SECRETARY'S ADVISORY COMMITTEE ON

HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

Friday, May 18, 2012

AFTERNOON SESSION

1:00 p.m. — 2:50 p.m.

Hilton Alexandria Old Town Hotel

1767 King Street

Alexandria, Virginia 22314

APPEARANCES

COMMITTEE MEMBERS:

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

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

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REPRESENTATIVES (continued)

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C O N T E N T S

P R O C E E D I N G S

CHAIRMAN BOCCHINI: All right. If everyone will take their seats, we'll go ahead and get the afternoon session started.

All right. We're ready to start the afternoon session. And first we're going to bring Don Bailey back up, and he'll give us further details about the newborn screening awareness strategy summit and what's come from that. So, Don?

DR. BAILEY: Okay. Well, I'll try to make this relatively brief. But I'd like to do two things, is summarize what happened in our meeting at the strategy summit two or three weeks ago, and then give more details about what CDC and APHL are planning, and how those two things fit together, and where in some cases they're different, and talk about how going forward the committee can be involved in certain things.

So just to give a little bit of background to everybody in this room, we know this, that newborn screening is rapidly changing. If you look at the number of conditions screened by States in

2001 and 2012, then enormous changes. And all of us have been a part of those changes, and we know all the details behind why this is happening, and why it hasn't happened, and the challenges and so forth.

So, like I said, we all know this, and for us this is our world. But for the rest of the world, they have no clue to a large extent about all this. And so we've got a big disconnect between what we know and how much we're engaged and what the public knows, and et cetera.

So if we think about public awareness and you think about all the different professional groups, every one of them have statements, or practice recommendations, or suggestions for people in their disciplines, so ACOG, the pediatrics, Institute of Medicine, American College of Medical Genetics, APHL, Maternal Child Health Bureau, CDC, and we could go on and on. Just about everybody says educating expectant parents about newborn screening is an important endeavor. But just like when we had the discussion earlier about everybody says family-centered care is good, but doing family-

centered care is a very different thing. It's the same thing here. Implementing these recommendations is highly variable.

This is not news to people in this room. Research consistently shows that many parents, if not most parents, are generally unaware of newborn screening. And there have been a couple of studies showing this is especially true for minority and low-income families. And those that are aware, usually they call it the heel stick or the PKU test, something like that. They have no clue about the enormity of the range of conditions, the reasons why different conditions are chosen and so forth. And, of course, I don't think it would be a reasonable expectation for us to assure that every parent understood all 50-something conditions. We're not looking at something like that.

Now clearly there is lots of information on the web. If you Google newborn screening, you can get all kinds of sources of information, so it's not that information is not out there, but you have to go to those sites. You have to want to get that

information to understand and to find out about it. And so most parents wouldn't think to, well, hmm, I'm pregnant, I'm going to go have a baby. Maybe I should Google newborn screening. People just don't do that. So we need to be more proactive.

Almost every State has some kind of brochure describing the newborn screening program. This is the brochure from North Carolina. But I think most research shows that they're generally not read, that some studies have looked at readability of these brochures, and I would say a lot of them are suboptimal in terms of readability. And often the brochure gets lost in the packet. It comes with a lot of other materials that parents get either in the hospital or in the OB clinic. And so wading through everything and finding the things that are most important, you're going to focus on things like breast feeding, or, you know, what are the things I'm going to have to deal with, or getting my baby to sleep.

And the newborn screening program, I mean, this does say a test to save your baby's life. So

for some people, they'll pay attention to that, but to read it and really understand it, it's not happening, and we know that.

So in terms of public acceptance, I think clearly despite this lack of unawareness, the screening in mandatory in most States. Very few parents object to screening. We had a little report yesterday showing that probably 99 percent of families across the Nation participate in screening. And so the lack of awareness -- despite lack of awareness, studies show high levels of public acceptance.

Now as we move forward in the future, for example, in our newborn screening study, when there's not a clear treatment and you're disclosing carrier status and so forth, as information becomes more uncertain with less clear benefit, I think we'll see more variation in public acceptance of screening, and that's in one way why we keep screening the way it is. We have pretty conservative criteria about what we include in the screening programs because we want to make sure that

in the vast majority of cases those are conditions that most people would say, well, yeah, as a public. This is, of course, important.

So do we have a problem? Well, in some ways you could say we don't. Everybody's getting screened, we don't have a problem. But the studies do show that most parents say when you ask them, they don't know about newborn screening, but they would like to know more about it, and they would like to know about it sooner.

Clearly the distribution of materials depends on the provider and on the settings, and so the role of the providers is going to be critical in all of this. So, like I said, things are going pretty well. But controversies over dried blood spot storage after newborn screening and other kinds of potential controversies in the future actually have the potential to spill over and affect the newborn screening program.

And so I think one of the goals in an awareness campaign would be to not only increase awareness, but to increase acceptance. We can't get

much higher than 99 percent, but to make sure that the acceptance rate doesn't go down as a part of -- as a result of perhaps some of these controversies.

So HRSA contracted with Porter Novelli to do a media scan, and this was done and reported earlier looking at kind of what's out there in terms of the kinds of information that parents could get.

And then Porter Novelli helped organize this newborn screening awareness campaign strategy summit. And the goals here were to consider strategies for improving parent awareness and continued support for newborn screening, to consider strategies for expanding active provider involvement in newborn screening. And in all these cases think about, as I mentioned this morning, the focus, the audience, and the messages. To provide input for CDC and APHL to continue planning their 2013 50th anniversary campaign. And then for us primarily as the Education and Training Committee to think beyond the campaign to other kinds of awareness goals and strategies as they might pertain to our mission.

So partners both within and outside of

newborn screening were convened to plan this campaign. So this was, like we said, people who are kind of in the newborn screening community and representatives of some advocacy groups, but also people who had done other -- maybe were in health communications or had done other kinds of public awareness campaigns not directly related to newborn screening, but we wanted to draw on their experiences for what an effective campaign might be.

So we talked a lot about, well, what would be the goal in this campaign, and so this is an example of a goal that we came up with. The ultimate goals are to inform and educate the public about newborn screening in order to maintain and/or increase understanding, acceptance, and follow-up of newborn screening among parents. And the follow-up piece is important in this, too, if we're having families not coming back in for follow-up, increased awareness of newborn screening could help maybe promote that.

So, of course, there are a variety of potential audiences. We've got expectant parents.

We've got healthcare professionals. We've got policymakers and the general public. And so can one campaign or even one set of activities address all these audiences, and clearly not. So these are probably going to require some targeted messaging and targeted strategies in a variety of different ways.

And one of the things that Porter Novelli helped us think through was, okay, what are we asking each of those groups to do? At the end of the awareness campaign, what would happen? What would we want parents to do? So, for example, we might want expectant parents to ask about screening and the results of it. We might want healthcare professionals to talk more with parents and to promote the benefits of newborn screening. We might want -- I mean, we would all want these things. So policymakers, we would hope that that they would support appropriation screening decisions in their State. We would want the general public, even people who are not parents, expectant parents, to still be aware of newborn screening and support it

as a public endeavor.

So Porter Novelli also thought about kind of thinking about parents, or professionals, or really any of these audiences, a continuum of what you might think about would be an outcome. And I think one of the points they made from this is you can't go from -- expect a simple -- one campaign to jump people from the beginning point in the continuum. For example, you probably can't read this in the back, but this says, a parent who says I've never heard of newborn screening, and I don't really know what it's about. And at the other end of the continuum is I know now that it's important to ask my baby's pediatrician to review the results with me, and if the test reveals anything, I need to follow-up on it. I will get a referral for further testing.

These are just examples of kind of the steps that people might move towards. And so it wouldn't be realistic necessarily to expect people to jump from one end to the other and sort of think about where's the public in general? Where are

practitioners in general? What would be the next step that we could most logically expect?

So for parents, of course, and I'll go through these fairly quickly, we would like for them to know the value of the program in general, that it saves lives by detecting problems earlier and getting babies to appropriate care, and then value to them specifically. Your child is going to get a health checkup at birth. Make sure you ask the doctor for the results. Or you know about your baby's height and weight. Do you know about your baby's newborn screening results?

These were not goals that we set, but these were more examples of goals that we could set as a part of a campaign, and all the kinds of things that you would need to think about. So if you really wanted parents to ask Steve or Beth or their pediatrician about their newborn screening results, then you would target a campaign specifically to that as opposed to if you just wanted parents to know that screening existed.

Also parents could learn about early

detection and early treatment. I think in the interest of time, we'll make these slides available to everyone, but I won't read through everything.

The same thing with help professionals. We, of course, would like for them to all know the value of the program, know the value of talking to patients about it.

And so we spent quite a bit of time in the strategy session talking about those potential messages and potential outcomes for any kind of a campaign, whether it be, you know, directed towards the media, or whether it be directed towards families in an OB office.

So Porter Novelli drew heavily on their experience in messaging and health campaigns in general, as well as the expertise of people in the group to suggest that, you know, for a truly effective campaign, what you need to do is develop a logic model with a strategic visual that talks about the resources, the activities, the outcomes, and the goals, that you really need to do audience testing of finding out whether it's, again, pediatricians or

parents or the general public, how do they think about these things, what kinds of information would they like. And then, of course, baseline data. What is it we're trying to change, and how can we measure that would be an important thing to do think about, so it's identified baseline data to collect for evaluation.

Then the next step would be to define a specific call to action for each prioritized audience, refine that definition for audiences for greater specificity of messages, and as you can see in different kind of audience segments.

Same thing with messaging then. So think about the overall -- of course the big picture messages. This is a great program. It's done great things for children. But then there are subtexts and sub-messages that need to be targeted for different audiences and the roles that we would want to expect from them. And in the ideal world, you would want to do formal testing of these messages to see if whatever strategies you're using gets those messages across.

So that really helped us, I think, think about, in some ways, the enormity of the task and what we're trying to accomplish here. But also the importance of trying to get a real focus, and not try to change the world necessarily, but to try to say, okay, what are the immediate and the long-term things that could be done? And I'll come back to some summary statements around that in a minute.

So then following yesterday the presentation from Porter Novelli about the summary of this strategy session. And then Carla Cuthbert from the CDC talked about, and we had a little preview of this this morning, next year's 50-year newborn screening campaign, which is a joint activity of the CDC and APHL. But we've had a number of conversations since yesterday about coordinating and collaborating with the committee and certainly with the education and training subcommittee.

So the audience for this campaign that Carla, and Jelili, and their group are planning on is broad. The potential audiences are the ones we

mentioned already: expectant parents and families, healthcare providers, policymakers, State and national media. And clearly they are still in the process of finalizing this and narrowing it down and seeking different funding sources.

The final audience choices and activities will be heavily depending -- I'm sorry for the typo there -- heavily dependent on available funding. I think you'll see from the next few slides that the policymakers at State and national media are going to be key recipients of this. Healthcare providers will be key recipients. Whether and how expectant parents and families are will be determined as they go forward in this planning, but clearly we think that from our perspective, the Education and Training Subcommittee, that's going to be a primary target audience for us.

So one of the big activities next year will be combined -- APHL every, I think, 18 months has a newborn screening and genetic testing symposium. And so this year it's going to be held jointly with the International Society for Neonatal

Screening. And it's planned for -- the dates have now been set. It's May the 5th through the 10th, 2013, and it'll be hosted in Atlanta. So this will be a great opportunity, and so we want to encourage all the -- I think when we were sending out dates for the Advisory Board meetings for next year, this was one of the windows of time we said, no, let's make sure we're available for this. Now maybe that was a strategy mistake. Maybe we should've had it during this time. But I actually think if we can have our -- I think separating the two, by us coming to this meeting, being able to focus on the meeting and not being focused on these decisions would be a good thing.

The focus will capture the 50th anniversary and, of course, include site visits to the Georgia State and Public Health Lab and the CDC. And the planning for that has already started, but it will begin in earnest in June once APHL finishes their current annual meeting.

In addition, there will be an exhibit that the CDC is planning, which includes various newborn

screening artifacts and historical memorabilia. Carla said they're exciting to her.

(Laughter.)

UNIDENTIFIED SPEAKER: Maybe we could have the 50-year old blood spot.

(Laughter.)

DR. BAILEY: Yeah, maybe we could have the 50-year old blood spot. That's a great idea.

But actually I think this could be done in kind of an interesting way. The goal here would be to have something that could be customized and made transportable to a variety of different relevant meetings. And so that's something they're planning on doing.

There'll also be a celebration book with some interactive media, and this could highlight the story of newborn screening. It would heavily be focused on patient and patient perspectives. This one would be targeted to the general public and legislative decision makers. You know, how fancy this can be and whether it's in an app or color and so forth is going to heavily depend again on funding

sources and needs, and also depend on the final campaign themes and messaging.

Then as Steve was mentioning earlier this morning, and Jelili mentioned it in his comments, there's going to be a commemorative event planned here in the D.C. area probably -- certainly in the fall, probably in October or November. And Jelili indicated it could be -- they're a little flexible on the timing right now. There'll be a lot of things that we'll have to think about in all that.

But this would be more targeted towards legislative decision makers, but the scope and the themes of the event are being defined, you know, who's coming, what would this event look like, et cetera. I think some of the parents in the group said this will be a great day for different advocacy groups to bring their children and to make visits to their congressmen and women. It would be an opportunity to invite some high profile speakers.

These kinds of things take enormous planning, and they all have to kind of fit together, and you have to figure out how would you get the

media. What would it take to get the media to come to an event like this?

So we've got a great story to tell for sure, and the question is how can we tell this story in a way that captures big media attention at this time in an appropriate way? And what's the role of our committee in that?

And so, again, we've had some discussions back and forth, and Carla, and Jelili, and the whole team have agreed that I will be involved in monthly calls and discussions with them to talk about both this event and the other activities so that we're not trying to direct it or control it, but just to keep having input so that we'll know, and we can provide input on things.

They're also planning a variety of different public service announcements, and the boundaries of this are unlimited. And, again, depending on what messages, and strategies, and funds. You know, the public service TV announcements cost a lot of money, and so is this where we want to invest funds? But there could be a

variety of things around raising awareness, calls to action, et cetera.

So Carla concluded her presentation with a list of the some of the ideas and themes that are driving their thinking about this right now, and some kind of themes whatever they do, whether it's a television spot or a commemorative event, that these would be kind of messages that we want to get across.

The newborn screening is a system, and it does all these things. It detects, prevents, it protects. It's not just getting the blood spot. That it really should be considered a standard of care. It's one of the many tests and evaluations performed on newborns. It's a part of the variety of things that are done. But it's what done. It's like when I go in for an annual checkup, I get a cholesterol test. It's just what you do. And newborn screening hopefully can be viewed in that something. It's just something we do as a standard of care. And that it has an impact. It's not something we do that doesn't have any consequences.

It has very real consequences for newborns and for families and communities.

Hopefully the campaign would help equip parents with questions that they should ask their provider, and correspondingly equip physicians with, I don't know, message cards, but certainly key messages that we can all send about newborn screening programs, regardless of the context in which we are interacting with children and with families.

Good data is always good, and so the more we can have some numbers that are not, you know, complex statistics, but some high-level numbers that can show benefit and impact in a positive way, those data will be very, very important.

So some examples of messages in newborn screening is your Baby's First Test. Twelve thousand newborns identified in 2009. Newborn screening is part of routine care for your baby. Expect it and become informed.

So just to summarize all of this then. So, you know, I think we all can agree that

awareness about newborn screening is low among virtually any audience you can think of. Parents, when asked, generally say that they would like more information about newborn screening, but I think they are not going to take an active role in seeking that out. So we need to be figuring that out and ways that we can do it.

I must say that there are a few people, and this is not a common theme, but there are some people that have raised concern about an awareness campaign. They say, well, you know, if we start raising awareness about newborn screening too much, maybe people would start knowing what we're doing, and maybe they wouldn't want it. Well, that's certainly a possibility. And I think to our committee and everybody who's involved with this at the planning level, the benefits of increased awareness, and hopefully the real benefit would be an informed acceptance of newborn screening rather than passive or unknown acceptance. That's really what we'd like to have. Probably outweigh the potential costs of increased awareness.

So how we go about these campaigns will be really important. We've got lots of ideas and big plans for 2013. Hopefully we can build in some evaluation of these efforts to determine whether and how they've been effective. But clearly the campaign is just at the beginning, and so we see awareness as a long-term goal for our subcommittee and I think for this committee as a whole for the foreseeable future.

So hopefully that wasn't too long, but that's a quick summary of several -- many days of work.

CHAIRMAN BOCCHINI: That was a really great summary, Don. Thank you very much. I think it's very clear that the efforts that the committee started to assess awareness are sort of coming to the point of understanding where the gaps are at the same time that we have an opportunity to celebrate 50 years of newborn screening. So I think the timing brings these two together very nicely.

Questions or comments from the committee?

(No response.)

CHAIRMAN BOCCHINI: Okay. None from the committee or liaisons? Go ahead. We'll take a couple from the microphone.

MS. HARRISON: I'm Katharine Harrison, the project director for the New York Mid-Atlantic Consortium. And obviously I'm so pro-newborn screening, it's amazing. And we do identify 12,000 infant newborns a year with one of these diseases.

But as Sue Berry pointed out so eloquently earlier, that's not the end of the odyssey for them. And when we say we identify them, we say -- and I don't want to, you know, put any damper on this celebration, which is amazing. We have to make sure everybody's aware that these kids now need constant care and treatment that's got to be paid for.

DR. BAILEY: I think you're right. We don't want to -- I mean, so there'll be thinking about this throughout the campaign. But we want to send a message this is a great program. It's been highly successful. But we also want people to know that it needs more support to really to see that the desired benefits actually come to fruition for

everyone. So thank you.

CHAIRMAN BOCCHINI: Nancy?

DR. GREEN: Nancy Green. So, Don, that was really fantastic. And having been associated with this committee since the beginning, we've been talking about a campaign since I think 2005. And so it's really just very gratifying to see how far this has gone and how well organized, and, you know, working with Porter Novelli is quite fantastic. So really, congratulations. Long time coming.

So I'm going to just suggest something that will probably make you roll your eyes. But I think that newborn screening, that terminology -- I've been doing a lot of work in March of Dimes days and now in my current work about what catches on with the public. And I think newborn screening doesn't do it for the public, I'm sorry.

And so because screening is a dead word. I don’t mean that in terms of life or death. But, you know, it's where society uses baseball metaphors, more metaphors, et cetera. And I just think that, you know, there was a reason that even

the nurses in the nurseries say that PKU test -- "PKU" doesn't roll off the tongue, but they can deal with that test.

And so I'm just going to suggest that you think about the public name. And I also learned working with Porter Novelli when I was at March of Dimes, is that you can call it one thing to one audience. It doesn't necessarily in your lingo have to be the same, which, to me, that was an epiphany. I thought it all had to be the same.

So I'm not smart enough or creative enough to think about what that would be for parents. And if they're still in the focus group phase, it may be worth capturing a better name. Whether it even becomes "newborn test," I don't know. And certainly, you know, as we think forward about point of care screening, we want all of that to be part of it. So the blood spot test is the other thing that people call it. So just sort of think about that.

And then the other side of -- the other half of my sentence is when you say 12,000 babies are identified a year, I'm sorry. The March of

Dimes says 12,000 babies are saved each year, and that's a much more powerful, for everybody, public message.

And so, you know, again, Porter Novelli is very sophisticated and understands about immediacy in a crowded media market, but I just would like to offer those comments. Thank you.

DR. BAILEY: So I did not roll my eyes.

(Laughter.)

DR. BAILEY: Those are excellent points, Nancy. And so I think the key question is, will we have the resources to do the messaging, and the strategizing, and the focusing, and the message testing. We're finished with our contract with Porter Novelli, and so that'll be a challenge for us. But nonetheless, well taken.

DR. GREEN: So the Genetic Alliance may be able to help you with this because of their previous and current work with connecting with the public.

DR. BAILEY: I'm sorry, who could?

DR. GREEN: The Genetic Alliance.

DR. BAILEY: Oh, yes. Oh, yes. Of

course.

MS. WEES: In an effort to save you some money, what about for the parents My Baby's First Test as the tagline or what to call it, because that rings true that you're not talking about baby blood spots, but you've had the general heart and hearing as well. It’s a catchy title, and when people hear, well, what is My Baby's First Test, it makes parents stop and think?

DR. BAILEY: I think Baby's First Test is a great, simple description. And whether that's going to be the ultimate theme or not, I don’t know. And I think that'll in part depend on how CDC and APHL want to frame that particular part of the campaign.

There's a part of me that doesn't want to lose the newborn screening word because I want to make sure people still understand it because that phrase will be used in every other kind of context. But it could be that they're together, they're paired together quite a bit. Carla?

DR. CUTHBERT: We won't take anything off

the table. I'm Carla Cuthbert from CDC. And to respond to Carol, we actually -- Nancy, I'm sorry. We did look at a number of different ways of phrasing it. We looked at "saved" and "benefit" and so on, but you have to be able to prove that every single child identified is saved or benefits.

And if you can do that, then that's great. That's why we actually chose "identified" because we have to be able to support with the outcome -- some sort of outcomes analysis for that.

But those words sound better if you're trying to sell and if you're trying to actually get people excited about this. And I do acknowledge what you're saying, but we do have to be careful.

MS. MERRITT: Jill Merritt with APHL. And this is exactly one of the issues. Working with scientists is one thing, and working with the general public is another. So we'll have to tread carefully, but reasonably.

The public is not going to understand that this is a system that we are promoting awareness about. That's a dead thing. But we can, in fact,

say this is the first -- this screen is the first, you know, part in a link of help. We'll think of -- we'll do some clever messaging. But that's going to be the real tuck in terms of partnering with CDC and being a scientific organization.

CHAIRMAN BOCCHINI: Thank you.

MS. MERRITT: I also just wanted to add one thing, that we really are hoping to make this a local celebration as well. We're going to create a set of exhibits that go out to at least 10 States, and have lab days where the public can come in and learn about newborn screening, how it happens, the whole process. And hopefully invite the local politicos to that so we can get an understanding on their part of who's interested in this.

DR. BAILEY: So I think that's a really good point and a great activity because newborn screening is under the purview of State health departments, and States legislators make many more decisions about newborn screening, or the health departments do, than the Federal government and Federal legislators. We have important advisory

roles, but what will happen in next fall, it will be ideal if that were replicated 50-something times.

CHAIRMAN BOCCHINI: So one last comment from the microphone.

MS. MCCORMICK: Christine McCormick. I'm a parent advocate. I just want to reiterate a point that was brought in the Education and Training session yesterday, that the biggest force you're going to have to spread awareness is the families that have been there like me, talking mother to mother. And I think it would be smart to identify families who are willing to do that.

For instance, my daughter died of CCHD, and I went on a mission to spread awareness of pulse ox. And through that mission, thousands of moms know the word "pulse ox" now and got their children screened. So working mother to mother is a smart move for all of us. Thank you.

CHAIRMAN BOCCHINI: Thank you. Coleen?

DR. BOYLE: So two ideas. One that Carla and I talked about, and it's the world I have some control over for complementing the 50th anniversary

and not as to maybe do a special supplement of the MMWR with a series of articles, you know, highlighting different aspects of newborn screening. So maybe just following up on that idea.

And then the other one was just thinking about what was done at the Smithsonian for smallpox. So there was a special exhibit on smallpox in the Smithsonian. So, you know, thinking kind of really big here. Is it possible to get private donors to think about doing something comparable? I mean, talk about bringing it to the public in terms of the achievements for newborn screening.

It may not be right for the 50th because it's obviously next year, but thinking longer term of reaching out to some private donors.

DR. BAILEY: Did you just volunteer for that?

DR. BOYLE: Sure.

(Laughter.)

DR. BAILEY: Great. Those are both exciting ideas. And MMWR, even though it doesn't go to the public, the media do pay attention to that

publication. And I think it would be one in addition to press releases and so forth that would be a good vehicle.

CHAIRMAN BOCCHINI: Melissa?

DR. PARISI: I was wondering if one of the ideas or themes that could be promulgated would be the value or the benefit of research. I know sometimes research is a bad word among the public, and it's not always perceived in a positive light. But this is a real wonderful opportunity to highlight some of what research has done to really benefit babies and newborns. So I'd encourage that.

CHAIRMAN BOCCHINI: Oh, Natasha?

MS. BONHOMME: Hi. Sorry. Just whenever I am volunteered for things, I like to be able to at least say yes or no. And I think --

(Laughter.)

MS. BONHOMME: Obviously that is a yes, and I do think that there are a number -- you know, the resources keep coming up. And that, of course, is a very real issue. But I think that there are a number of things that are already in place that may

be able to contribute those types of resources.

And I think particularly if you ask the people who really fought very hard for there to be a clearinghouse, it was thought to be more than just a mechanism to put resources in, but to be very active. And I definitely think Baby's First Test and the clearinghouse tried to do that, and we are more than happy to brainstorm and to put out that type of information.

And I think even beyond the 2013, I think it would be great to see, you know, 2013 be really oriented towards public awareness, and then maybe 2014 to be, like, well, taking it a step further and say, well, what's behind this system? And then you go into these issues of research and things. I think this could be really, not just in terms of a campaign, but really thinking about overall how do we message around newborn screening.

CHAIRMAN BOCCHINI: Well, it's clear that, Carol, we're going to give you the last comment.

DR. GREENE: And professional organizations will be definitely interested in

helping, and I am the SIMD for sure.

And a tiny, teeny thing, but I love the tee shirt suggestion yesterday. And another thing that's easily done, and I notice bumper stickers. I mean, I pay attention to them on cars, and that would be a great way to message.

CHAIRMAN BOCCHINI: Well, I think it's very clear that there are lots of good ideas, and that interacting with other groups brings up even more subjects that could be part of this. And so I think we'll keep this conversation going.

I think as a result of having Don sitting in conversations and then having feedback back and forth, not only between us and CDC and the public laboratories, but the other players, is going to be very helpful. So thank you.

DR. BAILEY: And there will be so many things going on, already are so many things going on, as Natasha and others have indicated, and will be that our committee doesn't have any desire or ability to try to control or coordinate all of them. But I think agreeing on some core messages and

making sure that we're all singing the same song to a certain extent would be great. Thank you very much.

CHAIRMAN BOCCHINI: All right. Next on the agenda, we'll bring Dr. Kemper back to update us on the condition review process.

DR. KEMPER: We're talking about evidence's first test.

(Laughter.)

DR. KEMPER: And I'd like to add that in 2009, Nancy Green and I read 12,000 manuscripts in the process of evidence review. So I'm going to be giving an update on the condition review process.

By way of background, at the end of April we had a two-day meeting focused on issues of evidence review that really came up for a few different reasons. One is that now that we've done a number of these evidence reviews, we wanted to take a look and see what kind of things that we should do differently in the future to make them even better. The second was there's the issues of the public health impact evaluation, which we really

needed to get a better sense of what that is going forward. And then the third thing is that we really wanted to bring our process into alignment with what other major evidence review groups do.

So we were very fortunate to be able to bring Dr. Virginia Moyer. Dr. Jenny Moyer is the current chair of the U.S. Preventive Services Taskforce. And we also had Dr. Ned Calonge, who many of you from working on this committee, who was the former chair of the U.S. Preventive Service Taskforce, and is now heavily involved with the community guide.

But we really had this huge representation both from the Federal government, including HRSA, ARC, the NIH, and the CDC. We had representation from this committee. We had Dr. Kus representing AMCHIP -- ASTA, that's right, but APHL, other experts.

I had to say I was a little nervous going into this meeting because I was, like, you know, are we really going to be able to engage people around these complex issues of evidence review over two

days? And I have to say that it was one of the most really engaging, thoughtful meetings that I've ever been to. So for those of you who were at the meeting who are in this meeting, I have just a tremendous debt of gratitude for your involvement.

What I'd like to do is I'm going to really talk about two things. One is I'm going to talk about process for evidence review. But what I really want to highlight as well is issues around how the Advisory Committee can weigh the evidence to make recommendations, because both those things have to be brought in line or brought together for us to really meet the standards that are set by other recommending groups, like the U.S. Preventive Service Taskforce. So I'm going to kind of jump back and forth.

And I want everyone to remember, too, that this is a work in progress, and it's going to be further refined. And I hope to get some advice from you in the limited time that we have here, but am happy to talk to anybody at any time about this going forward.

So just in terms of high-level principles for making recommendations, ultimately we want to make recommendations that are evidenced based, that the outcomes that matter most are health benefits to the individual being screened, although there are important health outcomes -- or not necessarily health outcomes, but outcomes in general that need to be considered that affect, for example, the family.

The recommendations take into account the readiness and feasibility of screening within States public health systems, so I'm going to be talking about that in a little bit. But the recommendations aren't modified to accommodate concerns about insurance coverage, medical legal liability, or legislation, that we're really thinking about evidence here about what's the best thing to do for individuals and their families.

So moving forward, the way that I can see the evidence reports is that they really have three separate components. The first is the systematic evidence review, and that's similar to what we've

been providing in the past where we, you know, kind of shake the trees, and pick up rocks, and look for evidence wherever we can find it, and synthesize it for the Advisory Committee.

The second thing, which we began doing for the bilirubin report, but we're going to really make more formal, is an estimation of the bounds of benefit and harm. So if you were to adopt screening, what's a reasonable range for what we expect for the outcomes to be? And that is primarily going to be based on modeling of evidence that would be obtained from the systematic evidence review.

And the third thing is an assessment of the readiness and feasibility of implementing comprehensive newborn screening, so I'm not just talking about the test, but I'm talking about the whole process from screening through follow-up, from the State public health department perspective. And sort of the ground rules that set forth what we're supposed to do, there's supposed to be a public health impact evaluation.

And what's clear when I talk about this is that that really means two different things to different people, depending on who you're talking to. The first is if you were adopt screening, what's the impact on the public health, on the general people out there? And that's really what I'm talking about when I talk about the estimation of the bounds of benefit and harm.

However, individuals primarily, those people that are in the State health departments who are concerned about how they're going to do these implementations when they hear about public health implementation, evaluation, or the public health impact, they're really thinking about the impact of screening on the health system kind of at large and, in particular, for them.

So I hope I described those two things. We can talk about it more. And I think as I go through these slides, you'll see what I mean better.

So as before for the systematic evidence reviews, we have an analytic framework. We looked at the analytic framework that's used by the U.S.

Preventative Services Taskforce and other groups, and we really modified the framework that we have, and I think did a better job of at least defining in general what the key questions are.

Now as we go through each individual condition, the questions are going to be modified to be particular to whatever it is. But you can see that in general, things fall into these eight key questions ranging from what's the life course and spectrum of disease related to the condition? What's the direct evidence that screening for the condition reduces morbidity or mortality? What's the analytic validity and clinical validity of the screening test or algorithm. And actually I should've added in there as well of the diagnostic strategy.

Key question 4 is are treatments available that make a difference in the intermediate outcomes when the condition is caught earlier, detected by screening? Are treatments available that make a difference in health outcomes when the condition is caught earlier, detected by screening? So sometimes

you'll only have the intermediate outcomes, and sometimes you'll know long-term health outcomes, so teasing that apart.

When you don't know the impact on the long-term health outcomes, it's important to ask how strong is the association between the intermediate outcomes and whatever important health outcomes you're looking for. What are the harms of the screening test, and what are the harms of treatment?

So, again, this is a very high-level analytic framework, and it'll be specified for each individual condition.

Once the key questions are formalized and the evidence is gained, it's important to assess the evidence at the key question level and using systems that have already been developed for evidence review. We'll be labeling each of those as either convincing adequate or inadequate. And we describe these in our manual of procedures.

But then after evaluating each question, you have to think about the whole framework. So what do we think would happen after we've looked at

all these key questions in terms of screening on the population? And it all really boils down to the magnitude of net benefit. So you can imagine the negative magnitude of net benefit where it looks like harms outweigh the benefits. It could be zero or small where there's a close balance of harms and benefits, or it could be significant where the benefits outweigh the harms. Now when we do this, we're not considering cost. We're just thinking about the benefits on the population to be screened across that analytic framework.

But then you have to think about how certain are you about that net benefit. And these raise questions like, are there critical evidence gaps in any of the key questions? To what extent are the results of the studies generalizable to newborns in the United States? Do the studies have the appropriate research design to answer the key questions?

And, again, unlike bodies like the U.S. Preventative Services Taskforce, most of the data are going to be from small case series and that kind

of thing. I shouldn't say most of the data, but there will be data from small case series, and we will continue to include them as we always have.

To what extent are the studies of adequate quality for each of the key questions? What's the precision of the evidence for each of the questions? And how coherent are the studies for each questions? That is, do the different studies tell you the same thing, or are they kind of all over the map in terms of what the results are?

And from that you can group certainty into low where there's insufficient evidence to have confidence in the assignment of net benefit, moderate where further research could change the magnitude or direction of findings within any of the key questions such that your overall assessment might change, or high where your assignment to the net benefit is unlikely to be strongly affected by results of future studies.

And, again, in the manual of procedures, we have this further defined. And we stole liberally from the U.S. Preventative Services

Taskforce manual and other things that are out there. I should've mentioned as well the manual for the Advisory Committee on Immunization Practices.

So as I mentioned before, we'll have this estimation of the bounds of benefit and harm based on decision analytic modeling. We did that before, the bilirubin report. And the key things that are going to go in there are the prevalences. Ned Colonge is fond of saying basically everything hinges to prevalence, and it's important to consider that. But also test accuracy, treatment effectiveness, and estimation of harm.

Again, we've talked about in this group how it's sometimes hard to find harm, that it's not reported, and we're going to have to come up with clever ways of dealing with that. We can talk about that later if you'd like.

So before if you remember, the decision making process was really a one-step affair. I'm going to be talking about a two-step dance to come to a recommendation.

This is the first matrix, and it's similar

to what was done before where you have to consider the magnitude of net benefit, which, again, can be significant, small to zero or negative, and the certainty of net benefit -- high, moderate, and low. And you kind of pick where you are and you end up with a letter.

And I think that it's important that we really, you know, are clear about what letter we're talking about, kind of which box that we end up with because this is really where the recommendations flow through. And you can see that in the process I'm going to lay out, there's going to be the ability to make a much more nuanced recommendation based on this process. So this is net benefit.

The other that's going to have to be thought about, as I mentioned before, was readiness and feasibility. And in terms of this process, you know, originally we were talking at the meeting that this process of assessing readiness and feasibility might only have to be done for those things with the A code. I think that in reality we're going to be assessing readiness and feasibility in parallel with

the evidence process so that there's not this gap in time before the two things can be assessed. But it's probably only most important in terms of making a decision for the things that are the A code. That is where you have good certainty that there's a significant net benefit.

But when we talk about readiness, by that we mean -- and, again, this is one of the areas that we're still in the process of defining, and I'm working with actually many of the people in this room to clarify this. But right now, how ready are State health departments to begin to do the screening? And this depends upon the availability of a validated high throughput approach to screening, systems for training and education, and processes for quality assurance, information systems that track people to short-term follow-up, and ideally through term follow-up, the availability of the diagnostic services, right? So if you have somebody who's positive screened, you want to make sure that there's ability to make the diagnosis. And then, of course, treatment and systems for

follow-up.

And for readiness, in the scheme that we have now, it's classified into ready, developmental where some further work is needed, and unprepared where there's significant challenges in immediately adopting comprehensive screening.

Now feasibility considers the availability of all the things that we talked about and the resources that it would take to be able to get things going. And that can be classified into high, so the resources for screening are available and the cost of screening is balanced against the other public health obligations; moderate where the resources aren't readily available, but implementation is possible; and low where the resources for screening aren't available, and the cost of screening is prohibitive.

And I don’t want to talk very much right now about the process of assessment of readiness and feasibility. I entered into some conversations with APHL and Jelili to consider how this is going to be done. And this is something that we'd like to come

back and get.

And, you know, I appreciate the tension that we're going to be talking about a little bit about in terms of the decision making process, which is at what point do you recommend that something be screened, so how much of the advisory committee is a push versus a push to the health system, versus waiting until things are ready, and then cutting to go. But I do think that it's important for the Advisory Committee to make explicit decisions about these things.

So this is the second matrix where we have feasibility like I talked about before and readiness. And you can see that things are coded. I'm going to show you in a second what I call the mother of all matrices that combines these things, okay? And I figured that at some point people needed a laugh because it's hard to talk about evidence that much, unless you're me, and I love it. It's probably a disease.

And so this -- and I apologize. I'm looking at this little monitor, and I can't see it

as well I can on the computer. And now I'm looking up there, and I can't see it as well either, which is probably actually good for me because then it'll let me get out of being in trouble.

(Laughter.)

DR. KEMPER: The no-brainer is the A-1, so that's the upper left-hand corner where you can see the red scribbling, which that's things are ready, things are feasible, and that you're confident that there's a net benefit, right? Those things would be recommended, okay?

The things that become more difficult is if you moved down, for example, the A-2s and the A-3s, where there may be some issue related to readiness or feasibility, but you're fairly confident that it's the right to do. And I think that here, the Advisory Committee is going to have to come up with some reasonable way to make a recommendation based on this, or maybe the recommendation that comes out of this is, for example, if you look at CCHD where the grants came out after the recommendation to do pilot

implementation, maybe there's some way to kind of reverse that to have more grants. Now that I'm telling you how to spend your money, but more funding opportunities to help States get things moving.

And, again, I think that we're not going to obviously in the next few minutes come to resolution on this whole thing. What I think the key thing, though, is that there needs to be a consistent way to evaluate all the stuff that we're going to bringing in and coding it, and then using those codes to make clear, transparent, unambiguous recommendations. Because the thing that I hear from a lot of people, both from the health department side and from people who have nominated conditions or advocated things to get screening, is that once the Advisory Committee goes through with the old kind of one-step process, they don't really understand why it didn't make it. What are the gaps? And I think that going into this process does a few things. One is it creates a more transparent way to understand those things that aren't

recommended what needs to happen. And the second thing is it allows you the opportunity to make more clear recommendations around these kind of health system issues, and really evaluate these health system issues which weren't done before.

I suspect that when I open this up again, too, there are going to be some people that are going to feel uncomfortable about these issues of readiness, and feasibility, and cost, which we haven't been explicit about talking about before. But I think that from the feedback that I've gotten from those people involved in the -- who were busy running public health departments in this era of very constrained resources that it's something that they need help with.

And the other things is, this is not really that different from what other advisory committees are doing, for example, the Advisory Committee on Immunization Practice.

I recognize that we need more clarity around these terms of readiness and feasibility, and that’s forthcoming. But what I'd like to do is in a

second kind of open this up to people's thoughts about this approach at the 30,000 foot level. And given the time constraints, I'd be happy to talk to anybody about other aspects of clarifying this.

Eventually the matrix is going to have to be voted on and approved by the Advisory Committee, but that's not so, if I understand correctly, from the evidence review process. But of course the evidence review process is hopefully less -- you know, engenders less hand wringing than this does.

So, like I just said, the Advisory Committee is going to have to approve the decision making process. The document right now is in final revision with meeting attendees. I say "final" because it makes me feel better that we're getting near the end. But I suspect that there's going to have to be a number of revisions before it's happy with the meeting attendees. And then we will start disseminating it in broader circles. But I would hope that we'd be able to vote - when I say "we," I don't vote at all. But I hope that you all are able to vote at the next Advisory Committee about it.

And the methods for evidence review is similar to what's been done in the past by these other groups, and it doesn't require a vote. And we can start moving ahead on the new topics that were assigned yesterday under that schema so that things aren't slowed down in the process.

So with that, I'd like to open it up to questions.

CHAIRMAN BOCCHINI: Thank you very much, Alex. That was a nice presentation, and I think it's very clear that you've moved us along quite well. So thank you.

And I think that the plan that he's put forward is the one that we've talked about about getting a few more iterations until we're all satisfied that we have that decision making algorithm settled, and then bring it to the full committee for additional valuation, and then a decision about whether that's how we go forward or whether we modify that. But you're right, that doesn't involve the evidence review. It involves the decision matrix that occurs after the evidence

review is completed.

Questions, comments? Don and then Coleen.

DR BAILEY: So thanks for taking the lead on this. I think this is a really important activity, and something that we should be continuing to do. But I think this is a good time to do this.

There are other pieces of it, like family benefit and the whole definition of benefit that I'll want to keep revisiting, but I won't bring that up at this particular point.

I think you've answered my question. So I was wondering whether you were saying that this was something that the Evidence Review Committee would actually do, which is making an assignment to in that grid, or whether you're suggesting that that would be something that the Advisory Committee would use based on the evidence review.

DR. KEMPER: Yeah. So two things. One is, first of all, one of the things I'm really happy about the revision is that we're going to be able to include the family perspective in a way that we haven't done. So I think that that's one of the

things I personally am most happy about.

The second thing is we do not assign these letters or numbers, and I'm sorry if I wasn't clear about that. Our job is to pick up the rock and let the worms crawl out and let you all see the evidence. I just want to make sure that there's a common approach that can consistently be used in the grading.

DR. BAILEY: I would agree with that, and I think it would be helpful also to the nominators and other people in terms of the things that we were talking about in terms of giving people feedback. To some extent that matrix will help with that.

DR. BOYLE: Your answer changed my question.

(Laughter.)

DR. KEMPER: Right direction or the wrong direction?

DR. BOYLE: I know. I know. I guess I have to give this some thought. What I was going to ask was, because I actually was thinking of the evidence review providing the fodder for us to be

able to put these --

DR. KEMPER: So let me be clear. We are going to assign all the other things at each key question level and those words that we used in terms of strength of evidence. And that's no different than what, for example, the art funded, evidence-based practice centers do.

So we're not just going to give you this 500-page document and expect it to be transparent. We will be assigning that verbiage that I talked about before in terms of the strength of evidence at each step.

What we won't be doing is saying that on matrix 1 this is an A, and on matrix 2 this is a four or whatever. That's a policy question that you all would vote on.

DR. BOYLE: I guess I have to read it. My question was going to be how sort of repeatable is this process.

DR. KEMPER: So replicability is the -- that's the sine qua non of what we want to do, and if it's not replicable, then we've failed.

DR. BOYLE: We had 10 different people sitting around this table, and we took the same information. Is it all not in the eye of the beholder in some way, our experiences and things that come behind us. I guess that's my concern.

DR. KEMPER: And with the replicability things, there's two things. One is the evidence review as to how we're going to grade this, the linkages and so forth replicable. And that part I feel fairly confident about because it's no different than what we've been doing for a long time now anyway in our other evaluations.

The question is, will you get to the same place on the matrix over time? And I think that the only way to have that happen is for us to be painfully clear about our definitions. And it's a no-trivial task. And I think that with the matrix 1 part, I think that we're there with fair confidence, if I can say that from using my other slide.

But I think that in terms of the issues of readiness and feasibility, we're not there, and that's going to require a lot more conversation.

DR. BAILEY: So can I just follow up on that then? So I guess one interpretation is that you will assign the scores to the different pieces. If what I'm hearing you saying then is that the matrix is constructed from those scores, and, in essence, you are putting -- if we just literally followed your scoring system, then it goes into a matrix. Is that correct?

DR. KEMPER: Right. So it's not our goal to lead you to something, but if we do this right, then the answer should be clear.

So we will -- right, because, believe me, I don't want to be the one giving things A-1s or not. But we will be able to -- getting back to this issue of assessing the evidence at the key question level, convincing, adequate, inadequate. Those kinds of things we will do. We'll be able to provide you with the numbers on the bounds of benefit and harm.

One of the art to making these decisions is thinking about what do these numbers means and kind of the is the juice worth the squeeze question

that comes up. But I think that's bringing back my North Carolina roots talking to you.

I think that that's going to be one of those things that we're going to have to work to make sure that that that information is consistently used to assign a grade.

Dr. Bocchini, not to put you on the spot, but if you could talk about your experience with ACIP that does this.

CHAIRMAN BOCCHINI: Yeah, and I think if you remember the template that we used to make the final decision once we saw the evidence from the Evidence Review Committee or panel, what we're doing here is adding the feasibility and public health impact to it, which has created a more complex template, but it's really the same thing.

And this is the responsibility of the committee is to evaluate what they bring forward, and then to assign a decision matrix -- using the decision matrix. Hopefully it makes it more transparent and more attuned to the evidence so that we can -- but it will be the collective wisdom of

the committee that's going to make that final decision.

Now part of what we're doing also is two members of the committee are going to be part of the working group that will be looking at the data and being involved as this process evolves. And they will have the first look at making decisions as to where we're going to fit these into the matrix, and that will come forward to the committee at the time of the decision. But the committee will be informed along the way as to what evidence is evolving, where we are, and all that.

So hopefully about the time the decision needs to be made, the committee will be well aware of the issues and any issues in terms of the data that might be missing or incomplete.

DR. BOYLE: Just one quick follow-up question -- not question, but comment. I did like your idea. I know you just said it as an example of using this to help guide pilot projects or studies prior to implementation. So maybe that's a committee decision about how to weave that piece in.

CHAIRMAN BOCCHINI: So Steve and then we'll take Ann at the microphone.

DR. MCDONOUGH: Yeah. I had a question specifically on the pilot studies, how they are funded, how the process comes into place with these pilot studies occur, what's the mechanism, and what's the role of the committee in that process?

So you have a list of things to do to discuss at upcoming meetings But, to me, from an outsider's perspective, it seems like a very haphazard, what happens here. There'll be a political process. We'll get a study or thing at it that ends up being a pilot study kind of. There'll be a funding agency, and NIH has got to take an interest. And they'll kick in some money, and then something happens. There'll be an advocacy group that creates something somewhere.

So the pilot studies I think will have a lot of impact on what goes forward and what doesn't, and that whole process of funding available for pilot studies, how things go I think. I think it's really important that we look at that and maybe

provide some advice on it.

So I would like that to be a topic for discussion at an upcoming meeting, and having some people at least to help educate me about how this works and how it could be done better.

CHAIRMAN BOCCHINI: Yeah, that's a good question, and I think that's something that we certainly can have as an item in a subsequent meeting. So I think that's a good point. Ann?

MS. COMEAU: Thank you. Ann Comeau. I think Alex did a wonderful job of outlining how evidence review can feed into this to help identify gaps.

One thing that is coming to my mind that I'm thinking maybe the Advisory Committee might still have some work to do on, is in assessing net benefit. And we discussed this a little bit at our meeting.

I'm just thinking about consistency. So if there's significant benefit to the individual, and significant benefit to the family, and significant benefit to the population, and great

data for all of that, that might be A-1. But within A-1, is there going to be another rule for significant benefit to the -- to everybody, but it's not really proven yet for benefit to the individual, and there is benefit to the family, and maybe presumed benefit to the population?

And that's kind of a policy on decision making that I see could be very critical to the consistency in evaluating condition A versus condition B. And I don't think that that was in our purview to put that forward, Alex, or do you -- I'm trying to -- the discussions were so intense.

DR. KEMPER: Right. So before I come up with a complicated question to your answer, thank you for your kind words. I just want to make sure everyone heard them.

(Laughter.)

DR. KEMPER: And Ann was at the meeting as well.

So what you're getting to, and it's probably a more complicated discussion we can have right here, is when we talk about net benefits, like

how big does the magnitude of net benefits have to be before you call it significant? And, you know, these are words that we've used before, and I think this is a nuance that the Advisory Committee is going to have to come to benefits with.

When you were talking about if you're not sure, then that gets to the certainty side of things. But in terms of magnitude of net benefits, if you're talking about, for example, being able to prevent some horrible outcome, but in a very, very, very small number of children, and you have to do a lot of screening to find those kids, how do you weight that? And how do you compare that against the harm?

So if the condition has a very, very low prevalence, even with a very good test, you're going to end up with a lot more false positives in general than you will true positives.

One of the things that makes me glad that I don't have to sit around this big table is figuring out exactly what the right threshold is. So I think that's an evolving conversation.

CHAIRMAN BOCCHINI: Other questions or comments?

(No response.)

CHAIRMAN BOCCHINI: Okay. Thank you very much, Alex. We appreciate it and look forward to the final, final drafts.

All right. Next we have updates for NIH initiatives and two presenters. First Kathryn Camp, who is a registered dietician and a consultant to the Office of Dietary Supplements at the NIH. And in addition, Melissa Parisi will also discuss NIH initiatives and updates. Dr. Parisi is chief of the Intellectual and Developmental Disabilities Branch of the Eunice Kennedy Shriver NICHD.

MS. CAMP: Thank you so much for the opportunity to report to this committee today. I think that Dr. Kemper had quite a nice segue into another area that I'm going to be discussing. The initiative that is underway that I will be discussing is one that actually parallels in a way what Melissa Parisi will be talking about. This is the nutrition and dietary supplement interventions

for inborn errors of metabolism. And it is an initiative to build an evidence-based research framework.

And I think that everybody knows that in this field of rare diseases, particularly in inborn errors of metabolism, that we do have a bit of a data problem in terms of the ability to obtain robust evidence regarding the treatments that we use. And this is principally because of the rarity of these disorders in the vulnerable life stage in which they are diagnosed. So it's difficult to conduct randomized controlled trials that would provide the evidence that would support review, for example, that an insurance company would buy in terms of providing coverage for a specific treatment.

So, of course, we know that early intervention and treatment saves lives and prevents morbidity and mortality. Yet the evidence that some of the treatments that we use is lacking.

So this recent Cochrane review, which looked at the efficacy of tyrosine supplementation

and PKU is an example of the difficulties that we encounter when working with small populations. You can see that there were only three trials that met inclusion criteria with results on 56 subjects. And they were not able to make any recommendations regarding the use of tyrosine in routine clinical practice in PKU.

Secondly, a review, which looks at the efficacy of tyrosine supplementation for PKU is an example of the difficulties -- excuse me. The second one, the Agency for Healthcare Research and Quality Comparative Effectiveness Review looked at a number of key questions relative to the treatment of PKU using KUVAN, or sapropterin, or large neutral amino acids compared to diet. The key question 1, the relationship between phenylalanine levels and IQ, they were only able to ascertain 16 studies that met review criteria. And you can see that of those 16, only one study was considered to be of good quality.

And the criteria that they used to make their recommendations concerns such issues as

research methodology, incomplete reporting of data results, and potentially confounding factors.

So I'd like to quote a very famous philosopher from my youth, Bob Dylan, who said "The times, they are a-changing." So now in addition to articulating the problems, people are working hard. And I can say this from the standpoint of my busy day and Dr. Parisi's busy day, to articulate the problems, we're working very hard to recognize and utilize existing opportunities that are available to advance a research agenda.

First of all, and these slides, I'd like to thank Dr. Steven Groft for coming up with some of these important ideas as he struggles with how to advance a research agenda in rare diseases. Traditional research and development is changing, so we must utilize available resources from multiple public and private sector partners with shrinking budgets. The Federal government cannot do everything.

Again, with our population sample size, recruitment, geographical distribution, and ethical

issues surrounding doing research, really will cause us to accept that many rare diseases and inborn errors of metabolism in particular will not go to phase three trials. So we're going to need to consider how we can use small pilot data or phase two studies to gather our robust data.

Utilizing novel clinical trial designs is going to be important, but we have to recognize that working with the Food and Drug Administration with their review divisions for proposed study designs and assessments of results is going to be important at the initiation of these projects, not after they've been undertaken.

Bridging the gap between scientific discovery and clinical application is going to be something that several new -- one particularly new division within NIH, the National Center for the Advancement of Translational Sciences, and several other NIH translational research programs are going to be in a position to undertake.

So just briefly I'm going to talk to you about the initiative. And I know this acronym is

kind of clumsy -- nutrition and dietary supplement interventions for inborn errors of metabolism -- but really if anyone has anything else better, I'd be very happy to change the name.

But it started in 2008. Dr. Paul Coates, the director of the Office of Dietary Supplements, and Dr. Steve Groft, the director of the Office of Rare Diseases Research, sort of sat down and scratched their heads over this whole problem of the evidence that simply isn't there for many of the dietary treatments, and came up with this concept to look at how to build a research infrastructure.

In 2010, I came on board. My background is in clinical dietetics, and I spent 20 years on the ground with patients in patient care. And while I understand the issues of providing patient care, some of the research implications have required a little bit of work on my part. But by January of 2011, we had brought together a meeting of Federal partners, and they were very strong in their recommendation that we move forward with our initiative and bring in additional stakeholders

outside from the metabolic community. So that meeting was held in December of 2011. And actually there are several people in the room who were at that meeting. And I'll tell you a little bit more about that.

We have begun our work on very specific activities. And just briefly, our mission is to identify gaps in the understanding of the safety and effectiveness of nutrition and dietary supplement interventions. And this is through collaboration and partnerships among a wide range.

We really recognize the need to not only harmonize across private and public partnerships, but also bring in people who could help inform us with this effort.

So we gathered 85 people, and many of these were very high-level individuals. We had NIH Institute directors, presidents of professional associations and advocacy groups, and a large body of experienced clinicians and researchers in the field of metabolism. And just to show you briefly, we had every newborn screening collaborative

represented, and this is a map of the newborn screen collaboratives. I put white dots where there were other individuals involved. And we also had representation from four different countries. That would be Australia, France, Switzerland, and the United Kingdom.

So all of this was in an effort to set a transformative research agenda. We had an action plan. We wanted to define short- and long-term priorities. We wanted to define a preferred sequence of events, so, in other words, what do we need to take on first before we can go to step two and step three? And what were the mechanisms that we would need?

And out of this came 21 hours of recorded talks and discussions, and I have not listened to all of them, but we do have an 80-page summary document that looks like this. And after spending quite a number of hours trying to get my arms around it, we ended up with a very old-fashioned technique of stickies on the office wall. And this actually is our prioritization, and you can see the top row.

You can't read them, but those are the categorizing them by topic and by their complexity. And the little pink one all the way up at the top says I hope we can get this done.

(Laughter.)

MS. CAMP: And we'll see in the long run whether we do.

So the activities that we have ongoing, we did convene a core planning group. This consisted of about 12 people. We've had two meetings. We are involved in now reviewing and actually identifying the short-term and the long-term activities. Agreeing in prioritizing on the steps that we need to take has been an important process.

We are now updating our website and making some enhancements to it so that we can extend the website to be on the participants in the workshop to open into the public. I don't know how many of you are aware that whenever you put anything on a government website, it has to be 508 compliant, which requires not only a considerable amount of money, but a lot of time. And we believe that

that's an important attribute that we can include in our efforts. But it does slow things down a bit.

We are preparing the workshop proceedings for publication. We have a writing group that has been formed. They've begun their work. And questions about whether this should be published as a supplement to a journal, or whether it should be just the workshop findings is something that they're working with right now.

We are developing a list of all of the screen disorders and the treatments that are used. And we are going to put them out in a survey form to metabolic specialists to determine which are on the highest on the hit parade to target for building research infrastructure. And in collaboration with that survey, the Society for Inherited Metabolic Disorders and Genetic Metabolic Dieticians International are working closely with us.

One of the items that really percolated quite high on the top of the list of things to do is to create a web portal to organize all of the available resources not only for researchers and

clinicians, but for patients and families regarding treatments -- dietary supplements, medical foods, et cetera.

We have a number of future activities. And if I'm not retired by the time we get the bottom of that, I would be surprise, but you can see that many of them are going to entail quite a lot of work.

And finally, our website is under development, and I would encourage all of you -- you're welcome to take a look at it. It has a very easy login and password, IEMIEM. There will be public access pages that will be put onto the Office of Dietary Supplements website, and we'll be -- I can tell you about those as they move along. And this is just a screenshot of our website that we'll have all of those tabs on the far side populated shortly.

The organizers for this initiative, Dr. Paul Coates, who is the Director of the Office of Dietary Supplements, and actually a geneticist by training, very interested in this issue, was really

the person behind moving this forward. Dr. Steven Groft, I'm sure many of you know, Director of the Office of Rare Diseases Research, and myself.

And by the way, of course, the Office of Rare Diseases Research is now within the National Center for the Advancement of Translational Sciences. And Dr. Michelle Lloyd Puryear, who many of you know is working on our project with us.

And I welcome any comments, questions. And if any of you want to help, raise your hands. I'll take your name and number. We'll put you on one of our working groups. Thank you.

CHAIRMAN BOCCHINI: Thank you very much for that presentation. Questions? Steve?

DR. MCDONOUGH: I commend you on your leadership on this. It's a nice development.

MS. CAMP: Thank you.

DR. MCDONOUGH: What timeframe would you see for budget funding grants? How many grants or how many research? Would you work with universities collaborating together so you have an adequate sample size rather than just institutions? And kind

of what's the -- you can't answer all these questions, of course. But the process of getting funding for this, is it going to have to come out of the existing NIH, or legislation to supplement the NIH budget?

MS. CAMP: So thank you. Those are very good questions, and if I can remember them, I'm going to go from the back to the top.

Is there NIH funding specifically for this project at this time? No. Are we working with universities with other institutes? Yes. In fact, we've got on our core planning group our funders from each one of the major institutes that funds these types of research. So we will be hopefully, as we move forward, developing RFPs with our institute partners.

And the whole issue of having adequate sample size, the metabolic community of course is a relatively small community in terms of numbers of researchers. And we have probably the most senior of those researchers involved in this project. So as we move forward, our hope is that we will be able

to build the research infrastructure that will include multi-center in order to be able to do these trials.

The other important aspect, though, is to come up with other ways to look at where the evidence is for the treatments that we use because we won't be able to do randomized control trials for everything we want. And can we bypass some of that in some other sort of unique ways?

And I am personally not a researcher, so these are things that have to come from our consultants and our partners.

And did I answer all your questions? Yes? Thank you. Very good questions.

CHAIRMAN BOCCHINI: All right. Thank you very much. Appreciate it. We look forward to the progress.

DR. PARISI: Well, thank you for giving me the opportunity to speak. I realize this is after the intended close of the meeting, so it's an unenviable task to try to get through this. But what I'm going to do is I'm trying to summarize very

briefly for you a recent conference that was sponsored by several groups within NIH, not only the NICHD, which I'm a member, but also the Office of Rare Diseases Research, which is now part of NCATS, as Kathy just mentioned, the National Center for Accelerating Translational Sciences, as well as the Office of Dietary Supplements.

And by way of background, I mean, everyone knows that PKU was one of the first conditions that was screened for via newborn screening programs. So we've been talking about this being known as the PKU test. And, in fact, there's still a lot that we don't know about PKU. I think that's probably the take home message.

But in October 2000, NIH published guidelines for screening and management as part of a consensus development conference on PKU. We recognized a number of years ago that there were new emerging therapies, new data. And it was really time to revisit those guidelines. So we embarked upon a year-long -- I think it was actually more than a year -- working group process and a

conference which was held in February of this year.

And many of you probably already know this, but this new medication that's now available for PKU, sapropterin dihydrochloride, also known as KUVAN, is a synthetic form of BH4, which is the co-factor for the defective enzyme in PKU. And it increases the activity of pH enzyme in those who have residual enzyme function. So not all individuals with PKU respond to this medication, and that was one of the dilemmas facing the community with regard to treating individuals with PKU.

So we convened a conference February 22nd and 23rd, and there were several different components to this conference. We included a presentation of an ARC comparative effectiveness review for adjuvant treatments of PKU. We also summarized the work of the five NIH-convened working groups that had been spending over a year discussing aspects of PKU, which I'll describe in a moment. We had invited speaker presentations and representatives from industry, advocacy groups, international partners and others who participated

in some of our panel discussions.

We had two major goals: to provide a form for identifying future research needs because NIH, after all, is very focused on research, and also to provide data for the development of clinical practice guidelines by professional organizations since that's what they are charged to do.

And this is an example, I think, of the Federal government working remarkably well together. We had been informed that AHRQ received a public request to conduct a comparative effectiveness review of the treatments for PKU, including sapropterin and large neutral amino acids. And AHRQ formed an evidence-based practice committee, charged them with doing this work. And they actually worked very collaboratively with us at NIH in our process, but yet they were very independent of our process as well. They posted a draft report in September of 2011 and then released their report formally at our conference.

And just to summarize, the most important points I think from what emerged from that evidence

review, and you're welcome to access this online. There had been a lot of support or a lot of interest in the need for lifelong treatment for individuals with PKU. And via a very complicated meta-analysis, the AHRQ folks actually were able to determine that in addition to the critical period -- zero to six years -- for needing to restrict protein and have a very formal diet for individuals with PKU, it turns out that there are effects on IQ beyond that critical period, and it continues throughout adolescence and adulthood. So, in fact, this report provides some fairly strong evidence for the need for lifelong treatment of PKU.

They also noted that many individuals may benefit from adjuvant therapy, and in two randomized controlled trials and three open label trials, there was shown to be a reduction in certain treated groups in those individuals who respond to sapropterin. But unfortunately long-term data to understand the effect on cognition and quality of life measures were unavailable.

And I think the conclusion was that

there's really a need for large, rigorous, randomized control trials, or at least very carefully designed studies in this metabolic community in order to have the adequate evidence to really support conclusions for management and care.

So what we were engaged in is we created five working groups, and each of those working groups was composed of clinical care experts, experts in the research community, patients and patient advocates, and NIH and other Federal partners, as well as co-chairs and coordinators. And each of these groups had 10 to 14 members. They met virtually via webinar for at least eight sessions over a year's time to discuss the questions related to their particular topic.

Many of these working groups also had international members, and you can imagine that coordinating conference calls overseas was a bit of a challenge. And they developed presentations based on their discussions and conclusions.

And the five groups -- each of the five groups had a particular topic and a question to

address. The long-term outcomes in management across the lifespan group was concerned with what evidence and practices should inform management of individuals with PKU over their lifespan.

The PKU in pregnancy focused on management for women of reproduction age, including not just preconception care, but conception planning, pregnancy, and the post-partum period, which has been largely ignored in the medical community.

The diet control and management looked at the dietary recommendations from the 2000 consensus statement and explored what knowledge should inform the development of new recommendations.

The pharmacologic interventions group really addressed the role of sapropterin dihydrochloride in individuals with PKU, and how to assess responsiveness to this medication.

And finally, the molecular testing new technologies and epidemiologic considerations addressed some of the issues that are near and dear to this group's heart, which is, should there be changes to the consensus statement regarding newborn

screening and molecular testing for PKU.

So to summarize a whole lot of work into one slide, here are some of the salient points that emerged from the work of the working groups. And by no means is this 100 percent consensus, but I think many of these recommendations, or at least many of these conclusions, can inform the development of revised practice guidelines. The lifelong treatment for PKU as being an essential element of care was very much reinforced.

And one of the workgroups really tried to identify the critical elements for medical nutritional, cognitive, emotional, behavioral, and social management of PKU at different phases throughout the lifespan.

There was consensus about the need for optimal management to prevent maternal PKU syndrome, and also the need for more research in the peri-partum and post-partum period.

Double blind placebo controlled studies have the greatest rigor for determining responsiveness to sapropterin. However, they may

not always be practical in the settings in which individuals are being tested for responsiveness to this medication.

The final workgroup concluded that genotyping is actually valuable for categorization of severity of PKU and also for prediction of responsiveness to sapropterin. And I think that the emerging data really support the value of genotyping for many of these determinations, or at least giving you strong hints about responsiveness.

Insurance issues and psychosocial factors influence access to and compliance with nutritional and other therapies, and this message was brought home very loud and clear by many of the individuals and advocates who attended the meeting who said over and over again the same message we've heard today about the difficulties in accessing these life-saving therapies for many of these disorders.

There's a critical need for more treatment options for individuals with no or minimal pH enzyme activity, and clearly revised practice guidelines need to be developed. And, in fact, the work to

start revising those guidelines has already begun.

As just one example of the work that one of the workgroups did -- I'm not going to go into any detail, but they developed a grid, and if you look across the top, they divided the lifespan into these categories and tried to identify tools that could be used to screen and measure outcomes in the medical, nutritional, metabolic, neurologic, cognitive, behavioral, emotional, and social domains. I know that if you get 10 psychologists in the room together, you won't always get consensus. There were challenging in reaching this as well, but I think this is a good start for considering what tools might be of use for this population, and not just the PKU population, but others.

One of the focuses or the areas of focus for the conference was also to look at new therapies and emerging therapies for PKU. And Cary Harding from Oregon gave a very compelling talk about some of the newer treatments that may be on the horizon, including gene therapy and the use of PEG-PAL or PEGylated phenylalanine ammonia lyase. And gene

therapy, I think, is not yet ready for prime time. It may not be ready for a while, but certainly people are actively engaged in studies to try to determine whether this might be a viable approach in the future.

PEG-PAL, though, is an enzyme that does not require a co-factor, unlike the defective enzyme in PKU, which is PAH. It's a relatively stable compound. It basically converts phenylalanine into a non-toxic metabolite tranexamic acid. And it doesn't completely eliminate the immunogenicity, but PEGylation actually helps sort of mask it from the immune system. So this is a very promising therapy, and currently there are phase two trials in humans which show quite a bit of promise. So stay tuned for that.

So just to conclude, I wanted to review briefly the future research needs that were identified during the conference. And these are framed in the form of a question by certain categories of topics.

The theme of outcomes and measures was a

recurring theme, and this is an issue that doesn't just impact PKU, but other inborn errors of metabolism. Really what measures can be used as screening tools and assessment tools in all domains of function across the lifespan for those with PKU? What are the appropriate and sensitive short-term and long-term outcome measures for identifying the effects of interventions for individuals with PKU? If we're going to developing effective treatments for these disorders, we need to be able to measure the effect that they have and do it reliably and consistently.

With regard to basic science and the neurologic effects of phenylalanine and PKU, one very critical question that needs to be answered is what is the mechanism is neurotoxicity of elevated phenylalanine levels? That still is an open question that has not been answered. Are there any promising biomarkers on the horizon that might be valuable for monitoring PKU, its neurologic effects, and the response to treatment?

With regard to access and social supports,

what are the social support systems that facilitate the best clinical outcomes for individuals with PKU? I think this also touches on the aspects of assessing the public healthcare impact of newborn screening and the treatments that we develop for inborn errors of metabolism.

What strategies can be used to overcome barriers and improve adherence to treatments in all phases of life? It's known that many adults with PKU go off treatment, and what can be done to help support them in continuing treatment?

What types of implementation research could demonstrate the value of treatments? And one possibility that was suggested was to look at comparative studies between different countries that have different practices and policies. And, hence, the benefit of having international collaborations.

With regard to clinical trial design, which individuals should be eligible for new treatments for PKU, and what are the best methods to study their responsiveness? And what should be the guiding principles when designing clinical trials

for pharmacologic agents or combinations of therapies to be used in PKU looking at diet as well as other interventions? As Kathy Camp just pointed out, when the evidence review was done, the number of studies that actually had a degree of rigor that was considered good was relatively small. And this is a real urgent need in clinical trial design.

With regard to genotyping, can genotyping be used to determine responsiveness to therapies? And should clinical trials for efficacy always incorporate genotype information? I think this is also a broader question than just related to PKU. And given that PKU exhibits phenotypic variability, what is the role of modifier genes in the disorder?

And then finally, with regard to resources and technology, is there a role for a national PKU registry of individuals to inform future clinical trials and natural history studies? Can resources that have been developed for other rare diseases be used by the PKU community? And we were thinking here about the Newborn Screening Translational Research Network, certainly the Rare Disease

Clinical Research Network, the common data elements, the CTSAs. These are all NIH and other resources. And, again, if we can utilize these to the benefit of PKU and other inborn errors, that would be of great benefit.

And finally, can the technology for home phenylalanine monitoring be developed to facilitate disease management? The development of home monitoring has not been terribly successful for PKU given the sensitivity of the machines. But there's hope that there might be a future in which this could help facilitate monitoring, much like home monitoring for diabetes.

So what's next? The conference was a really productive endeavor, and I want to thank many of you here in the audience who actually participated not only in the working group process, but also in attending the conference. We're developing a white paper to summarize these findings.

The conference webcast, if anyone is interested, is available on the NIH video cast site

for free. If you would like some summary documents, I'd be happy to send you my slides, and some of the summary documents are also posted at this website. And please feel free to contact me if you have any further questions. Thank you for your attention.

(Applause.)

CHAIRMAN BOCCHINI: Melissa, thank you very much. I think this is a fitting presentation to end our meeting today because here we're talking about the first test, the first inborn error to be screened for. And 50 years later we're talking about all of the things that we're talking about about considering a new condition for it to be nominated and adding to the RUSP.

So I think this is very telling about how much needs to be done, and how much work is head, and how new technologies and new potential treatments change what we're doing.

So additional questions or comments. Carol?

DR. GREENE: Thank you very much. That was an amazing summary. I was at the meeting and to

get it into that short -- that was amazing.

I want to add to what Dr. Bocchini just said and take it a step farther and say, just because there's lots of unanswered questions -- this is a double negative -- doesn't meant that it's not ready for prime time. There are people out there who have normal intelligence and have had healthy babies who, if we hadn't been screening for 50 years would have an IQ of 20 and seizures.

So to see 50 years later we still have lots of questions doesn't -- it reinforces that you can't let the perfect be the enemy of the good.

But the thing that I really wanted to say is I don't think you mentioned too much about the cross-cutting workgroup that worked on definitions. And it illustrates, I think, the needs sometimes for definitions and perhaps to connect up with some of the -- because there were some problems with what we're even talking about. And I wonder if you want to just mention something about that.

DR. PARISI: Right. So from the five working groups, we called one or two members from

each of those groups to try to work on definitions because we realized that we don't always know what we're talking about when we talk about PKU specifically with regard to the different subcategories -- classic, severe, moderate, mild. What does mild hyperphenylalaninemia really mean? And it was very informative to try to reach some consensus with regard to that effort.

And I think we were able to reach something that was workable for the purposes of this effort. But I know the definitions and making sure that we're all on the same page with regard to language is extremely important.

CHAIRMAN BOCCHINI: Questions, comments?

(No response.)

CHAIRMAN BOCCHINI: If not, thank you very much. We appreciate the presentation.

Is there any additional business? If not, I certainly want to thank everybody. I think we've had a lot of input from everybody and attendance, and I think it has been a very productive and worthwhile meeting. And I want to thank you all for

all your contributions.

So with that, we'll adjourn the meeting. Thank you all.

(Whereupon, at 2:50 p.m., the meeting was adjourned.)