful speakers to this. Perhaps our subcommittee can report back on our thoughts on it and maybe have more of an interactive discussion about this issue among the committee members.

CHAIRPERSON HOWELL: Are there any other comments?

DR. BOYLE: There are several in the back.

DR. THERRELL: Can I make a clarification to the part about Wisconsin? There are actually about eight or ten states that already require the serial number on their birth certificate, three or four of which make it a mandated field. Wisconsin -- the comment about Wisconsin was it was started in Wisconsin this year without the knowledge of the program. So states are moving forward with that.

CHAIRPERSON HOWELL: Nancy, you had a comment?

DR. GREEN: I did, thank you.

Thank you, Coleen. That was really very well described. The point that I want to make may already have been discussed in depth at the congenital heart disease meeting and so maybe we'll hear about that. But as we think

about point of care testing, I think the obvious question to raise is whether we should have a formal representation on this committee from the American Hospital Association and-or additional relevant hospital-associated agencies.

CHAIRPERSON HOWELL: Could you bring -- could you discuss a bit some of the discussion that surrounded the difference between universal practices and newborn screening? You obviously spent a good bit of time discussing universal practice as opposed to a mandated newborn screening procedure.

DR. BOYLE: Well, I'm going to ask Chris and others around the table to help me with this. But obviously there are professional guidelines. There are -- and I think "Bright Futures" is probably the best example of that -- that describe, you physicians here, describe well child care and the appropriate screens that should occur for every child.

The one I guess I know the best is the ones I worked on, which is the ones on autism. There are very firm recommendations about developmental screening and autism-specific screening.

So how do we balance -- how does that differ from -- they would say there's an urgency there, that if we miss children there's a critical developmental milestone. If we miss children in that, we may in fact have poor outcomes in

those children, similar to the rationale we have for Eddi screening.

So I guess we were trying to balance that versus when we think about critical congenital heart disease, where -- you were at the meeting. With that paradigm, there's obviously a very short time window, and the severity of the issues that we're talking about are perhaps death. Again, these are some of the issues maybe that we need to be thinking about. But we were trying to think about how some of the conditions that might come up to this committee, how their attributes might differ in terms of trying to decide which one really falls more within the clinical care lane and responsibility versus what's the role of public health and when is there a heavier hand perhaps for public health versus the clinical world.

Others around that issue? Chris, Joe?

CHAIRPERSON HOWELL: Chris, would you comment? I think that as we move along this might become an increasing issue.

DR. BOYLE: Right.

CHAIRPERSON HOWELL: Is this really a clinical practice issue that should go to the professional or the hospital group, or is this a newborn screening issue? I think that might --

DR. BOYLE: Or, as Michele keeps telling us, a child screening issue.

DR. LLOYD-PURYEAR: Don't take "children" off.

CHAIRPERSON HOWELL: I'm not taking "children" off. "Children" will stay. In my head at the current time, we're thinking about hyperbilirubinemia, and one may say, well, goodness, this really shouldn't be a practice issue and how does it fall in the newborn screening issues.

Chris?

DR. KUS: I think Coleen did a great job of synthesizing the discussion that we had yesterday. I thought that was excellent. I think actually the best way that I was trying to look at it is, if you look at the conditions that we're looking at right now, you look at the screening for critical care, for critical heart disease -- rare condition, life-threatening -- and then you look at the screening for hyperbilirubinemia, which is in a way in the pediatric realm -- I started to think, who wouldn't come up with a specific recommendation for critical heart disease screening, because that wouldn't be something the Academy of Pediatrics usually would do.

So I guess we got into the issue of rare conditions, just kind of the way we've gone. Even when we talk about the ACMG and looking at their things, that was

within the lens of blood spot screening. So I think we just laid out that probably this discussion is going to come out as we review, I think, hyperbilirubinemia, and this group might be able to help people clarify definitions, things to think about.

It really talks about the way of, the relationship between public health per se and clinical practice. I just think it expands. So I don't have a real answer other than that.

CHAIRPERSON HOWELL: It sounds like you had an extremely productive meeting yesterday.

DR. BOYLE: There's two people in the back.

CHAIRPERSON HOWELL: I see, Ann has a comment.

DR. ZUCKERMAN: Thank you. I also want to agree that it was a great summary.

With respect to your last question, Dr. Howell, one of the things that we discussed was not only taking into consideration the condition, but what the state does with the recommendation for the condition. That is that once a state decides to mandate a screen, that that changes the picture as to whether or not the state then holds the responsibility for follow-up on quality assurance. So there is that aspect.

Then there is the more voluntary aspect of whether or not, even if the recommendation is not mandated by the

state and if the recommendation is to follow professional clinical care guidelines, that there might be an advantage to use of the state data systems for maintaining quality assurance. That whole boundary I think is a moving target when it becomes a voluntary aspect.

CHAIRPERSON HOWELL: Thank you, Ann.

I think I see Marie, if you can pull the microphone down for Marie there.

DR. MANN: I just want to agree with everyone. I think that was a wonderful summary. It was a very -- there were so many ideas being flown around that I think it's amazing that the summary is so succinct.

But I think what will need to be done at the May meeting is really what everybody has talked about, is defining -- it's that interface between public health and clinical practice, helping to define gross responsibility and then ultimately resources. I think that's going to be our charge, to really outline that.

That's why Nancy and I started, when we were thinking about matrixes, trying to begin that process. But certainly we would appreciate everyone's participation and thoughts in helping us down that road.

DR. GREEN: Can I say one thing? Thank you very much, both Ann and Marie, but I want to make one point to Ann

because I think what she brought up is critical here. Again, I keep trying to bring everything back to the committee's thinking. Obviously, if we have a recommended panel, those of you who are working in states and state health departments, you know that there is pressure. There is pressure and guidance from groups like the March of Dimes and others to have states embrace this recommended panel.

I think that, even though Ann suggested that perhaps a state doesn't include that within their recommended panel, I think there's just such pressure to move these conditions on. So I think that the committee in some ways has to help states, and that's why we were thinking about this tiered system in terms of trying to manage these conditions.

CHAIRPERSON HOWELL: Michele wants to read something for us.

DR. LLOYD-PURYEAR: I also want to -- there's a context also for all of the committee's recommendations that are framed by the Department's regulations for the prevention guidelines for the Affordable Health Care Act. I think the committee needs to be cognizant of the implications of anything it puts on the recommended uniform screening panel.

So I'm reading this. This is from the regulations that were created: "The comprehensive guidelines that are

illustrated in the uniform panel of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children went into effect May 21, 2010. Plans and issuers are required to provide coverage without cost-sharing for these services in the first plan year in the individual market policy year that begins on or after May 21, 2011."

So anything that goes into what's called the recommended uniform screening panel has implications not only for states, but also for payers. So I think the committee needs to be very thoughtful about what it puts there and what it may recommend in another context.

DR. BOYLE: One last thing I forgot to mention, that Bob Bowman and Alan wanted to make a short recommendation as part of our subcommittee. So, Alan.

DR. ZUCKERMAN: Again, most of the work of the HIT workgroup is now embedded within the other subcommittees. You already heard about the lab messaging, the vital records linkage, and tablets for family history. But there are areas of comments on emerging regulations and activities outside of this committee. In the past this committee commented on the stage one meaningful use recommendations, and the HIT Policy Committee has just come out with a request for comments on stage two, meaningful use, that will be due on February 25th. Our workgroup is putting together, drafting some comments

we'd like to circulate by email a week from now, to see if the committee wants to submit these on the stage two meaningful use.

In addition, we're trying to look, in anticipation of stage three, at the new types of evidence-based that's being required to add objectives to meaningful use so we can try to pursue these in the area of newborn screening and, rather than just try to influence the regulations, also take kind of a bottom-up approach to get stakeholders to apply meaningful use concepts, such as engaging patients and family, improving care coordination, even if newborn screening isn't mentioned in the regulations.

So we'd like to know if the committee is interested in reviewing draft comments that would be due February 25th.

CHAIRPERSON HOWELL: I'm sure the committee would be interested in that, and I'm sure you'll make them available through Michele's office. Thank you.

Coleen, is there anything we need to vote on? I don't think so; is that correct?

DR. BOYLE: No.

WORKGROUP ON EVIDENCE EVALUATION METHODS

CHAIRPERSON HOWELL: Thank you.

The final session in this morning group here is --

this committee is fully aware of the fact that our Congressional mandate requires that we make evidence-based recommendations for conditions to add to the panel. I think this group, aided by some very talented people such as Jim Perrin and others, has really made a tremendous amount of headway as far as developing evidence-type recommendations for newborn screening. That area is always in some flux and refinement.

So we have established a workgroup on evidence evaluation methods that will be looking extensively at the evidence methods that are being used by this committee to make recommendations. It's a large and distinguished working group, with representation from a variety of places -- AHRQ, obviously, other societies, other experts, and so forth.

I'm going to ask Ned to please give some comments about that. Ned, I trust you're on the wire?

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

CHAIRPERSON HOWELL: Crystal clear. So tell us what this distinguished workgroup is going to do?

DR. CALONGE: Well, first of all, we didn't have -- I wasn't there to comment on the last presentation, but I think there's actually a lot of synergy in what Coleen and her group are pursuing and kind of the issues that we've been wrestling with in the methods area.

I'm reminded, having just come out of state government, that when you're in government regulation is the answer to every problem, and once you step outside you recognize that people have gotten along pretty well with other methods in terms of getting guidelines put forward, standards implemented, and helping people do the right thing.

So I think the idea that the holy grail of getting a condition added to the uniform panel is not the only answer to how we standardize the approach to childhood screening and newborn screening across the country. I'm very encouraged by the fact that this group is thinking about other strategies.

In the adult world, guidelines are implemented all the time without a mandate or a uniform panel acceptance, and we are able to do quality improvement and quality assurance along those lines. So not every problem is a nail that our hammer has to address the current way we're doing it, and I hope we keep that in mind.

So that brings me ought to the Evidence Evaluation Methods Workgroup and to kind of tell you where we're at. We have recruited a number of methodologic experts and evidence-based medicine experts from different sectors across the country and internationally. So in addition to people from the U.S. Preventive Services Task Force, representatives from AHRQ, and representatives from evidence-based practice

centers, we've also reached out and gotten membership from the Community Guide to Preventive Services, which is the CDC public health equivalent of the U.S. Preventive Services Task Force, as well as the ACIP, that just adopted its evidence-based methodology based on a modification of the grade approach.

We've actually got good representation from the GRADE work group, which I'm excited about because I think it will bring to the table additional methods that will help us deal with the contextual issues that make our work very difficult. And we've gotten representatives from EGAP, kind of the genetics task force, as well.

So that and the addition of economic experts and modeling experts and basically good thinkers around evidence-based recommendations, I think the workgroup is well poised to be successful.

We are having our first meeting coming up on April 13, and I appreciate Alex Knapp and Michele and everyone's working in getting that put together. Our approach in that first meeting is to really share the methodologic approaches from the other review groups, kind of set the stage for what's out there, and then to start the discussion on modeling and how modeling could help inform the work of the task force, then finally thinking about how to move forward

in refining our methods to better address the issues that we face now that we've been through a couple of recommendations.

I just would like to present the main areas where I see the workgroup needing to work. The first -- and I hope these resonate with Jim Perrin. I know they will with Nancy and Alex Kemper. The first is kind of the quality of evidence assessment.

We have a framework that was provided to us primarily out of the clinical trials world and the evidence rating system that was given to us by McMasters, which puts grade one evidence as randomized control trials, and then you go rapidly down into consensus, depending on what schema you use.

What we've realized is that we are unlikely to have grade one evidence or category one evidence or randomized control trials for the rare diseases that we are going to consider adding to or otherwise addressing through the work of this committee. So re-looking at how to assess the quality of evidence in what I would say the very rare disease framework of low prevalence, low incidence, small numbers to get together for randomized control trials and treatment issues, is something we're going to have to wrestle with. What do we do when the state of the art of evidence is simply a case series, and understanding that

there are innate biases in the case series approach?

So the quality of evidence assessment and reframing that for rare diseases is one issue.

The second issue is how do we approach weak links in the chain of evidence? So when we come up with -- I remember the phrase from the last meeting specifically, when Alex Kemper and Jim Perrin used the phrase "We have a critical evidence gap" as they were talking about screening for major hypoxic heart disease. I had a hard time getting to a positive vote and rationalizing that with the phrase "critical evidence gap." Of course, that's my problem. I'm an evidence-based methodologist.

But we're going to have these weak links in the chain of evidence. We saw that in the hyperbilirubinemia presentation, where, if you were paying attention, there was this phrase where we don't have evidence that treating hyperbilirubinemia prevents kernicterus. Now, that would be a potential critical evidence gap. We filled it in with a lot of other words, like there are these children that we've obviously helped or we've detected, or that the treatment clearly makes a difference because this person who does all of the cases has told us that, but that's not in evidence. So how do we wrestle with these weaker links in the evidence in reaching a decision?

The third area is the role of modeling. I think we're really looking at modeling as something that will help address and inform these critical evidence gaps. So, given the kind of overwhelming gestalt, if you will, that this must work, which is what I think we hear a fair amount of in this group -- obviously this works, or it must work, or we just haven't done the studies -- how can we help fill in the gaps or strengthen the links in the chain of evidence by using modeling to give us a better sense of what the benefits might be, or at least the upper bounds of benefits?

So if there are X number of cases of kernicterus a year that continue to occur in the current system where screening for hyperbilirubinemia is more of a professional standard, if there are X number of cases, the best we could do from a benefit standpoint is to prevent or make better that number of cases, or at least in the case of hyperbilirubinemia the number of kernicterus cases that we believe could be attributable to hyperbilirubinemia at the levels that we're screening for.

So that's upper-bounding the benefits. Similarly, we can use modeling to help us understand the potential bounds or the upper bounds of the harms. So, given that we can only help this number of kids and the way we get to those number of kids is to treat this number of children, we can

better kind of balance the issues of benefits and harms in these areas of weak evidence.

The fourth area -- and I'm almost done, Rod. The fourth area is rethinking where we set the certainty bar. I know that's kind of jargon, but the USPSTF uses a bar of certainty that's actually quite high, that before we give an A or B recommendation our level of certainty or, if you will, our belief that we are wrong, we set that bar extremely high because we want to make sure that the recommendations we have have very, very little chance of doing more harm than good or, I guess another way, a very, very good chance of doing more good than harm.

In setting the methodology for the Advisory Committee, I think we've kind of borrowed that certainty bar level, and I think that's where some of us, or at least me, around the table wrestle with making a positive recommendation when that certainty bar is borrowed or that kind of level of proof needed to make a recommendation is borrowed from kind of the adult medicine, adult preventive medicine world.

So kind of thinking about where we feel that certainty point should be, and then being consistent about it. I will tell you that I am convinced that that bar is at a different place for different people sitting around the

table there in D.C. And there's not a problem with that, but I think trying to address where the bar should be so that it's most appropriate to benefit the children in the United States and that we apply the bar consistently across conditions I think is vital.

The last area, number five, really is I think what Coleen was talking about, which is our approach to decisions when the evidence leads to what I would say a higher risk of being wrong or a lower level of certainty. How do we approach those? So we have the four categories we have. I think our experience with the conditions we've looked at so far has, I would say, unveiled some discomfort with those four categories alone.

So, listening to the SCIDs presentation yesterday -- and I said this to Michele -- I thought that was fantastic. It was a great presentation, and what it did for me was it kind of reaffirmed that the decision we made in approving SCIDs was the right decision, and I think it lent a real sense of legitimacy to the process that we used in getting to the SCIDs recommendation.

So this **category of a conditional approval**, where we're actually going to look at the outcomes, to assure that we're actually doing good and we're doing more good than harm, that we aren't subjecting children to treatments that

could be harmful in order to achieve a less than certain outcome.

I think these re-looks at the information could be a critical piece of our work going forward, that we could, for example, make a conditional recommendation and then have the discipline to re-look at the data after we have some experience, and then really have the discipline to say we're going to take this condition off the list because it doesn't look like we're meeting our objectives.

Another issue I think that feeds right into that is, would there be categories of recommendations that aren't to put it on the uniform panel, as Coleen had talked about, and instead pursue it more as a quality improvement, quality assurance, standard of care, best practice, or other outcomes that we think would meet the needs of the children of the country without putting it as a mandate in the uniform screening panel.

So there, that's my diatribe for the day and I've used up my 15 minutes of infamy, and I'd be happy for any questions or comments.

CHAIRPERSON HOWELL: Thank you very much, Ned.

Are there questions for Dr. Calonge? Gerry?

DR. VOCKLEY: Not so much a question -- am I on here? -- as a comment. At the last couple of these

discussions, having found myself in very much different places with recommendations than Ned, I think I can be counted as one of those who maybe has a different bar. I don't see that as a problem. I see it as appropriate. With not only individuals around the table are going to have a different idea of what is appropriate and where that bar should be set, but that it by necessity needs to be different for every disorder.

There are too many vagaries related to each of the diseases and how we can study them, what has been done, and how best to push forward the goals for screening with any one disorder. We could argue, discuss, whatever you want to call it, the rest of the morning about it and we wouldn't resolve it. So I think this is an important group and it's also important to remember it won't end up being any more homogeneous than anything else that we've done up until now.

I just want to reinforce Ned's last point, though, second to the last point, whichever. I think the SCIDs presentation absolutely validates the process that we've been using, and that's incredibly important. Even if we have to pat ourselves on the back, I think we did a great job with SCIDs, and I think we used the same criteria when we looked at critical congenital cyanotic heart disease. I do believe our processes are working and, while democracy may not be the

best route to good science, we will have a certain amount of negotiation that is inevitable in this process.

CHAIRPERSON HOWELL: Coleen.

DR. BOTKIN: This is Jeff Botkin. Can I make a comment?

CHAIRPERSON HOWELL: Please.

DR. BOTKIN: In relation to gaps in the evidence, I think this whole process is going to be extremely valuable. The gaps in the evidence is something I'm interested in seeing the discussion focus on, and whether we want to get away from what looks like sort of a binary outcome, either a thumbs-up or a thumbs-down on a test.

I think that there is going to be this grey area where we want to think about the committee's authority and the ability to leverage the system. In other words, now I think we're stuck in a situation where a thumbs-down may put off further consideration for a period of time, when it may in fact be a promising test. And on the other hand, we may have a thumbs-up on something for which there's really not the system in place to be able to deal with that.

So can we use our status as an Advisory Committee to the Secretary to help fill those gaps in a prompt way and have some leverage, energy, to make sure that the proper studies are done to fill those gaps in a timely way?

CHAIRPERSON HOWELL: Coleen.

DR. BOYLE: Thanks very much, Ned. I think what you have laid out is just a wonderful plan and I guess it's going to for me personally help with some of the frustration. Again, I think this is a natural process because we're charting new territory in many ways, and I think we have some particular challenges in the fact that the body of evidence that we are dealing with is not, will never be, just by definition will never be as strong as we would like it to be.

So I personally am frustrated with the ability of our Advisory Committee to use the evidence reviews in a careful way because of that lack of clarity. I guess I'm hoping that -- and maybe I'm hanging too much faith on this one, but I'm hoping that the modeling part of this will really help us understand the consequences, both the positive and the negative consequences of action. It might be helpful -- I don't know if your committee thought about this or workgroup thought about this -- but actually including costs within that framework as well, so we were able to put that in context with other conditions that have been considered or are moving toward the total universe as well.

Just another thought, again hoping to use the information, the great information that's put together for the evidence review, and help with the interpretation and the

actions.

DR. CALONGE: Coleen, thanks for the comment. We actually have an economist and an economic modeler.

DR. BOYLE: Right. I forgot.

DR. CALONGE: I left that out. But we are, unfortunately, going to have to use modeling to do these economic assessments that we are charged with by Congress. As the cost information is not readily available, we're really going to have to do modeling to get there. So I appreciate that comment.

CHAIRPERSON HOWELL: I think that this is an exciting committee, workgroup, that's coming along here. As I mentioned, it has a very distinguished constituency and it's perfectly clear to me that this group is developing a really systematic approach to evidence base in rare diseases will be one of the big products of this committee. I think it will have implications far beyond this committee. It will have implications in the entire rare disease community.

So I'm very excited about that and I think that there's going to be a wonderful opportunity as they proceed.

Michele.

DR. DOUGHERTY: This is Denise Dougherty. Hi, everybody. I'm close to laryngitis here, but I'm glad to be not sharing the germs with people around the table.

But I would like to say that -- and I can hear. When I'm not on mute, I can hear what other people are saying. So you'll have to let me speak and then I'll hang up and listen. We're on the radio call-in show.

In any event, I think the conversation that is happening on a deeper look at the different approaches to evidence criteria is a wonderful idea. I'm really looking forward to this April 13th meeting. I would just like to say, for the person who said our process has been working, I think the issue is that the formal process that we put in place does not really have a place in it for the kind of process that we've been using in reality for CCCHD and for SCID and now possibly for hyperbilirubinemia, where the recommendation is really proceed in the context of doing further research, not a formal recommendation that we all said we would agree to.

So I would like to put on the table that we make a formal recommendation here that for our formal process that making a recommendation to proceed with further research should be one of our possibilities for recommendation.

Thank you. I hope that made some sense.

CHAIRPERSON HOWELL: I'm sure that those sorts of discussions will come up in this committee. Again, I think that I will echo the comments that have been made on the

recommendation on SCID, that it would be important to do some very carefully done pilot studies to look at the implementation. That recommendation was, fortunately, able to be followed by the cooperation of CDC, NIH, and the states, and I think it has indeed been a wonderful success. I think we'll go a similar route, I'm sure, with congenital heart disease.

Are there further comments?

DR. LLOYD-PURYEAR: Are you making a motion?

CHAIRPERSON HOWELL: Who?

DR. LLOYD-PURYEAR: Denise, are you making a motion?

CHAIRPERSON HOWELL: No, she did not make a motion.

DR. DOUGHERTY: Yes, I did. Yes, I said I'd like to recommend that the committee vote. You may decide that it's not timely to vote on that right now, that we may need to come back in May, but I did make a formal recommendation.

CHAIRPERSON HOWELL: I'm sorry. I thought you were just making a recommendation.

Is there a second to her recommendation?

(No response.)

There is no second to your recommendation, so we will look forward to hearing from the committee as they go

along.

Any other comments? We need to stay on time.

(No response.)

Thank you very much. It's time for a break, and we'll return at 10:20. So we're going to shorten the break, so be back on time because we're looking forward to hearing from Dr. Kaufman, who's been very patient. He keeps getting moved about and cancelled. So we need to be on time.

(Recess from 10:08 a.m. to 10:24 a.m.)