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

Friday, January 27, 2012

Morning Session–Part 1

8:30 a.m.–11:00 a.m.

Park Hyatt Hotel

Washington, D.C.

APPEARANCES

COMMITTEE MEMBERS:

DON BAILEY, PhD, MED

JOSEPH A. BOCCHINI, JR., MD (Committee Chairperson)

JEFFREY BOTKIN, MD, MPH

CHARLES HOMER, MD, MMPH

FRED LOREY, PhD

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EX-OFFICIO MEMBERS:

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DENISE DOUGHERTY, PhD

KELLIE B. KELM, PhD

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SARA COPELAND, MD

APPEARANCES

(Continued)

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P R O C E E D I N G S

CHAIRMAN BOCCHINI: All right. Thank you all.

I want to welcome you to the second day of the 26th meeting of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. I think we had a good, productive day yesterday, and we're going to start again this morning.

So, first, we need to do a roll call. Sara?

DR. COPELAND: Don Bailey?

DR. BAILEY: Here.

[Laughter.]

DR. COPELAND: Joe Bocchini?

CHAIRMAN BOCCHINI: Here.

DR. COPELAND: Jeff Botkin?

DR. BOTKIN: Here.

DR. COPELAND: Charlie Homer? Are you on the phone?

[No response.]

DR. COPELAND: Okay. Fred Lorey? Fred?

Is anybody on the phone?

[No response.]

DR. COPELAND: Okay. We tried.

Steve McDonough?

DR. MCDONOUGH: Present.

DR. COPELAND: Dieter Matern?

DR. MATERN: Here.

DR. COPELAND: Alexis Thompson? Not yet.

Cathy Wicklund?

MS. WICKLUND: Here.

DR. COPELAND: Andrea Williams?

MS. WILLIAMS: Here.

DR. COPELAND: AHRQ?

DR. DOUGHERTY: Here.

DR. COPELAND: CDC? Coleen?

DR. BOYLE: Here.

DR. COPELAND: FDA?

DR. KELM: Here.

DR. COPELAND: HRSA? Not here yet.

And NIH?

DR. GUTTMACHER: Here.

DR. COPELAND: Okay. Great.

CHAIRMAN BOCCHINI: All right. Thank you.

So you can see, we've modified the configuration a bit. So Sara and I are here so that Chris will stop throwing spitballs at us when he wants to talk.

[Laughter.]

CHAIRMAN BOCCHINI: So I think we're in good position.

We're going to start this morning with subcommittee reports. And the first report is the Subcommittee on Laboratory Standards and Procedures, and Sara will give that report for Fred.

DR. COPELAND: Fred did promise he would be up at 5:30 in the morning his time, but apparently not this morning, and he may be anticipating his trip to Mexico.

Oh, yes. That's it. Thanks.

So we had very good discussion on the second screen study. It's been 3 years in the making. Dr. Shapira, from the Centers for Disease

Control and Prevention, presented preliminary data from the retrospective study that they've done.

And some of the interesting findings that they found is that there's a higher incidence of congenital thyroidism in the two screen states, that there tends to be a 2-to-1 female-to-male preponderance in congenital hypothyroidism, and birth weight/feeding method have shown some difference on the thyroid incidence.

We need to figure something a little better out for me, but that's okay.

For CAH -- so the purpose of the second screen study was mostly to look at how they're picking up thyroid and congenital adrenal hyperplasia and what the differences are. And again, in the congenital adrenal hyperplasia, in the two screen states, the incidence of CAH is higher, particularly for nonclassical. But for salt wasting, which is the main purpose of screening for CAH, there's about twice as many cases picked up in the two screen states, which is fairly interesting.

There was not much difference based on gender, but significant difference based on weight. More picked up in the normal birth weight range in the two screen states, and there's no difference in types of cases picked up on the first screen between groups.

And as noted previously, the simple virilizers and nonclassics contributed to the higher incidence in the two screen states, and they were picked up more on the second screen. Also of interest is that there's a higher proportion of Hispanics picked up on the second screen. There's an "n" missing.

Just in kind of summary, they're still cleaning that data. They're going to do some modeling of the cases and try to evaluate the clinical significance of those detected on the second screen.

There's quite a bit of limitations. This is a retrospective study. There's limits due to lack of long-term follow-up information available to them, screening algorithms, and as with any

retrospective data, there is missing data. But he's going to follow up with another presentation at the Labs Subcommittee in May and then, hopefully, a final report to the whole committee in September.

And then we had our standing item, the National Library of Medicine talking to us about LOINC codes and standardization, and Swapna Abhyankar presented to us on the work they're doing with cystic fibrosis and mutation reporting. They're working to standardize the lists and the ordering of the lists. They have 116 LOINC codes, which is 116 mutations that they have developed, and they're using cDNA, protein, or traditional name in a searchable database.

Reports will need to be very clear for reporting purposes since reporting out molecular diagnostic results is always problematic.

And then we talked about hemoglobinopathy reporting. They're developing codes in conjunction with many of the newborn screening programs, and they're trying to accommodate for those that

confirm the diagnosis at the newborn screening lab, as well as those that just do the screen itself.

And they're using the CLSI guidelines to develop results reporting terminology, as well as looking at reasons for lab tests. So they're just to develop a really robust dataset so that when people are ready to do HIE and reporting that they'll be able to just plug in already developed standardized codes.

And that is it. The one talk was a nice, long, good, robust discussion.

CHAIRMAN BOCCHINI: Okay. Thank you.

Questions or comments?

DR. BOYLE: I have a quick question. For the CH and CAH, you said it's higher. I'm just wondering higher than what? Higher than --

DR. COPELAND: The incidence in the two screen states --

DR. BOYLE: Yes.

DR. COPELAND: -- is higher than the incidence in the comparative group, which was a one screen state.

DR. BOYLE: Okay.

DR. EATON: Are you taking comments from other people?

CHAIRMAN BOCCHINI: Yes, certainly. I think, since we're done with those others, we have a microphone that we could hand --

DR. LOREY: (on telephone) Fred Lorey. I'm here.

CHAIRMAN BOCCHINI: Okay. Go ahead. Your name, please?

DR. EATON: Roger Eaton, UMass Medical School.

I think there was one bullet that was incorrect, and it was an important one that I don't think the implication should stand. Other people who were at that meeting can chime in.

You said that there were two times the number of salt wasting cases in the two screen states. I don't -- Dieter, do you remember? I don't think that that was part of that data.

DR. COPELAND: Maybe I may have misstated it, but there was a higher incidence. Whether or

not it's two times.

DR. EATON: It was mostly in the less important -- I mean, the simple virilizers.

DR. COPELAND: It was -- yes, the vast majority, the vast difference was in the simple virilizers and the nonclassic. But there was a higher incidence of salt wasters that were detected in the two screen states than in the one screen states.

DR. THERRELL: This is Brad Therrell from Texas.

I think that there are some salt wasters picked up in the two screen states on the second screen, not so many. Most of those things picked up on the second screen were simple virilizers, which are also classical cases that need to be treated, and then the nonclassicals, which are not being picked up on the first screen and wouldn't be expected to pick up on the first screen.

DR. COPELAND: Thank you for clarifying.

CHAIRMAN BOCCHINI: Additional comments?

DR. LOREY: Could you please speak a

little louder or closer to the mic, please?

DR. COPELAND: I will.

Did you have any other comments, Fred? It is your subcommittee.

DR. LOREY: Say that again.

DR. COPELAND: Did you have any other comments?

DR. LOREY: No.

DR. COPELAND: Okay.

DR. LOREY: Oh, you're asking me? No.

CHAIRMAN BOCCHINI: Yes, go ahead.

DR. TANKSLEY: Hi. I'm Susan Tanksley. I'm from Texas.

And I wrote down the numbers. This is what I wrote down. So, in one screen state, salt wasting, the incident was 1 in 43,500. In two screen states, it was 1 in 20,800 -- for salt wasters.

That's what I wrote down.

DR. COPELAND: Okay. That's more than I did.

CHAIRMAN BOCCHINI: All right. We can

look at the exact data and clarify all that. So we can fix that.

Thank you for the comments.

Let's move to the second subcommittee report, the Subcommittee on Education and Training. Don Bailey will give that report.

DR. BAILEY: Okay. Good morning.

So, just to remind you of the charge for our subcommittee, it's to review -- it's a broad one: Review existing educational and training resources, identify gaps, and make recommendations regarding five groups. We did a sophisticated statistical analysis and grouped these five groups into two clumps, parents and the public, and then health professionals.

So, currently, we have 19 subcommittee members -- six from the advisory committee, another eight from organizational representatives to the advisory committee, and then five more from what we call consultant members. And I'll come back to this in a minute, because we have a large committee already, and we have a lot more people that would

like to be involved.

The goals for our meeting yesterday were to review a variety of things that are going on in the education and training world, to look at our charter briefly and discuss possible linkages with other committees or other subcommittee, and to begin some discussion about future education and training needs, both for parents and the public and for health professionals.

So in terms of major current activities for parents and the public, we talked about the Newborn Screening Awareness Campaign, the 2013 newborn screening 50-year celebration the CDC is organizing with APHL, the Newborn Screening Clearinghouse, and brief updates in a number of other initiatives.

We also had updates from the Genetics in Primary Care Initiative, the family history for prenatal providers, brief reports from professional organizations. And I'll give a little bit more detail about each one of these.

So the Newborn Screening Awareness

Campaign, this is something that HRSA has been leading, and it came out of a recommendation from our committee a few months ago. So I think you remember from our last meeting Porter Novelli reported the results of Phase I media scan, talking about what's out there in terms of if a typical parent went to look for something about newborn screening, what would they see? What would they find? Where would they go to get it?

So the next step is to convene what we're calling a "strategy session" to determine what would actually be the goals, objectives, audiences, and approach to a media awareness campaign. So a steering committee was formed a couple of months ago to nominate attendees for this strategy session. We're looking at a 1 1/2-day meeting sometime in late March or early April.

A report will come from that meeting. It will be discussed probably on the telephone and then in our Education and Training Committee meeting on the first day of the May advisory committee meeting. And then we'll have a report on

the second day.

So this will basically be what are we trying -- what problem are we trying to solve through this campaign? What would be the key messages?

So then we had a report from Carla Cuthbert from CDC about activities related to the upcoming 50th anniversary. I don't know how many of you are aware of this, but next year, 2013, will be I guess the 50th anniversary that states began screening for PKU and -- or at least some states did.

So it's been determined that this would be a good opportunity to highlight newborn screening nationally. So the goal is to create a public that's informed about newborn screening. CDC is going to -- is leading the planning of this, but APHL will take a major lead in actually doing the implementation of these activities.

There are quite a few activities that are being planned over the next 18 months, from media campaigns to webinars and a variety of other

products that will be put together. It's very exciting.

And this will culminate in a 50th anniversary celebration in 2013. This will be a joint meeting between APHL and the International Society for Newborn Screening. That meeting will be in Atlanta. I know the dates are specified, but I can't remember. I didn't have them written down.

But that should be a very important and exciting event. So I hope everyone here will plan to be there.

We also had -- Natasha gave us an update from Genetic Alliance. As you remember, last year there were some Challenge Awards that were given, and there was another competition this year for Challenge Awards. And so, they received more than double the number of applications that they got last year, indicating interest from a variety of different constituencies about products and materials that could be developed.

They received very interesting applications from a diverse array of groups. We

couldn't find out who the awardees are yet because the final contracts haven't quite been made, but the formal announcement of these will be made in February.

Natasha, I would assume you'll make sure that gets out to the Secretary's committee at that time.

Natasha also reported on the Consumer Task Force that Genetic Alliance is organizing and gave us an update on the Web site that they're developing called Baby's First Test.

So just some musings, thoughts, or reflections about next steps from the committee with parents and the public. So, first, this is really a pretty huge audience that we are dealing with here. So if you think about parents and the public and professionals, there's not many people left.

So we really need to be careful about how we're -- be strategic about what our activities are. And so, one of our goals over the next few months is to say are there other important, big-

picture strategic initiatives that we need to be undertaking?

Going along with that is the need for multiple input from these diverse constituencies and, again, our deliberations. So we already have 19 committee members. We feel like we need to add at least one new committee member, representing the parent and public communities. I'll come back to this at the end of the presentation because we also feel like we need more professional input, and that raises some questions about how we function as a subcommittee.

We applaud the collaboration to date. At first it seemed to us that the HRSA awareness campaign and the CDC campaign were trying to accomplish the same thing, and we didn't understand really the differences between the two. But as we got further into the discussion, both in the meetings and after the meeting, it was quite clear that there is quite a bit of collaboration between the two organizations.

And so, we applaud that collaboration,

and then we just urge continued integration of activities to minimize the redundancies; of course, to harmonize messages, making sure we're all on the same page; and to maximize our resources.

So there are two major questions about the awareness campaign that I think we continue to need to ask, and the first one is what problem is it that we're trying to solve? We had some discussion about are we really trying to solve the problem of the public not being that aware of newborn screening, or is there another problem regarding the issues around dried blood spot storage and use? Is that the real problem that we're trying to solve?

Those are two very different kinds of things, and really, the primary goal, I think, is public awareness about newborn screening as an enterprise. But clearly, we can't ignore the dried blood spot issue in this campaign. We'll have to be very careful about how we approach it so that it actually doesn't undermine public perceptions, which are in general very positive for people who

know about newborn screening.

And then I think a second thing we're curious about, and this will be a long-term concern, is how can we move awareness away from a single campaign to something that's a more enduring institutional activity?

Awareness, we might have a great campaign over the next year, but people will keep having babies after that, and we need to make sure that everyone -- that we sustain whatever momentum we can get from this. And how can we institutionalize this in day-to-day practice?

We also talked a little bit about a topic that we mentioned last time, which is -- and we think this probably falls both under our committee, as well as maybe the Follow-Up Committee and the Laboratory Committee, and that is how can we help advocacy groups maximize their efforts in bringing their favorite condition to us for review?

Certainly, we have information on the website about our processes, but we're thinking that maybe a more advocate group-friendly set of

materials so that people will know when foundations are investing money or trying to push things with their legislature, that they will know very clearly the processes we go through and the information that they need to bring to us before we can move a recommendation forward.

So, in terms of health professionals, Beth Tarini, who has also agreed to be co-chair of the committee -- thank you very much, Beth -- reported on the Genetics in Primary Care Initiative. I think, was there a whole committee report on this last time, or was that just in the -- it was in our subcommittee? It was in our subcommittee?

Just in our subcommittee. Okay.

So this is -- for everyone's information then, this is a joint effort funded by HRSA and Maternal and Child Health -- it's including -- well, these are all together, but HRSA and Maternal and Child Health Bureau. It's a 3-year award. It's a cooperative agreement to the American Academy of Pediatrics. Beth and Bob Saul are the

co-PIs, and there's an advisory committee comprised of representatives from a variety of different important organizations.

So the key here is to -- the vision is to increase primary care provider knowledge and skills in provider genetic-based services. So these three broad goals: mobilize a community of learners, implement a strategy to address systems and policy, and then to think about how to embed this information into residency training.

So the Goal 1 is a quality improvement project. A subcommittee of the advisory committee has been established to develop what they're calling change packet, a series of key topics that they feel like everyone should know about. They're utilizing a quality improvement network through the AAP to test implementation of this change packet through a modified learning collaborative.

They also have a technical assistance and education center. A core piece of this will be a website that will have key pieces of information about genetics that primary care providers need to

be aware of, as well as a series of ongoing educational activities.

Then, finally, a residency training, and so a major goal of the core group is to identify -- is to assess current residency training curricula regarding genetics and develop activities, objectives of curricula that could supplement existing accreditation activities from across a variety of different specialties and primary care providers.

So we also had a report from NCHPEG on the family history for prenatal providers. So the goal here of this activity is to develop and evaluate a family history and genetic screening tool for primary care prenatal providers. This tool will help primary care providers collect patient personal and family history data, perform an assessment for the clinician, and then give clinicians a tool for making decisions about how to support families and patients in future decisions.

So how this works is there in the waiting room or in the exam room, there's actually a tablet

that includes family history questions that the patient will complete I guess while they're waiting for their appointment. The clinician then prints and reviews this report and then discusses. It helps give the clinician information about topics to discuss with the patient and some guide in decision making. And also targeted educational materials that are provided in association with that.

We're very pleased to see because this is something as a committee we're very interested in, is constantly looking at evaluation activities. So not only do we want to do evidence-based reviews of the conditions, but we also want to make sure that the activities that we're doing for education and training have a database behind them.

So we're pleased to see the evaluation questions that are being asked as a part of this project, and you can see the range of those. I won't go through with them. But they range from satisfaction to improving provider knowledge and improve adherence to guidelines for screening.

So here are just some reflections and thoughts about next steps with health professionals. It's clear to us that there are several great and important activities underway, and we're pleased to see that all of them have an evaluation component, and we want to encourage the continuation of that.

I think Freddie brought up a point yesterday that we can think a lot about the core competencies for residents, for residency training, for example. But the key is going to be the faculty who implement that. And so, they need to be a target audience for how we're preparing or making any changes in those areas.

And we do feel like, and I think we mentioned this last time, that both the subcommittee and the Secretary's Advisory Committee would benefit from input from the nursing community. So we talked about should we go straight to have a nursing representative on our subcommittee, or should we wait and have the advisory committee have a nursing liaison, who

would then be appointed to our subcommittee?

And we can go either way, but we think the latter strategy would be better. And so, we're hoping that the advisory committee will consider appointing a nursing liaison, and then that person would serve on our committee.

And then, finally, just some broader thoughts about the subcommittee as a whole. So actually, yesterday and today, and before the meeting, several people have contacted me about serving on a subcommittee, which is unusual, I think, for subcommittees. Sometimes people don't want to do that.

But I think this points to the importance of this topic, of these topics and the diverse audiences that are very much interested in how we get the word out and how we change practice.

So, clearly, the breadth of our charge means that there are many different stakeholders and people who do want to make a difference. And we would benefit from multiple perspectives. So, but there's a tension between wanting to get a lot

of input and also we've got 19 members already. If we want to add at least one more consumer perspective and one more professional perspective, that puts it to 21. At what point do we get to be a group that's too large to function efficiently?

So I think, as a subcommittee, we need to be thinking about how we address this issue. We need to think about whether we should have a sub-subcommittee structure, maybe two or three subcommittees within our subcommittee. Some kind of other liaison arrangement. I don't know. I don't want to create too much of a bureaucracy, but we need to figure out how to manage all this because this is very important.

We also need to figure out ways to promote cross-subcommittee communication. Joe and other subcommittee chairs and I have discussed this. Certainly there are education issues that I'm sure that Follow-Up and the Training Committee -- I mean Follow-Up and Treatment Committee need to be addressing. And so, I think we would benefit from some cross-subcommittee discussions.

Joe Leigh Simpson and others brought up this question about how much are trying to react to solve problems that are already facing us right now vs. maybe paying attention to things that are on either the near or slightly far horizon, like whole-exome or whole-genome sequencing and how that might impact providers or patients and families and the public and public awareness of what that might mean. So when do we start thinking about that, either as a subcommittee or as an entire committee?

And then, finally, I don't know if "products" is the right word, but certainly the results of things like the Genetics in Primary Care Initiative or the NCHPEG activities or even the Baby's First Test website or other things that a variety of people are doing to promote education and training. And I think we talked a little bit about this in your four levels of things that our committee -- that the broader committee should be thinking about.

Are there points in time where we would want to endorse or encourage or somehow say the

advisory committee has reviewed this particular product and put our "good housekeeping" stamp of approval on it? I think there is some appeal to that.

On the other hand, there are many different groups out there now developing materials, and we could get bogged down in reviewing each one of them. And I don't think we want to do that either. So I think we'll have to think about that in terms of our committee role going forward.

So that's the end of my report. Let me just ask if any of the other subcommittee members had any recollections of things that happened yesterday that I didn't recall.

Steve?

DR. MCDONOUGH: One addition. As far as the 50-year campaign, I think there is planned to be an event in D.C. in the fall of --

DR. BAILEY: Right.

DR. MCDONOUGH: -- September, October of 2013, which could be really exciting. And also to

tie this in somewhat to the authorization, which will be also that year as well.

DR. BAILEY: Thank you.

CHAIRMAN BOCCHINI: All right. Other questions, comments?

DR. DOUGHERTY: I'm just thinking, trying to think ahead. I didn't notice on the cooperative agreement with the APA -- I may have missed it -- is there a relationship with the American Board of Pediatrics Foundation in that?

DR. BAILEY: Beth?

DR. TARINI: I don't believe they are formally represented on the project advisory committee, but they are part of who we reach out to.

DR. DOUGHERTY: Okay. Just one thought --

DR. TARINI: I can take your concern back to the committee.

DR. DOUGHERTY: Well, I mean, just one thought. The foundation, the American Board of Pediatrics Foundation or the American Board of

Pediatrics has the maintenance of certification and is encouraging pediatricians to do a lot of quality improvement and measure their activities.

And one thing you might think about doing is having a project where the goal is for the primary care physician during the first visit to actually talk about the newborn screening results, and then track to see how that goes. And you could learn something about how that could most fruitfully be done.

DR. TARINI: That's actually a good point, and I'll bring that back. Because that links -- there was the last large project from QuIIN, quality improvement, was about newborn screening results and reporting, doing a change packet, which is the QI terminology for the project, and specifically focusing on communicating normal results to parents.

So it would be a nice link. That's an excellent point. Thank you.

DR. HINTON: Hi. Cindy Hinton from the CDC.

And actually, CDC has just funded or finished funding AAP to develop an EQIPP training module on newborn screening. It is in beta testing, I believe, going through review. It builds off of the QuIIN project, which brought in 15 practices to develop quality improvement protocols. Using the ACT Sheets actually was a primary goal, but what we really ended up focusing on was closing that loop for all newborn screening results, both in range, out of range.

The EQIPP module builds on that and really expands it. They also address hearing screening. And so, now, as part of the Part 4 MOC, pediatricians can sign up, take -- or will I think starting sometime this year, take the EQIPP module, get the certification. And they're really learning how to put in place practice protocols to make sure that every newborn coming into their practice has been screened, that they have discussed every result with the families and really build that network of support and connections they need to meet the needs of that newborn and their families.

So I think it will be a really great addition to all of this.

DR. TARINI: And as someone who's recently taken an MOC in the last 30 days, I think that the committee can do wonders to increase awareness of this module for the primary care pediatricians. So I'll definitely work on this. I appreciate that.

DR. BOTKIN: I asked the question about whether we can get access to that data to take a look at it.

DR. BOYLE: Yes, just a quick comment on the HRSA awareness campaign, or whatever it's going to be. So when this was originally discussed at the committee a couple years ago, the thought was -- and maybe those of you who have been here along with me -- was to really try to focus on some desensitizing the issue of newborn screening so that families expect it and want it, and it's like considered an essential benefit.

And if they don't get it, they're worried. "Why didn't I get this kind of thing?" I

mean, obviously, they will get it, regardless. But, so I don't know if it's taken -- where it is right now. I know that right now it hasn't really gone anywhere? No? Okay.

DR. BAILEY: I think the thing is consistent with just what you said, yes.

DR. LOREY: This is Fred. I'm not sure if this -- I know in the beginning, you briefly mentioned the dried blood spot storage thing. And one of the things that we're being faced with now is the -- I believe it comes from NIH, this whole GWAS and dbGaP issue, and we had a meeting, actually. And we're not going to participate in the studies.

There are other grants and research, et cetera, but in the midst of all of this criticism we're getting about the Government -- and it's giving it to the Federal Government and this, that, and the other thing, we've been saying -- one of the things we've been saying is we're not extracting these DNA -- and then the DNA we extracted is destroyed at the end of the test.

But what GWAS wants any researcher to do is if you're providing genetic data and they have sequencing data, you're supposed to upload this -- which means we lose complete control of what people are doing with it. And we've made a decision now that we're not going to allow that.

And I think that's going to cause a problem for NIH, and I'm just curious if other people like from Michigan, who have encountered this -- we just had our third study commissioned with this. Is that like a whole other issue or what?

CHAIRMAN BOCCHINI: Alan, did you want to say something?

DR. GUTTMACHER: Sure. This is Alan Guttmacher from NIH.

It depends certainly what funding pot one is getting money from. There are certainly some studies funded by NIH, and there are multiple different mechanisms by which genome-wide association studies and other related studies are funded. And some of those clearly do require data

that position in dbGaP with the idea that it goes along with a larger NIH principle, which is getting more comments. I mean, not pervasive at NIH, but it's becoming more so. And that is that data does not belong to the PI. It needs to be shared with the research community so that work can advance most expeditiously to benefit the public.

At the same time, clearly, there is a large amount of recognition that issues of privacy, confidentiality of participants, those cannot be compromised. So it depends very much upon the individual situation, the funding source, and other kinds of things what requirements are there. But regardless of what the requirements are, the expectation is that whether it be through the safeguards that are put on the use of dbGaP, because it's not just sort of freely available to anyone.

In fact, researchers need to be qualified to access it, et cetera, et cetera, that this issue continues to be looked at. I think there has been concern that in some situations, and what we're

talking about is not one of those, that some PIs have hidden behind the sort of curtain of patient confidentiality and privacy when their real interest was not about that. It was about PA solo use.

So that there really are these three different I think competing at times all goods, and one of them is the principle of privacy and confidentiality. The second is absolute recognition of the role of the PI and co-investigators, et cetera, in a project who really have put time, intellectual effort, et cetera, and need to be recognized in various ways for that. And at the same time, the idea that research funded especially by the Federal Governments belongs to the public.

So that we need to try to balance all three of these, and I think you're right that with more of this happening, there's clearly a lot of sensitivity about the issue of genetic information being made available to anyone. And we're still trying to figure out all of the balances in this.

I hope that's helpful.

CHAIRMAN BOCCHINI: Thank you.

Additional questions, comments? Chris?

DR. KUS: Yes, relative to the Genetics in Primary Care Quality Improvement, I'm involved with a HRSA/MCHB-funded grant that was given to Albert Einstein College of Medicine that's called the Bronx Ongoing Pediatric Screening Program in the Medical Home, affectionately known as BOPS in the Medical Home, where they're supposed to look at three and four different domains.

One of their domains of screening is newborn screening, and this project, we've been working on this for the last year and with outcomes like making sure that the results are in the chart. And then once the results are in the chart, that they're discussed with the family, and the group is going to be presenting at the February AMCHP meeting, the Association of Maternal and Child Health Programs.

And they've done some nice stuff because particularly it's linked to the electronic records.

So they're able to produce what they call smart reports for practices to see how they're doing as they're doing this improvement project.

CHAIRMAN BOCCHINI: So I think with these kinds of projects, it's going to really be up to the committee, the subcommittee whether you want to start looking at those, and those would be things that potentially could overwhelm the subcommittee.

DR. BAILEY: Yes. We're already overwhelmed.

CHAIRMAN BOCCHINI: So I think -- but those are obviously important parts of education of professionals and very essential to getting things into the office with individual patients. So, very important.

Other questions or comments? Okay.

DR. BAILEY: I just want to thank the members of the subcommittee. There is tremendous, enthusiastic participation, and I'm looking forward to working with you.

Thank you.

DR. COPELAND: Oh, I would like to

comment on the nursing liaison. Once we develop a process for the nomination for the organizational reps, I think that we'll see how that goes. But I don't want to do anything in the meantime, if we're going to try and establish processes, to circumvent that.

CHAIRMAN BOCCHINI: Thank you for a very thorough, complete report.

DR. BAILEY: Thanks.

CHAIRMAN BOCCHINI: Next is the Subcommittee on Follow-Up and Treatment, and Coleen Boyle will make that presentation.

DR. BOYLE: Well, thank you, and good morning, everyone.

It's my pleasure to report back to you all on the excellent work of the Follow-Up and Treatment Subcommittee and acknowledge my committee members, as well as those -- I think we have a very robust and dedicated group. Many of you have been with us for many years and working on this subcommittee.

I do want to also point out, in addition

to what I'm going to report today, this morning, that this afternoon we're going to hear several presentations that are really products from the subcommittee, including the presentation by Brad Therrell on the vital records, newborn blood spots linkage.

Nancy Green is going to be talking about our white paper on point of care newborn screening. That really was -- the CCHD was really the impetus behind our thinking about sort of this evolving paradigm of the newborn screening in the context of all the different kinds of conditions that are being proposed for the recommended uniform panel.

And then we're also going to hear some additional presentations on the implementation around critical congenital heart disease that will complement what we heard in our subcommittee yesterday afternoon.

So our committee really has focused over the years on we've called it follow-up, but it really is newborn screening implementation beyond short-term follow-up. We've done a number of white

papers in regard to trying to define what follow-up is, trying to provide guidance to the field in that regard.

And one of the issues that I know you know that we have been working on in that context is this issue of making sure that children who are identified through newborn screening are provided the appropriate services and that those services are equitably distributed.

So, within that context, medical foods has been an issue that we have been putting considerable energy towards in the subcommittee. So we did hear a couple of very targeted presentations yesterday, one by Kathy Camp on NIH-related activities. There was a workshop. I didn't put the date on that. But there was a workshop in December, which was really trying to focus on identifying gaps in the safety and efficacy in regard to inborn errors of metabolism. It really was a stakeholders' workshop.

And then, following that -- and I don't know if Cathy is in the room?

Cathy, if you are, just raise your hand. She's not.

I know she provided information to us on a meeting that NIH is also conducting next month, which is essentially to update the NIH consensus statement around PKU.

Many of you are familiar with that. I know, I think Rod actually chaired that consensus conference many years ago. And so, that's an update. Clearly an important and needed activity, and Cathy did provide for us some background information and a website link, for those of you who are not aware of that.

So that was just some very concrete activities that NIH is embarking on around the issues of medical foods, the continuing science associated with that.

Another big bundle of activities, and Christine Brown presented on that regard, and that is this issue of medical foods. And reimbursement has been an issue that the committee has brought to the attention of the Secretary numerous times. I

think we put forward four different letters in that regard.

So now with -- we heard yesterday in the context of the Affordable Care Act and the essential benefit package, there is concern that medical foods may not be incorporated at the state level in the context of what states end up adopting. So Christine gave us a very nice update, for those of us who weren't intimately familiar with this package.

Many of you know that HHS held regional listening sessions, and Christine let us know that medical foods were discussed at each one of those listening sessions. And HHS issued a pre-bulletin around the essential benefit package, which includes these 10 essential services. But the bottom line is there's really going to be flexibility for the states to choose among four options, and the decision really rests with the states.

And Christine's summary was essentially that states that currently have coverage will most

likely continue to have coverage. Those that don't probably won't. So it's sort of a -- her analysis was a sort of full circle, kind of back where we are.

So we did discuss what the advisory committee could do to try to understand and continue to monitor this complex issue. And so, we will, as an advisory committee -- subcommittee, excuse me -- continue to get information about how this rolls out and try to inform the process. Because I think that's really what we can do is really education and information.

So, in terms of education and information, that really goes to the next bullet here, and our subcommittee, in collaboration with the regional centers, worked together to conduct an evaluation of insurance coverage, using the regional centers as an opportunity to do a survey. And Sue Berry and others in the room, Ronnie Singh and -- help me out with names, guys.

Yes, Kathy Harris. Thank you, Kathy. From those three regions were engaged in that

study.

The analysis of that study is complete. A manuscript has been drafted, and Sue Berry will tell you that has been through at least 40 different reviews, or more. But she has had great patience and a wonderful sense of humor through the whole thing and quite the dedication, as has everyone else that's been engaged in that.

So it really is a descriptive study, in my regard, in terms of the use of medical foods within the context of families receiving services and tries to identify the limits of insurance coverage. So I think that at some point we will bring this back to the committee for I don't know which one of those four categories that you outlined yesterday this might be appropriate for, but that is for further discussion.

So, again, medical foods is kind of illustrative for us in terms of some of the complexities around the implementation and the follow-up for children identified through newborn screening.

I mentioned that we had a presentation by Dr. -- that's actually Dr. Badawi from Maryland. I'm probably not pronouncing her name correctly. But this was really, I thought, an enlightening presentation on the complexities of clinical congenital heart disease implementation at the state level.

So Maryland is in the process of adopting CCHD newborn screening, and they were actually tasked to put together an expert panel to really look at the challenges and the issues around implementation. That extra panel delivered a product to their I guess state legislature. I think it was on Tuesday that this report went forward.

But I tried to highlight for you some of the issues that the report discussed, and this would be nice thinking about our presentations this afternoon by two other states, Indiana and New Jersey. Again, I think it really -- it behooves us, as an advisory committee, to stay very closely in tune to how these new conditions, implementation

of these new conditions are rolled out, as we have done with SCID. I think we've done a very nice job in terms of pilot studies for SCID.

So I'm just going to run down this list in terms of how -- these are in the broad bundles that we heard about, that, first of all, hospitals should follow the protocol that Kemper, et al., put forward in the Pediatrics article, that the birth hospital is actually charged with the screening and follow-up from positive screens.

So the context there is similar to newborn hearing screening, where the hospital is charged with that responsibility. Their assessment was that all hospitals have the capacity for screening, but that they must establish the capacity for follow-up, whether that's in regard to a telemedicine component or the need for transport for children.

The hospitals are responsible for the protocol for follow-up and clinical management, though obviously there needs to be harmonization across hospitals in that regard.

The health departments -- again, these are the roles and responsibilities very clearly identified here. The health department is responsible for surveillance data on screening and evaluations. So there needs to be some -- we did ask the question about a longer-term follow-up to understand how these children do and the linkage to the Birth Defects Surveillance Program.

They did say that the linkage is going to happen with the Birth Defects Surveillance Program. But in terms of trying to get ongoing data for those children, that would be done within the context of those existing programs.

Education is a clear component to this, and it should be. So, Don, more work for your subcommittee or more thoughts. Education should be provided to consumers, clinical staff, and community providers. So, again, everybody.

But there was no one -- at least I only had the executive summary there. I don't know if anybody remembers Deborah talking about this, but there was no one identified for the education

piece.

And then, cost. So they talked about -- this summary report talked about the main costs, which is really for the hospitals and staff time to screen and track results in a very broad sense, and then the cost to states is the infrastructure for evaluation.

We did ask them if they had received any negative pushback from hospitals, and at that point, she said they actually had not and that many hospitals, at least their largest hospital -- which some of you who are in this region might know what that hospital is -- has already been engaged screening. So just it was good to hear from them, and I wanted to give you enough details so that you could put this context with what we will hear this afternoon.

So I think our subcommittee will definitely stay on top of this issue.

The latter half of our discussion for the subcommittee was a continuing sort of reflection about where the subcommittee has been. And I tried

to paint a broad picture for you. I know we're clearly seeing our lane as trying to stay abreast of implementation and how well implementation is carried out.

And I think that the angst for the subcommittee is that we perceive this -- we perceive newborn screening and the mandate for newborn screening as a real disconnect between the actual screen that is equitable and fair and goes to everyone, and yet the mandate for follow-up and treatment is not there.

And so, how do we best identify those issues? How do we best target our energies on those things as inequities that are maybe the easiest ones, the low-hanging fruit? The easiest ones to change, I mean, that's the challenge for our committee.

So it's easy to identify the issue. It's much more challenging to identify what it is that we can do. So, as a committee, we've taken a fairly broad view on this, trying to set the landscape. But my own personal feeling is that I

think that we need to start to take some -- maybe do some deeper diving. Medical foods might be an example of that.

So what we talked about, that second bullet, that is what to do about this? You know, we really need to be monitoring implementation better, and that's not just for the new conditions, though. It's for conditions that are already -- we've been monitoring for years and years, the work that NIH is doing in terms of PKU, my introductory slide, and keeping abreast of the science and the changes and the treatment and understanding of long-term outcomes, understanding the issues on pregnancy and PKU, all of those evolving issues.

As children survive into adolescence and adulthood, which is great, great, great news, we need to stay tuned to what those complex issues are.

We did some work as a subcommittee a couple years ago about clarifying roles and responsibilities in follow-up and treatment. And what I just presented to you for CCHD implement

might be very illustrative of maybe what we need to do and what those around the table yesterday felt like we needed to do, is be very explicit about whose lane these different activities fall in.

Yes, that may vary from state to state, based on implementation. And that given that we highlight those, at least states, as they implement or reevaluate how things are done, can deliberatively make changes in those roles and responsibilities.

We talked about taking some -- to do that, several people -- Celia Kaye, others, I think Jeff Botkin, when he used to be with us and then turned coat on us --

[Laughter.]

DR. BOYLE: But his notes from September was that maybe we should leave this at sickle cell disease. You know, there are considerable Federal resources that have been going into sickle cell disease, but yet in terms of -- I don't know what you all, the physicians in the room would call this. But in terms of continuity of care and

assuring that every child, adolescent, and adult receives good, consistent care and treatment, I mean, I don't think we're there with that.

I think we've made vast improvements in the survival of individuals with sickle cell disease, but I think we have -- I mean, I've said this many times in my own context, I think we can close that gap in terms of a 30-year disparity in survival in children with sickle cell, of individuals with sickle cell disease. And I think it's because we're not applying what it is that we know that can work well.

So what we thought we might do, and again, these are still evolving thoughts here, is trying to clarify roles and responsibilities, try to look at implementation issues and maybe take three, at least sickle cell disease and then the two new conditions that the committee has added to the newborn screening panel, SCID and critical congenital heart disease. Because we do feel like we have a responsibility for those and that sickle cell disease because we do think there's a

considerable Federal Government investment, and it would be great for us to help align that investment with what we see as appropriate gaps.

The other idea that was tossed around a bit, and I'm just going to put it out there for your own consideration was maybe providing to decision makers, particularly around the cost of care, is like we've done -- and I don't think this could be the work of the committee, but perhaps the work of agencies or others, but identifying the cost of providing care. So this could be used by decision makers, insurers, others in trying to understand what this all means.

And then, finally, I think Bob Bowman made this excellent suggestion, and the more I thought about it overnight, I think that this is something that I know, Don, you were saying the same thing about your committee. I think we have a lot of great ideas. Sometimes we just follow them up because we have an interested person, but I think what we need to do is we need to, following on Sara's idea, sort of rethinking how we do things

in the committee.

I think we need to come up with a process, some method in terms of trying to prioritize the work of the committee and align it better with really what the needs are out there. So that's it.

DR. COPELAND: If it's okay, I'd like to comment. I think the committee priorities, what you've outlined there should actually be the advisory committee priorities and that maybe it would be better to come from the advisory committee to the subcommittee and help direct the work. And that would definitely help with the prioritization, et cetera, and this is something that could be definitely a topic and a discussion at the next committee meeting is just looking at these different issues. What are some of the options, et cetera?

But monitoring implementation is an advisory committee role. Whether or not it gets delegated to a subcommittee or it stays at the advisory committee level I think is something that

needs to be decided by the committee. These are all very key issues, and I don't think that -- and I think that we all realize that this is something that is more than just follow-up and treatment, and I think that we need to make sure we get -- as opposed to having three separate subcommittees work on the same thing.

So we can discuss probably in the meantime about how best to present it to the advisory committee, but I'd like the advisory committee to take the lead, and the subcommittee, various subcommittees to follow through with it.

DR. BOYLE: Having had some experience with other committees, just a comment to that, it might be good if we, as a full committee, reflect on what those issues are and then charge the subcommittee to sort of follow up on that.

DR. COPELAND: That was what I hoped to get through.

DR. BAILEY: I would certainly echo that. I think within our committee, we feel we're doing a lot of things, but instead of everything coming

from us to the primary committee, let's charge the subcommittees to do the major things.

CHAIRMAN BOCCHINI: Jeff?

DR. BOTKIN: I've got a real specific question. I'm wondering whether Maryland talked about how they were funding the increased state responsibilities for the congenital heart program? Were they just going to add that onto the workload, or were they going to increase kit fees, or is there some mechanism that they describe for funding?

DR. BOYLE: I don't remember. Does anybody else remember?

DR. KUS: I don't think there's any funding.

DR. BOYLE: I don't think there's any funding, yes. They're applying for the HRSA grant.

DR. KUS: Yes, it was legislation that didn't have appropriation.

CHAIRMAN BOCCHINI: Other questions, comments? I think, clearly, the committee has a very insightful report, and it's right on target

with where we are. And I think that bringing this forward to the full committee and now having the chance, as you indicated, to reflect on it and think about it and then come back an opportunity to spend some time discussing that, prioritizing I think is very appropriate.

And as Sara said, I think that it's very clear that this committee's responsibility includes implementation and follow-up and being aware of what has happened, based on the recommendations of the committee to the Secretary, is very important and needs to be looked at carefully.

And it will inform the committee for subsequent decisions, and so I think that's important.

All right. Well, thank you all. I thank the presenters for the three subcommittees. I think, clearly, in 2 hours, you each covered significant topics, and we didn't have a lot of time.

Next, we are going to have the final report from the Evidence Review Group on

hyperbilirubinemia. I know we're a little bit ahead of time. Jim, are you ready and the group ready so we can go ahead and get started?

As you know, this is a condition that was nominated, and the Evidence Review Group has been working diligently for a considerable period of time to put together a review and a final report. It's now available, and we're going to have a presentation of the final report.

And then I asked two committee members to sit in on the final discussions of the Evidence Review Committee and to then look at the evidence and formulate, using our template for decision process, what the potential recommendations of the committee might be. And so, after we hear the final report, we're going to hear from the two committee members and their reviews and their initial recommendations.

So they're going to do this, and then we can sort of frame the discussion and then get input for the committee as to the final recommendation. A vote will be required subsequent to the

presentation.

So, Jim, thank you.

DR. PERRIN: Thank you, Dr. Bocchini. It's a pleasure to be here today to present this report.

I believe you all know that we have transferred the primary responsibility for the Evidence Review Group from our team at MGH and Harvard to Alex Kemper and his team at Duke. So we've gone from Harvard, otherwise known as "the Duke of the North" –

[Laughter.]

DR. PERRIN: -- to the real thing. And I'm presenting this report primarily because our team took the initial responsibility for the development of the hyperbilirubinemia report, and thus, I have the opportunity to share it with you.

The members of the team, many of whom are here, include John Co and our group in Boston; Alix Knapp, who I believe is on the phone; Danielle Metterville; Lisa Prosser, who took responsibility for decision analysis that we will describe for the

end of the presentation; and then a number of other consultants and staff who were very much involved with this project.

You have a very full report in your book. It is a very broad and complex area. We reviewed quite a good deal of literature. I'm going to try to summarize the report in the next several slides.

As background for neonatal hyperbilirubinemia, bilirubin elevations, as I think most of us know, are very common in newborns. The elevations of bilirubin arise from a variety of etiologies.

Hyperbilirubinemia is a detectable risk factor for acute bilirubin encephalopathy, which I'll describe in a little more detail in a few minutes, and for chronic bilirubin encephalopathy, otherwise known in general as kernicterus. And the primary concern of screening and treatment is to prevent the neurotoxic effects of hyperbilirubinemia.

I want to review very briefly two previous really key reports. One was backed by the

American Academy of Pediatrics in the development of clinical practice guidelines initially in 2004 and then updated in 2009. And this was the prevention and management of hyperbilirubinemia in infants of greater or equal to 35 weeks gestational age, i.e., not smaller, more premature infants.

The main recommendations of this report were to promote and support successful breastfeeding, recommended systematic assessment before discharge with measurement of bilirubin levels either with total serum bilirubin or with transcutaneous bilirubin measurement individually or in combination with clinical risk factor assessment to help assess the risk of subsequent hyperbilirubinemia.

A third recommendation was for early and focused follow-up based on risk assessment and based on these predischarge screening results, gestational age, and other risk factors. And then, when indicated, phototherapy or exchange transfusion to decrease serum bilirubin, prevent hyperbilirubinemia, and possibly -- that was the

term used in Academy report -- bilirubin encephalopathy, or kernicterus.

The U.S. Preventive Services Task Force in 2009 released an evidence review regarding screening infants for hyperbilirubinemia, and their assessment at that time was that the evidence regarding the benefits and harms of screening newborn infants to prevent chronic bilirubin encephalopathy was lagging. And the recommendation, therefore, was to say that the evidence is insufficient to recommend routine screening.

So let me now move to our work and our report activities. With the help of a subcommittee of this committee and discussions also with some experts, we tried to come up with case definitions for three primary areas. What do we mean by neonatal hyperbilirubinemia, which we defined for this report as serum bilirubin levels above the 95 percentile for age in hours in term and near term newborns.

For acute bilirubin encephalopathy, which

is very widely and diversely described in the literature, we limited our definition to advanced manifestations of bilirubin toxicity in the first weeks of life. Things like loss of Moro, extensor hypertonia, high-pitched cry.

Some authors do use this term, ABE, to over substantially less severe symptoms with basically the more subtle signs, such as somnolence, hypotonia, and fever. For our review and as we present it to you, we actually did not consider this acute bilirubin encephalopathy.

And then, of course, the thing that we're particularly interested in defining and preventing is chronic bilirubin encephalopathy, or kernicterus, defined as persistent and permanent brain damage related to bilirubin toxicity and characterized by four areas. One is movement disorders, such as athetosis, spasticity, dystonia; auditory dysfunction, oculomotor impairment; and dental enamel hypoplasia.

So this is the conceptual framework that we used here. I will go through parts of it. It

is a bit complicated, and it's one we've used before for some of our earlier reviews with the committee.

So we, of course, begin with the general population of newborns on the left here. We then do some screening for hyperbilirubinemia, trying to understand where we can the harms of testing and/or identification. We develop risk assessment of increased bilirubinemia, and then we talk about the issues of treatment of hyperbilirubinemia and the relationship of the acute phenomena in the newborn period with outcomes especially of chronic bilirubin encephalopathy with the question here to discuss as to whether screening and/or treatment are related to reduced rates of both acute bilirubin encephalopathy and chronic bilirubin encephalopathy.

So our literature review, we searched for all relevant studies published between January 1990 and October 2011. We did present earlier versions of this report to this committee in the past, but we have updated the literature review to October of

2011, English language human studies only.

We have about 3,000 abstracts for preliminary review. We looked at 201 articles for more in-depth review, and 112 -- forgive me, it's not 113. It's a mistake in this slide. One hundred twelve articles met all inclusion criteria for abstraction.

So let me just briefly overview these 112 studies. This, I think, will give you, among other things, a sense of the quality of the studies and the quality of the evidence there.

There is a very small number, as is always true in our reviews, of experimental interventions. There is a relatively large number of cohort studies. There is a smaller number of case control studies, and about half of the studies that we reviewed are really case series. And again, there are things once can certainly learn from case series, but there are real limitations about understanding case and effect and real prediction of outcomes in case study literature.

So this gives you a little bit about the

background of the studies that we have. I'd say that if you look at some of the rarer disorders we have studied with you, this is actually a few more experimental interventions, but not a lot more.

So, the condition, let me give you some of the statistics that arise from the review on the prevalence of this condition, which is, first of all, if we look at incidence of bilirubin levels in newborns above 30 milligrams per deciliter, the ranges in reports are between 3 and 12 per 100,000. So it's a pretty uncommon phenomenon to have this high a level of bilirubin.

The estimated incidence of acute bilirubin encephalopathy, using a fairly strong definition of substantial symptomatology, is estimated at less than 1 per 200,000 live births. And the estimated evidence -- I'm sorry, incidence of kernicterus ranges from about 0.5 to 2.7 per 100,000.

However, that 2.7 is very much of an outlier in the studies that we provide to you in the larger report, and most of the evidence would

indicate rates really between 0.5 and 1 per 100,000. So these are all relatively uncommon phenomena.

So let's talk a bit about the relationship that's known between hyperbilirubinemia and acute and chronic bilirubin encephalopathies. First is that no specific bilirubin level is associated with acute or chronic encephalopathy, although in general, higher levels of neonatal bilirubin are associated with higher likelihood of both acute and chronic manifestations.

Most, but not all, cases of chronic bilirubin encephalopathy have total serum bilirubins above 30, but rare cases do occur below 25 and even lower, with co-morbidities and/or significant risk factors.

And although some neonates do develop less severe signs of hyperbilirubinemia, less severe than fairly dramatic acute bilirubin encephalopathy, we have a very large majority of studies indicate no long-term effects at all of

that level of increased bilirubin and minimal evidence of neurologic involvement.

We move to screening and say that there are three major forms of screening that exist for hyperbilirubinemia. One is visual assessment. Just looking at the baby, using certain criteria for where you can see jaundice in the baby and using that to estimate levels of bilirubin. Transcutaneous bilirubin measurements and total serum bilirubin.

In general, the evidence that we have is that TcB appears as a valid screening tool for detecting significant hyperbilirubinemia, i.e., it is pretty high correlation with TSB at higher levels. But when you get down to fairly low levels -- 10, 8, 7 -- it's much less well correlated with a total serum bilirubin.

There is an hour-specific bilirubin nomogram that's based on total serum bilirubin values that allows prediction of subsequent hyperbilirubinemia, and there has been some work that applies this same risk nomogram to the use of

TcB rather than TSB values.

Treatment evidence. The treatment evidence basically is that phototherapy does effectively decrease levels of bilirubin in the neonatal period. A number of very good studies that document this quite well.

There is indirect evidence, but only quite indirect, that screening and phototherapy decrease rates of chronic bilirubin encephalopathy. Case series provide evidence -- this is one of the things that we did learn from the case series -- that symptoms of ABE, children who have quite severe neurologic findings in the neonatal period, in fact, may be perfectly healthy at 1-year and 2-year follow-ups.

There is direct evidence that early treatment with phototherapy effectively does lower bilirubin level and seems to lower the need for treatment using treatment guidelines for exchange transfusion. I might say that adverse events remain common after exchange transfusion, although this is a relatively unused -- not underused,

forgive me -- relatively unused technology today.

Economic studies, and I will defer a little later to Dr. Prosser here. But as is true in most of the other reviews we've done, there is limited quality and quantity of economic evidence. There is limited evidence for the cost of these three or four areas that seem to be most critical: jaundice readmissions, phototherapy treatment, long-term outcomes.

There is one study of cost effectiveness. The strategy is to prevent kernicterus. He estimated costs of doing TcB, transcutaneous bilirubin, testing ranged from less than $1 to not quite $8, with most in the lower range here.

And the cost per case that we've estimated of preventing kernicterus using TSB is somewhere around $5 million or $6 million. You can see our sensitivity analyses here, using TcB are closer to $10 million.

So the harms and benefits of universal predischarge screening. The harms are to the literature relatively limited harms found. There

are some risks of phototherapy that include fluid loss, temperature instability, corneal damage, skin rash, diarrhea, delayed parenting and bonding. All of these in the literature appeared to be minor risks.

The use of exchange transfusion, which, of course, is not screening, but rather is a form of treatment, is associated with substantial morbidity and some mortality.

The benefits potential of universal predischarge screening include the identification of newborns who are likely to develop levels above 30. We do -- the benefit may be that lowering bilirubin level reduces the risk of a newborn developing ABE and kernicterus. And that early identification and treatment with phototherapy may prevent the need for exchange transfusions and readmission to hospital.

So our report gives you many tables. I'm going to try to go in a little bit of detail in these last few tables about the key findings of the report, based on the questions that we worked out

with the committee to try to address.

In these tables, where we have the number of studies, you can see in the first column, for example, we have 27 studies that include about 50,000. The design is in the second column. The quality or risk -- I'm sorry, the risk of bias and study quality is in the third. And then some aspects of the quality of the data in the areas of consistency, directness, and precision.

And then our overview of the quality of this particular item is moderate strength of evidence, and the evidence is that when compared to controls, newborns with increased total serum bilirubin experienced an increase in acute clinical manifestations.

The second question is additional sensitivity of TcB over visual assessment. Visual assessment being sort of routine looking at the child again. And here, the evidence is fair. There's really two decent studies or two studies that we reviewed in some detail.

Here TcB appears to detect most cases of

neonatal hyperbilirubinemia that may necessitate further assessment. Adding TcB to visual assessment increases the sensitivity from about 6 percent to 30 percent. So a substantial increase.

And there is some evidence that indicates that TcB leads to less subsequent TSB blood draws and a greater number of newborns identified at or above the higher risk 75th percentile. This is, again, comparing a TcB with visual assessment.

The third question is the specificity and sensitivity of risk assessment/screening prediction. This is where you're looking at whether the test will predict whether after discharge in the immediate neonatal period children are going to have higher bilirubin levels. The strength of the evidence here is moderate.

You can see that we have seven studies. The specificity of predischarge screening and risk assessment nomogram at or above the 75 percentile is high. As you can see here, sensitivity at or above the 75th percentile is also high. And above the 40th percentile, the specificity drops, as one

might expect, to about 65 percent. But the sensitivity is still quite high there.

So the evidence again, though, does not address whether this prediction assessment decreased their incidence of kernicterus.

And then the next question is really whether screening for hyperbilirubinemia prevents kernicterus. We use the term "label" -- the label of poor, excuse me. Indeed, there are no data here at all that we were able to identify.

And then, the effectiveness of early intervention for hyperbilirubinemia, the strength of evidence is moderate. Twelve studies, again indirect evidence that early intervention is associated with improved outcomes for those with neonatal hyperbilirubinemia. Direct evidence that treatment lowers elevated bilirubin concentrations. That seems to be quite clear. And that lower bilirubin levels seem to be associated with less acute clinical manifestations. Again, no evidence relating to longer-term kernicterus.

So this, again, is sort of the quick

overview of what I've just said. I don't think I'm going to read through this table again. But this, basically, is what we've just covered in the last few slides together.

And I'm going to comment on what the gaps in evidence are. One of the roles of our Evidence Review Group is to sort of let you know where we think we need to know more information.

Again, the relationship between high bilirubins and kernicterus, we still have insufficient evidence. And there's no clear evidence that treating clinically significant hyperbilirubinemia prevents kernicterus.

There's no evidence regarding universal discharge bilirubin logistics and the impact of large-scale screening, something that Dr. Boyle was really describing in some aspects of her previous report for other conditions. And we really don't have much evidence about cost effectiveness in this area.

I'm going to try to describe what Dr. Prosser did in the decision analysis, and she can

certainly correct me if I get any of these parts wrong. But partly based on our last discussion with the committee, we went ahead and carried out a decision analytic model to project outcomes.

We convened three meetings with six experts who are listed at the bottom of the slide. They're Drs. Bhutani, Johnson-Hamerman, Maisels, Newman, Stark, and Stevenson. And worked with that group to confirm and revise the model structure to identify key outcomes, which really are kernicterus.

We developed a series of assumptions, based on our work with this group, that include really focusing on three large-scale pre-post studies. Some of the only really good studies that we had here that gave us these kinds of data and that we were, again, interested in reducing the proportion of children with severe neonatal hyperbilirubinemia who would then develop kernicterus.

Key findings at the beginning of this work and consistent throughout again is the lack of

data relating to hyperbilirubinemia and kernicterus. And it also became clear from the studies at least that TcB screening in practice may not be exactly what's happened in descriptions in the literature, that there is almost always in practice some follow-up with TSBs, and it's variably described in the literature on those studies.

The assumptions that we used were that the U.S. birth cohort is about 4 million, that the incidence of kernicterus is about 0.5 to 1 per 100,000, and that the impact of screening based on those studies might reduce acute hyperbilirubinemia by 45 to 73 percent.

Using those assumptions, the boundaries of benefits with these assumptions, that the range of projected annual cases of CBE before implementation of universal screening would be between 20 and 40 in the U.S., and the range of cases that are potentially averted by screening, potentially averted -- need to stress that -- are about 8 to 29 per year. Again, not all cases of

kernicterus would be prevented by universal screening.

I believe that is my last slide. So thank you very much for the opportunity to present this.

CHAIRMAN BOCCHINI: Thank you, Jim, and thank you for the work of your group for putting this great stuff together.

This is open for discussion. The committee certainly has the full report that they were able to review before the meeting.

DR. GUTTMACHER: Can you say -- can you tell us anything more about the relationship, either observed or projected, for screening with exchange transfusion, since exchange transfusion, as you showed, has such high mortality associated with it.

DR. PERRIN: So we actually don't -- did not find data looking -- that described a change in rates of exchange transfusion. But we have tons of anecdotal data that it is vastly less common, and especially in term and near term infants, it's

almost never done at this point. It's really pretty much limited to sick prematures at this stage.

So I think it's really not a critical issue at the moment.

CHAIRMAN BOCCHINI: Steve?

DR. MCDONOUGH: Is there any information on the incidence kernicterus decreasing in this last decade with the fact those guidelines have gone out?

DR. PERRIN: There is a little bit of evidence that, indeed, kernicterus rates may have decreased. It is not overwhelmingly convincing data, and there is some disagreement in the literature about that fact.

And of course, associating that specifically with the publication or the distribution, dissemination of the guidelines of different kinds is hard to do.

CHAIRMAN BOCCHINI: Denise?

DR. DOUGHERTY: Just a couple of questions on criteria. One is when you say in

those charts that a study quality is good, does that mean the study quality using some criteria for, say, a cohort study is good for that kind of a study?

And do you have I think it's in the article that we all wrote about what should be used to judge the study quality, but is that what you used? Because I see that only one reviewer actually assesses the quality of the study.

DR. PERRIN: So I actually don't think we said good at any point, but maybe we did. We may have. We may have.

DR. DOUGHERTY: But under "risk," that column "risk of bias/study quality."

DR. PERRIN: Oh, I'm sorry. Yes, yes. Okay, yes. So we use actually essentially a variation on the grading criteria for these studies. And as I said at the beginning, we have almost no experimental studies. These are predominantly cohort and case series studies.

And so, grades case studies extremely low.

DR. DOUGHERTY: Right.

DR. PERRIN: As you know, right. Does that answer your question? I'm not sure.

DR. DOUGHERTY: Well, I guess my question was, you're not using the typical grade study criteria so that every cohort study would be judged low. You're saying for a cohort study, this study is pretty good, or most of the studies are good quality?

DR. PERRIN: Yes.

DR. DOUGHERTY: Okay.

DR. PERRIN: They're a very small number, I think, even there. The answer is yes.

DR. DOUGHERTY: Okay. The other question goes in the other direction where on the harms, you listed a lot of things like corneal damage and things that -- and then said all the risks are minor risks. So I'm wondering if "minor" means that they infrequently occur or that the corneal damage, per se, is minor and doesn't affect eyesight.

DR. PERRIN: Yes. I will have to go back

and look at the corneal studies. There are two, if I remember correctly. My memory, but I don't want to be held to this without going back to the literature, is that even in that context, there was resolution. And it's quite rare.

But indeed, as you likely know, there are a series of guidelines for how to do phototherapy, among others, which does include a substantial amount of ordinalities to protect the cornea, among other body parts.

DR. DOUGHERTY: Thank you.

CHAIRMAN BOCCHINI: Jeff?

DR. BOTKIN: I wonder if you came across any literature that gives a better description of which kids end up with kernicterus. Are they the kids who got G6PD or Rh incompatibility or prematurity or glucuronyl transferase deficiency conditions, et cetera? I mean, are they enriched by some subset there?

DR. PERRIN: So the answer, they seem to be -- again, you're dealing almost always with pretty small samples. So probably on the order of

two-thirds are in the high bilirubin level. Depends a little bit on the series. And the others are typically children for whom there are any of a number of risk factors, including the ones you just mentioned, Jeff.

DR. PROSSER: Can I add something to that?

DR. PERRIN: I was going to say you went over that more recently, too.

DR. PROSSER: So there was a lot of discussion on this point. Well, on the point of what categories or subgroups of children with hyperbilirubinemia would not be impacted by screening. So the discussion on the expert panel was that there were these certain conditions that were not likely to be impacted by screening, and that's reflected in the decision analysis projections of where screening is not likely to be 100 percent effective in preventing cases.

DR. PERRIN: And of course, there are some conditions which increase susceptibility but also do increase bilirubin well above 30. So

there's a bit of an overlap in some of these to a certain extent.

CHAIRMAN BOCCHINI: Fred?

DR. CHEN: My question about the evidence review is in relation to our discussion yesterday about our efforts to harmonize with other Federal groups, like the U.S. Preventive Services Task Force, which did this evidence review just a couple years ago, 3 years ago or so. Your sense, Dr. Perrin, about the difference in methodology, the difference in sort of implications for what it might mean for our evidence reviews to be comparable to their evidence reviews?

For example, I do know that they haven't done decision analysis. They don't do cost effectiveness analysis, at least that's my understanding.

DR. PERRIN: So, thank you for that really interesting question. We did pull together a group of people about a year ago to think through how to do an even better job of weighing the evidence in the context rare to extremely rare

conditions with very limited evidence, which is what the issues before the advisory committee typically are.

We benefited at that time from about six or seven people who either then or had recently been members of the U.S. Preventive Services Task Force to discuss ways of weighing evidence, which was very productive. Ned Calonge, who used to chair the Preventive Services Task Force, has been an adviser from the committee in this process essentially from the beginning.

So I think that I can say is we've benefited a great deal from the wisdom of the Preventive Services Task Force. It is absolutely true that the evidence procedures that we have carried out differ in substantial ways from those of the U.S. Preventive Services Task Force, which provides a substantially different and especially higher bar for evidence.

It gets back to Dr. Dougherty's comment before, which is we've tried to use grading criteria in our evaluation of evidence. But even

grade, which has tried very hard to be thoughtful about the variations in evidence that exist, it does typically label our primary series of data or studies very low. And we've tried to say -- they do provide us some information that we think is valuable for committee decisions.

A long-winded answer. I hope it gets to what your question was.

CHAIRMAN BOCCHINI: Additional -- yes?

DR. GETCHELL: I have two questions. First of all, the TcB test, is it a needle stick?

DR. PERRIN: No, it is not. It's just --

DR. GETCHELL: Just transcutaneous?

DR. PERRIN: Correct.

DR. GETCHELL: Okay. And the other question is, as with CCHD, what are the implications for public health with this? I know you didn't look at it, but I think it's something we need to think about. Would public health, for example, have to provide surveillance monitoring, education, follow-up, and so forth?

DR. PERRIN: Well, that again I think is

really a committee discussion and decision. And our task, of course, is to provide you what we can learn from the evidence from experts. But I think that's a very important topic that I would leave for your discussion.

DR. GETCHELL: Yes. That isn't currently in place, the ability to assess that. And so, that's part of the whole condition review.

CHAIRMAN BOCCHINI: Jeff?

DR. BOTKIN: Yes. As you spoke with the experts in the community about this condition, I don't have a sense of what the experts feel about universal newborn screening. Is this something that they're advocates of?

DR. PERRIN: You want to try that?

[Laughter.]

DR. PROSSER: We simply did not ask them that question. So, in the expert panel, we really had a very focused discussion on the specific questions we were asked around the evidence and how we would use it to project outcomes that would be of use to the committee.

And so, we really didn't get into that. I would say that there was certainly the spirit that it would be useful to have more evidence. And one of the interesting outcomes of the sets of calls were the areas that could be identified for future research in this area. But that wasn't our discussion.

DR. PERRIN: I think it's also important to remember what our roles and tasks have been. And in our work for any of the reports we've done, when we have talked with experts that include people doing research in this area, clinical in this area, advocates and families, we have not really assessed what do you think should happen, or what do you think the committee should recommend or whatever else.

Our roles and responsibility have always been simply to gather what evidence they can add to what is published in the literature. So I think that's the reality of how we addressed this, Jeff.

CHAIRMAN BOCCHINI: Okay. Denise and then --

DR. DOUGHERTY: Just what Jim is saying reminds me, just as a matter of process, since we have almost all new people on the committee, maybe it would be good to redistribute sort of those articles that do lay out what the process is, the roles and responsibilities, and also the article about how the evidence review is done with the criteria for judging different things. It might be useful to the rest of the committee.

CHAIRMAN BOCCHINI: Okay. Thank you.

Nancy?

DR. GREEN: Thank you. I'm Nancy Green, Columbia University, as part of that workgroup.

I just want to mention that, you know, very nicely done and correctly, assiduous attention to the information. But I would like to say that the evolution of the transcutaneous monitoring, I think, has sort of thrown a monkey wrench in the analysis, right, because some of the data were done before.

And specifically addressing the question about the experts and, of course, didn't ask them

for their opinion about what ought to be done, but in the context of this juxtaposition of practice and public health, several of those, that panel of six -- and I don't know what proportion because we didn't ask -- do practice universal transcutaneous monitoring in their own institutions. So I just wanted to add that.

Thank you.

CHAIRMAN BOCCHINI: Carole?

DR. GREENE: Thank you.

I should probably mention that years ago, when I worked for HHS, I was involved in the beginning of this. And so there's a long history involving efforts with the AAP, asking the AAP to make this standard practice.

It became a JCAHO sentinel event, which is something that made hospitals more conscious of the issue and more hospitals moving towards monitoring. So there is a very long history of a community of experts who believe all babies should be tested, and the question came to this committee after this long history.

Having said that, I personally think that the question is now coming back to what's the public health role here? And we are framing it, I think, as should this be part of the newborn screen? But I don't think that's the right question.

I think that there's a lot of evidence that suggests that this is a fairly noninvasive test. Speaking as a pediatrician, I would like to see every baby have the test. That doesn't mean that it makes criteria for addition to the newborn screen with all the public health implications.

And I think we got into this with the CCHD, and I don't think we have to do an up or -- I personally don't think that it would necessarily be an up or down newborn screen. But I think in the process for the committee, there is now room for a different kind of recommendation. And if the committee wanted to say all babies should be tested, even though it's not part of the core newborn screen, I think that should be an option on the table.

CHAIRMAN BOCCHINI: You're raising the issue about whether this is a practice standard rather than a newborn screen, and I think that's certainly an important issue. And the way our evidence review had been conducted, obviously, we don't have public health implication in that. And as you know from our prior discussion at the last meeting, there is the need to add that.

And so, one of the options, if we were to accept this to go forward, would be to go forward for a public health impact analysis. And so, that certainly is an option, as is the option you raised.

DR. GREENE: Thank you.

And I would just say that we're just exploring the implications of CCHD on the newborn screen and how the public health department will follow up. This would dwarf it because the amount of data and the amount of time it would take, and then questions coming back to how many of them have a genetic basis or a liver disease and ABO incompatibility. It would be huge.

And of course, this committee doesn't -- isn't -- we're not in the -- the committee is not in the business of making professional guidelines, but that doesn't prevent people from saying we have an evidence review that's just beautifully done that shows all this useful information and kick it back to people who might not have to struggle only with the question of should it be added to the newborn screening.

CHAIRMAN BOCCHINI: Okay. Chris and then Michael.

DR. KUS: Jim, you mentioned that the evidence review process that is used is significantly different from the preventive health services. How would you summarize that? What's the significant differences?

DR. PERRIN: So I think the differences are basically two. One is where a number of studies would be essentially withdrawn for review by the U.S. Preventive Services Task Force, we have included those for review, recognizing their substantial limitations.

So out of the 112 that we reviewed, my guess is U.S. Preventive Services Task Force might have reviewed 25. That's one part of it.

And the second gets back to really what Denise was asking about before, which is, again, I think we have "lenientized," made more lenient the grade criteria so that we can look at case series. We actually had a very useful discussion back in March with the people from the U.S. Preventive Services Task Force and others about where case series can actually be useful to us.

And in fact, one specific piece of evidence for this report has to do with is there evidence that children who develop acute bilirubin encephalopathy with substantial neurologic signs can define over time it comes really from the case series? That's a very important, we think, valuable piece of information for this committee.

So those are the two differences.

DR. PROSSER: I would add to that, too, based on the meeting that we had last March, the application of decision analysis for newborn

screening is also very different from how it's been used on the U.S. Preventive Services Task Force. Because there, it's typically a case where there's a lot of evidence, and it's a question of building the model of either for health outcomes or cost effectiveness, based on fitting data from a number of large studies.

But we're operating for newborn screening, an area where there's far little data, and there's a lot of discussion at that meeting that the application of decision analysis would be different here but still advantageous as a way for synthesizing what little evidence that we have to provide some additional information.

And so, that would -- most of the decision analyses that we will do here are likely to be cases where we would say there's not enough evidence to do it.

DR. LU: So just sort of the public health kind of impact part of the discussion and based on your presentation of the few studies that are on cost effectiveness, just based on back-of-

the-envelope, quick calculation, projecting that if we were to do universal screening, it would cost around $200 million to $400 million a year? Does that sound --

DR. PROSSER: So we haven't done those calculations. So I can't comment on that. But that's one place where we could --

DR. LU: I guess --

DR. PERRIN: Your numbers are right if you think about what the costs are.

DR. LU: Well, I guess the other side of the equation is that the benefit and what's the benefit of screening? Do we have any evidence in terms of what cost savings might be accrued from universal screening?

DR. PROSSER: The little evidence that's out there suggests that universal screening is not likely to be, on the whole, cost saving, that it's likely to require an additional investment. And so, that's where there isn't an update to say so is it then worth the additional investment that's likely to be required, looking at the balance of

cost to benefits?

We don't have that information now to say is it cost effective or not. So that's a thing that could be looked at in the future. And that was something that came up on the expert panel as well.

DR. PERRIN: But your evidence, your analysis you put together said that the range of potentially averted cases of kernicterus is in the order of up to 30 per year.

DR. PROSSER: Right. Correct.

DR. PERRIN: That's the savings potential.

DR. HOMER: Jim, what was that?

DR. PERRIN: I'm sorry? Is that Fred?

DR. HOMER: This is Charlie. I'm sorry. I just couldn't hear Jim's estimate --

DR. PERRIN: Could you repeat that?

DR. HOMER: There seems to be an echo. I couldn't hear what Jim Perrin's estimate was of dollars per case.

DR. PERRIN: I was just saying that

Lisa's decision analysis basically said that the maximum potential benefit in the sense of numbers is in the order of 30 averted cases of kernicterus per year. And that's, of course, based on many, many assumptions.

DR. PROSSER: And that we did not specifically look at cost effectiveness. The limited evidence that's available suggest a fair amount of cost savings. But again, just to comment, that's not the bar that we used to decide if something's cost effective or not. There are many interventions that we decided to invest in for improved health outcomes.

So we don't have that event for bilirubin screening.

DR. HOMER: But the cost issue, the cost of the test plus the public health costs associated with establishing a tracking system for these kids and appropriate follow-up, et cetera. That's what you would be using to balance against the potential savings or the number of cases, not savings. But the number of cases averted. Correct?

DR. PROSSER: We're having trouble hearing you, Charlie.

DR. HOMER: Oh, I'm sorry.

DR. PERRIN: You're saying that we have case numbers, but not cost?

DR. HOMER: That's correct.

DR. PERRIN: Yes, that's correct.

DR. PROSSER: Yes.

CHAIRMAN BOCCHINI: Okay. Michael?

DR. WATSON: Thanks.

I'm curious about the -- one of the problems certainly with congenital heart disease screening was the question of whether something should be in sort of the standard of care versus public health environment. And I don't think the committee has ever looked carefully at how nursery-based screening is organized or how it would be addressed at the state level.

I know it was a major problem in California because the newborn screening group dealt with laboratory-based screening, and it was a clinical part of the public health department that

would have had to deal with congenital heart disease, independent of the newborn screening group. And certainly, it was a major problem with hearing screening when this pile of money came down and formed an entire new part of screening, independent screening program, independent of the laboratory-based parts of the programs in many states.

And because it worked so well, they're sort of merging them back together in some states. But I think it might be worth looking at that infrastructure across the country at the state level to see really what happens with nursery-based screening, just to have a sense of whether making a recommendation of something like that is actually going to require a tremendous amount of restructuring in state public health departments.

DR. PERRIN: As one minor comment, we tried to identify data that would tell us what the current standard of care is in most American nurseries and were unable to find those data.

CHAIRMAN BOCCHINI: Stephen?

DR. MCDONOUGH: Could I ask a question to the Academy of Pediatrics? Is the current guidelines in October 2011 from the academy that recommends that all children 35 weeks gestation or older be screened at 24 hours with either a transcutaneous or a serum bilirubin?

DR. TARINI: I'd have to go back and review the guidelines.

DR. MCDONOUGH: No. I don't have another question.

CHAIRMAN BOCCHINI: Okay. Freddie?

DR. CHEN: Just a comment. That bilirubin screening is really -- continues to be a mainstay of clinical practice for newborn care. Many of us in the room are well aware of the issues, and actually, I think it really raises for me -- the other thing I'd say is, clearly, the task force recommendations actually, in my estimation, have minimal impact on that part of clinical care. So that's one observation.

And then the second piece is your evidence review really raises some questions about

something that we've never really handled, which is are we looking at some over utilization of this? I mean, given the numbers, and I mean, that's really been a question in clinical practice for a long time about really how appropriate is the care that we're currently providing now.

That cost effect is really overwhelming. The number, the cost per case and that kind of stuff. So, anyway, it's just a comment. It's something that we may see as this committee continues to go into new territory.

CHAIRMAN BOCCHINI: Additional questions, comments?

Okay. No further. Thank you both very much.

And now let's go forward -- oh, all right. Let's bring forward Catherine Wicklund and Alexis Thompson. And as I indicated, I had asked them to sit in on the final discussions of the Evidence Review Group to hear the evidence. And then after review of the evidence document, to look at our template for making a decision and to frame

the discussion for us by looking at that and giving some preliminary recommendations.

MS. WICKLUND: Thank you.

And thank you to the Evidence Review Workgroup. That was a really thorough document and really made our job easier in being able to think about this issue. And also thank you, Joe, for making us the test case.

[Laughter.]

CHAIRMAN BOCCHINI: You're very welcome.

MS. WICKLUND: Yes, we were thrilled.

Let me say that just for a little bit of clarification, when Alexis and I were brought into this, I was able to sit on the call with the Evidence Review Group. I think Alexis was not able to. And it really was geared towards going through the slides for the presentation and giving me an opportunity to ask additional questions or clarifications at that time, which was extremely helpful. But I just wanted to be transparent about the process.

And then Alexis and I independently

reviewed the document, went through the key questions that are in the policy manual and came together then to discuss our views on this, and we independently kind of came to our conclusion about what we would recommend. And luckily, we came down on the same -- in the same place.

So we had consensus. So that's what we wanted to do today was to just basically -- we're not going to reiterate the evidence that Jim presented. It was very thorough. But just kind of through the key questions, the answers that we kind of came to on our own and then what our recommendation would be, given the matrix that we used.

So the first question was, is there direct evidence that screening for the condition at birth leads to improved outcomes for the infant or child to be screened or for the child's family? And I want to be clear that we were using the chronic bilirubin encephalopathy or kernicterus as our defining outcome when we were looking at this.

And we came to the conclusion that there

really was not any direct evidence that screening for neonatal hyperbilirubinemia prevents CBE.

MS. THOMPSON: The next key question was whether there is a case definition that can be uniformly and reliably applied? If so, what are clinical history and the spectrum of the disease, of the condition, including the impact of recognition?

This was somewhat challenging. We thought that there was a clear definition of CBE in terms of its clinical manifestations. There is a bit more challenge in looking at instance rates of factors that you can use to characterize either the acute vs. chronic and the relationship between the two.

We certainly appreciated from the evidence review that there is a spectrum for those infants who have an elevated bilirubin alone versus those who are symptomatic with acute. And then the infants that we were most focused on with CBE, and we felt that this spectrum was not well defined. And so, as a consequence, it was quite difficult to

look at the case definition if one is looking at combining the bilirubin level and CBE.

MS. WICKLUND: Okay. Key question three was, is there a screening test or screening test algorithm for the condition with sufficient analytical validity? And there does appear to be a reliable screening tool, either TcB for detecting significant hyperbilirubinemia, and also wanting confirmatory follow-up with total serum bilirubin.

The other thing that I got from maybe the call was that the screening methods vary and really can either be dependent upon the institution. So I think that was a lot -- and correct me, the workgroup, if I got that wrong. But that even from the expert panels, there was just a lot of discussion about really what was happening in hospitals and how it was being carried out.

But there was analytical validity. I guess if you think about the fact that you can measure bilirubin and find that it is elevated. So, again, screening has been associated with a lower incidence of hyperbilirubinemia. But again,

that's the hyperbilirubinemia, not the CBE that we're talking about.

MS. THOMPSON: The next key question was related to clinical validity of the screening test or the screening algorithm, which can be considered in combination with diagnostic tests and whether we can actually look to see whether the validity is adequate.

We felt that newborns with increased serum bilirubin levels do experience acute manifestations, but that the linkage between those levels and CBE, that the clinical validity was really insufficient.

MS. WICKLUND: And key question five, what was the clinical utility of the screening test or screening algorithm? I think the workgroup nicely laid out 5A and 5B, which are the benefits and harms. But the clinical utility is unclear. That is what we came down on.

Again, earlier treatments with phototherapy decreases the likelihood of the exchange transfusion. The treatment lowers the

total serum bilirubin, but there's really limited evidence that the treatment actually ends up preventing cases of CBE. Again, it's more indirect.

And the last question really we felt about how cost effective is the screening, the diagnosis, and treatment for this disorder compared to the usual clinical case detection and treatment, there just really is a lack of data in general. And we were really unable to kind of assess that.

So what we did then was we went to the decision matrix and really walked through that and asked ourselves if a policy of universal screening was implemented, what would be the magnitude of net benefit? And both Alexis and I felt that it would maybe be minimal to unknown.

And Carole brought up -- well, maybe I'm jumping a little bit. So it kind of put us in the level of 3 or 4 to begin with right off the bat, when we looked at the magnitude net benefit. And then when we asked ourselves what the level of certainty about the magnitude of net benefit, that

was where we got a little muddled maybe about whether or not this is really a 3 or 4.

Three is insufficient evidence and substantial additional evidence is needed to make a conclusion about that benefit. We believe that's true, that there is a huge lack of evidence. But what we struggled with was the issue that Carole brought up, which is, is this really a condition that needs to come back this panel or, I'm sorry, advisory committee to make a decision on?

So that it was more that, yes, there is research, further research that needs to be done. More evidence needs to be generated. But are we going to land on four, recommending that it not be added to the panel and that it doesn't necessarily come back to us, vs. three, the way -- and Alexis jump in here -- that maybe it was possible it came back to us as a committee. And I'm not sure this is the best place for this to play out, that it really is more of a practice guideline kind of issue rather than an advisory committee kind of issue.

MS. THOMPSON: I think we felt that that was important to state, in terms of making recommendations about what work should be done moving forward. Arguably, certainly an advocacy group may very much want to bring it back to the committee, and I think that if we think that there's a likelihood of the advisory committee reconsidering and adding it to the panel, we would strongly encourage them to do that.

But if we do not think in the deliberations that we are likely to move in that direction, then perhaps it is better for the committee to be clear that we are probably not the group to bring back additional research, research that we'd like to see done, but it would instead be more beneficial for that advocacy group to think about redirecting their efforts to another organization and considering it, for instance, perhaps as a clinical practice guideline rather than a universal screening kind of an issue.

But to make it clear so that as opposed to simply leaving it out there and instead of

having people do work, that, in fact, we know it's not likely to actually change our deliberations.

CHAIRMAN BOCCHINI: Thank you both very much.

Discussion by the committee?

We're going to project the decision matrix. So if we can get that put together. Oh, we've got it? We got it. Thank you. Okay.

MS. THOMPSON: I would also say that even though I think we both initially thought that the task was daunting, if you look at the responses and concerns that were brought up yesterday, in terms of selection, I think that honestly neither Cathy nor I really came into this with any predisposition one way or the other. We used our expertise as best we could in the area, and so I think that it is conceivable for a selection to be made by the Chair, as opposed to a process, unless you choose to develop a process.

But I think it is possible to have committee members just using your judgment, I think, to determine who sits in on this process in

the future. Also, the notion about coming in earlier in the process, I think there really would be some benefit to that. Although the Evidence Review Group did a fantastic job, obviously, we really didn't have much of an impact on that, given how late we were inserted into the process.

CHAIRMAN BOCCHINI: Thank you for those comments.

Beth?

DR. TARINI: I just want to respond to Dr. McDonough's questions about the AAP and hyperbilirubinemia. First, the report in Pediatrics 2011 October focused, it seems, on phototherapy. I think which types of phototherapy are most effective. It didn't focus on management guidelines.

And as I have it, the last set of management practice guidelines I have are from July 2004.

To your questions about whether TcB or serum bilirubin, it is in the recommendations of clinical assessment. Throughout it says TcB or

TSB, and it defers to the nurseries and the providers as to which is more preferable to them.

CHAIRMAN BOCCHINI: Thank you.

Questions, comments? Jeff?

DR. BOTKIN: Yes, thanks for that analysis. Generally with your assessment data, I guess I wanted to question about the last set of comments and where you were going with that. If we did -- in the next 10 years, if somebody did a big randomized control trial and showed definitive benefits and limited harms, why wouldn't that come back to this committee?

MS. WICKLUND: I think for us thinking about the public health impact and whether or not this is really getting back to the public-health issue vs. the standard of care, that should be implemented in the newborn period, and what the professional organizations and guidelines of the role is and in that vs. the Secretary's Advisory Committee.

DR. THOMPSON: I think that is actually right. It is not that we don't think it should be

done. The question is who is responsible for overseeing it. If in fact it becomes a standard of care, and that there is not that additional overlay that is required with quality assurance as well monitoring data collection that would be required if you were to move into the realm of the universal panel, if in fact we can ensure the health of more infants using the guidelines that are set out by the task force or the AAP.

I think that if we have some assurances that we can obtain a benefit, I'm just not completely convinced it would be required that it comes through the universal screening panel.

DR. BOTKIN: This is getting to the point of care screening issue that we will talk about here in a minute.

DR. MATERN: I'm just wondering if we were to decide to not include this or not to recommended as part of the uniform screening panel, with the AAP for example go back and say, well, we didn't treat review this for 8 years. Maybe we should do it? Or will they just say, well, the

SACHDNC just reviewed it. They rejected it; we don't have to deal with it anymore. I don't think we would want that to happen.

CHAIRMAN BOCCHINI: I know every AAP statement is required to be reviewed every 3 years, and at that point it is either reaffirmed, rescinded or rewritten. So there is a requirement for that, ongoing reviews, so that would be independent of the actions of this committee. And it may be currently under review; at the present time, I don't know that.

DR. MATERN: They might review our deliberations and what we came up with and say, well, there is no need to change anything. The question I think is on the one hand is it worthwhile to look for these conditions in babies; our question is whether it should be a public health issue or it should be something that stays with the hospitals and with the pediatricians and family physicians who take care of the babies.

That's all I'm saying. I don't want people to think that we don't think this is

important.

CHAIRMAN BOCCHINI: I agree with you.

DR. BOYLE: So I don't know what happened to four, but anyway I was going to talk about number four.

Oh, there it is. That's fine.

So my recollection about what level four is supposed to be is that this is for conditions where there is sufficient evidence that there is zero benefit, or there's essentially harm, so I don't think this falls under level four.

So regardless of the point of care, the newborn screening, universal screening, I don't think this gets to that. This is really more levels of evidence here.

So my sense is it's three.

MS. WICKLUND: I think that is where we struggled with three. We didn't know that exactly either, in the sense of this other issue about maybe having groups come back with more evidence for us to deliberate as a panel. So we did struggle with that. So I agree. Four did not

necessarily fit well.

CHAIRMAN BOCCHINI: Chris?

DR. KUS: I just want to follow-up with what Jeff said. If there's evidence that came back and said screening prevented kernicterus, I think this would come back to the panel to decide whether you would do it. So I think that's the issue, as opposed to the issue of how does it play out in clinical practice, because there aren't anything in clinical practice where they get 100 percent of kids screened. So to me that is the issue. The evidence here says you screen; you can't prove that it's going to prevent kernicterus.

DR. THOMPSON: The other part of it is that not every good thing that happens to children comes from newborn screening. I think it is quite logical that there are a number of things that are done for infants that is good medical care that don't require it coming through uniform screening panels, so you're absolutely right.

If the evidence were there, we would adopt it. We don't mandate anything. So it's

almost as if, if it occurs and it is not through us, I think that is okay.

DR. KUS: I guess just to follow-up, I don't agree with that concept to me, because the idea is, again, if the evidence here was strong that said, I could prevent 30 babies having kernicterus, if everybody got screened, if there was good evidence, I think that is a message for universal screening. That is my take.

DR. LOREY: This is Fred. I appreciate the review. That's been very helpful.

And I wanted to talk about -- a couple people specifically brought up the issue for public health, that is what I did with the congenital heart discussion, and so what you have given to us now is the newborn screening. And as we know, the other thing I wanted to say is that limited screening coming from a hospital is that we are responsible to keep track of our HTC and we have to report the various values, including bilirubin. And if they are not good, we have to consult with specialists to develop our algorithm instead of

like coming up with cutoffs for values.

We have to say, well, is it steadily rising, but we thank you for at least considering the public-health labs' approach to this.

CHAIRMAN BOCCHINI: Okay, thank you.

Beth and then Michael.

DR. TARINI: I'm speaking now as an individual, not as a representative of the AAP. It seems to me, following onto Dieter's comment, and also on Chris's, that the discussion is focused on two different levels. One is screening itself. Is it self-effective either by TcB or TSB? And the clinical assessment. And secondarily, would screening if placed in the institution of public-health screening be effective? Would it enhance that screening?

And to my personal opinion, having been at this committee for a few years and listened, is that this is a paradigm shift that is being discussed in the way newborn screening is being handled. So I don't think the presumption should be taken lightly that simply shifting it to the

public health and newborn screening level will enhance the screening. I'm not saying it doesn't, but I'm saying the presumption should be considered.

MS. WICKLUND: Let me just add to one of the things that came out with our discussion of the evidence review committee was that when they were making the prediction about the number of cases that could be presented per year, a lot of that was based on studies from the early 2000s, which was before the implementation of the guidelines from AAP, so that the actual, if universal screening was adopted, that the actual incremental benefit of adding -- it would be varied. It might not even be the 8 to 29, but it could be even smaller than that number as well.

DR. LU: My concern about this disconnect between what we recommend and clinical standards is that our recommendations could potentially impact on the coverage. And now we have this problem of what is considered clinical standard isn't covered.

And I don't know how we address those

questions, whether it is a conflict between our recommendations and what is considered standard practice.

CHAIRMAN BOCCHINI: That is important, because I would like to know whether this is a good lead-in to a discussion we're going to have this afternoon about point of care screening.

DR. COPELAND: I have consulted with the attorneys. I love that when she is sitting at the table and the attorney shall remain nameless.

[Laughter.]

DR. COPELAND: The consideration was, can we do anything besides yes or no, and this gets back to the discussion yesterday. We can ask the Secretary to make recommendations and provide advice to other groups. And so that is not a yes/no attitude, but we could say that this is "I'm not voting," and keep that in mind, but an option that, "No, we feel there is evidence at this point in time that it would probably benefit from a review of the guidelines," or whatever, so it doesn't have to be an addition to the RUSP or no

addition to the RUSP.

CHAIRMAN BOCCHINI: Stephen?

DR. MCDONOUGH: When we vote, should we vote by category one, two, three or four?

CHAIRMAN BOCCHINI: I think we will need a motion for a category recommendation and then we can with the motion and a second, we can go forward and vote on the category.

Is there additional -- let us complete the question, so we can then go forward.

DR. HOMER: This is Charlie. Are you able to hear me?

CHAIRMAN BOCCHINI: Does someone on the phone have a question?

DR. HOMER: Yes. This is Charlie. Are you able to hear me any better?

CHAIRMAN BOCCHINI: Yes.

DR. HOMER: Good.

So I just want to amplify or find out more about that last set of questions, because it does seem to me the question of, for example, whether universal newborn screening performed in

the hospital is covered as routine preventive service benefit is a different and very important question as to whether universal newborn screening for hyperbilirubinemia should be performed through a public-health mechanism, because I, for example, believe there is sufficient evidence to recommend that as a routine clinical preventive services, which should be covered through the level of care.

I don't think it should be like the congenital heart disease or hearing screening, so it would help me to know what the implications are of our recommendations for those two points.

CHAIRMAN BOCCHINI: Okay, well, I think that some of the public from the public-health standpoint, if we were to go forward with this recommendation, we would then want to do a public-health impact review before making the final decision. I think that is the way we would need to go on this matter, if we decided to move ahead.

Denise?

DR. DOUGHERTY: Just to confuse things more, I actually had to go look at the charter for

the committee to see what we are really supposed to be about. This may have been superseded by the ACA. I don't know.

But it says under the objective and scope activities, the committee provides advice to the Secretary about aspects of newborn and childhood screening, and technical information for the development of policies and priorities that will enhance the ability of the state and local health agencies to provide for newborn and child screening, counseling and healthcare services for newborns and children who are at risk for heritable disorders.

DR. COPELAND: So we can provide advice to the Secretary about what we think needs to be done?

DR. DOUGHERTY: At the state and local health agency.

DR. COPELAND: We can provide advice.

DR. DOUGHERTY: But not other advice around clinical standards. This seems contradictory to the ACA.

DR. COPELAND: I think if we're going to get into that, we really need to think it through. We need to frame our recommendations and we can circulate that. I think that is the second vote, and I think all of the optics would really like to be vetted before we would vote on that.

DR. DOUGHERTY: Absolutely. I'm not suggesting we change the charter.

DR. COPELAND: Not the charter. I'm talking about even making recommendations at that level.

CHAIRMAN BOCCHINI: I think that the thing that would be before us is the determination, whether to move ahead with this nominating condition. And that would be the vote we would take. If there are additional recommendations that might come after that, then we will certainly look at those, but there are additional questions.

Let's go -- I think Anne had her hand up first.

DR. COMEAU: I'm just a little concerned about precedent-setting with regard to vote number

four and with regard to the Jeff's question, given that the decision matrix was thoughtfully put out about what the committee would think, how they would release the recommendations based on the evidence. It was never my understanding that number four mean never come back. And I would really hope that, especially since this particular evidence review really did not evaluate public-health impact, but for any condition that if they were to bring new evidence that that would be considered.

CHAIRMAN BOCCHINI: Thank you.

Coleen?

DR. BOYLE: I guess I am usually -- about the point that Michael brought up. I think that is an important consideration, because this is not -- this test or screening is not something that is endorsed by U.S. Preventive Services, so I guess I'm just wondering about payment relative to essential services benefits package, et cetera.

Not that I am advocating for this, but I do think we need to think it through carefully. Do

we take this, the next step in terms of doing a public health evaluation to get a better sense of cost perspective on this?

DR. CHEN: As I said earlier, screening for bilirubinemia remains a mainstay of clinical practice. I have not heard any insurers not paying for screening in clinical care right now because the current clinical guidelines are that clinicians should decide whether or not to screen a patient based on clinical considerations for hyperbilirubinemia or not. So that takes it outside of universal screening and actually takes it outside of preventive services covered by insurers, because it is a clinical medical decision.

DR. GUTTMACHER: I apologize for a point that may be more telemedic than public health, but as I look at issues three and four, thinking more about the points that Jeff and Anne appropriately raised, I guess I've always thought that, too, that it could come back at some point. In which case, then you begin to really parse what is the

difference between three and four.

To me, it is in the third column, which we haven't talked about so much, the magnitude of net benefit. I guess I'm not ready to say that is zero or net harm. To me, it is unknown. So for me, it is a pretty close call between three and four. But I guess I would lean a little bit more toward three, because it could come back and one of the other things that is unknown to me, the magnitude of the net benefit is one of those.

MS. WICKLUND: I think that is really -- well, we felt we couldn't say it is zero. We could say minimal, although it is hard. There is no direct evidence of measuring this prevents cases of CBE.

I think we struggled with that, too, zero. When you say sufficient evidence for zero, I'm not sure we get there.

CHAIRMAN BOCCHINI: Jeff?

DR. BOTKIN: Now the committee is in transition with our methodology here, but if I have the sense this was moving toward a positive

recommendation, then I think not having the public health impact assessment would be a serious problem. And I would see circumstances in which we might see that screening is a good idea. But the public-health impact is significant, to where I'm certain that we would not want to move forward at that point with a positive recommendation.

I think the other element that makes us different from other groups out there is linking this to state mandates. I think sometimes we lose track of the fact that states are mandating this. Parents don't have a choice, so that ought to raise the level of significance to a higher level than may be the case in other circumstances.

We ought to have pretty select data to make that sort of positive recommendation. But at the same time, I guess in this particular field, we want to make sure we express our opinions in a way that doesn't imply that physicians ought to change current practices, and whatever they're doing seems to be working pretty well, so I don't think we want to say we have evidence, they ought to stop

whatever they are doing.

So a negative implication of a negative vote here would be that folks give up on a lot of bilirubin screening. And maybe that is good, but I don't think we know that.

CHAIRMAN BOCCHINI: I think again, specifically, this vote is to determine whether this becomes part of universal screening program, so that I think that we should be very careful to indicate that we are not voting against the current practice for management of hyperbilirubinemia, as Fred said.

Everybody who does primary care is taking care of children who have elevated bilirubins. This is a part of normal practice, common practice, and there are guidelines. And we certainly don't want to interfere with that.

So our goal is to really determine whether this nominated condition belongs in the universal screening program.

So is there additional comment? If not, would you like to make a motion or would someone to

else do that?

DR. THOMPSON: So based on the discussion and also our interpretation of the evidence review, our suggestion is in the decision matrix, is that hyperbilirubinemia to prevent CBE most appropriately should be a category three.

DR. DOUGHERTY: Second.

CHAIRMAN BOCCHINI: So first I begin with asking if anybody will abstain from the vote?

[No response.]

CHAIRMAN BOCCHINI: If not, we decided we are going to go in backward order, okay?

[Laughter.]

CHAIRMAN BOCCHINI: I saw Don sort of walking out of the room, and we wanted to make sure he stayed.

DR. COPELAND: So National Institute of Health?

DR. GUTTMACHER: Yes.

DR. COPELAND: Health Resources and Services Administration?

DR. LU: Yes.

DR. COPELAND: Food and Drug Administration?
DR. KELM: Yes, I agree.
DR. COPELAND: Centers for Disease Control?
DR. BOYLE: Yes.
DR. COPELAND: Agency for Health Research and Quality?
DR. DOUGHERTY: Agree.
DR. COPELAND: Andrea Williams?
MS. WILLIAMS: Agree.
DR. COPELAND: Cathy Wicklund?
MS. WICKLUND: Agreed.
DR. COPELAND: Alexis Thompson?
DR. THOMPSON: Agreed.
DR. COPELAND: Dietrich Matern?
DR. MATERN: I agree with number three.
DR. COPELAND: Stephen McDonough?
DR. MCDONOUGH: Aye.
DR. COPELAND: Fred Lorey?
DR. LOREY: Yes.
DR. COPELAND: Charlie Homer?

DR. HOMER: Agreed.

DR. COPELAND: Jeff Botkin?

DR. BOTKIN: Agreed.

DR. COPELAND: Joe Bocchini?

CHAIRMAN BOCCHINI: Agreed.

DR. COPELAND: Don Bailey?

DR. BAILEY: Agreed.

DR. COPELAND: Thank you.

CHAIRMAN BOCCHINI: Thank you all.

Thank you for the careful and thorough review. And thank you for the comments and discussion. I think it was very helpful in framing the decision that the committee just made.

It is 11 o'clock and our plan is let's take a 15 minute break and come back at 11:15. We're going to take a 15 minute break and come back at 11:15. Thank you.

[Recess.]