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

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Thursday, January 27, 2011

Renaissance Dupont Circle Hotel

1143 New Hampshire Avenue, N.W.

Washington, D.C.

MORNING SESSION

The meeting was convened at 10:33 a.m., R. RODNEY HOWELL, M.D., Chairperson, presiding.

PARTICIPANTS:

MEMBERS PRESENT:

RODNEY HOWELL, M.D., Chairperson, presiding

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

TRACY L. TROTTER, M.D., F.A.A.P.

GERALD VOCKLEY, M.D., Ph.D.

MEMBERS PARTICIPATING ELECTRONICALLY:

JEFFREY BOTKIN, M.D., M.P.H.

REBECCA H. BUCKLEY, M.D.

BRUCE NEDROW CALONGE, M.D., M.P.H.

EX OFFICIO MEMBERS PRESENT:

COLEEN BOYLE, Ph.D., M.S. DENISE DOUGHERTY, Ph.D.

ALAN E. GUTTMACHER, M.D. KELLIE B. KELM, Ph.D.

EXECUTIVE SECRETARY: MICHELE A. LLOYD-PURYEAR, M.D., Ph.D.

ORGANIZATION REPRESENTATIVES:

American College of Medical Genetics:

MICHAEL S. WATSON, Ph.D., FACMG

Association of Public Health Laboratories:

JANE GETCHELL, Dr.PH.

Association of State and Territorial Health Officials:

CHRISTOPHER KUS, M.D., M.P.H.

March of Dimes:

ALAN R. FLEISCHMAN, M.D.

PARTICIPATING ELECTRONICALLY:

American Academy of Family Physicians:

FREDERICK M. CHEN, M.D., MPH, FAAFP

American Academy of Pediatrics:

TIMOTHY A. GELESKE, M.D., FAAP

American College of Obstetricians and Gynecologists:

WILLIAM A. HOGGE, M.D.

Department of Defense:

THERESA HART, M.D.

Society for Inherited Metabolic Disorders:

BARBARA K. BURTON, M.D.

P R O C E E D I N G S

(10:33 a.m.)

COMMITTEE BUSINESS

CHAIRPERSON HOWELL: Ladies and gentlemen, let's find your seats. Those who continue to talk will be put out into the snow. That is a promise and a threat.

(Laughter.)

Let me welcome everyone to the 23rd meeting of the Secretary's Advisory Committee on Heritable Disorders. I'm thrilled to see all these folks that have braved the incredible D.C. weather this morning. We have a great attendance here at the table of our members. We also have a considerable number of persons on the phone. I think before we begin I would like to see -- we'll ask Michele to do a roll call of the persons who are on the phone. Michele?

DR. LLOYD-PURYEAR: I'm doing this alphabetically. Jeff Botkin.

DR. BOTKIN: Present.

DR. LLOYD-PURYEAR: Rebecca Buckley.

DR. BUCKLEY: Present.

DR. LLOYD-PURYEAR: Ned Calonge.

DR. CALONGE: Here.

DR. LLOYD-PURYEAR: Mike Skeels.

(No response.)

DR. LLOYD-PURYEAR: So he doesn't get paid.

Then I'm going to go to the organizational representatives. Fred Chen.

DR. CHEN: I'm here.

DR. LLOYD-PURYEAR: Tim Geleske.

DR. GELESKE: Yes, I'm here.

DR. LLOYD-PURYEAR: Mike Watson.

(No response.)

DR. LLOYD-PURYEAR: He probably never got home.

Chris Kus.

DR. KUS: I'm right here.

(Laughter.)

DR. LLOYD-PURYEAR: And then DOD, Theresa Hart or Mary Willis, one or the other, okay.

(No response.)

DR. LLOYD-PURYEAR: William Hogge.

DR. HOGGE: Here.

DR. LLOYD-PURYEAR: Hi.

DR. HOGGE: Hi, Michele.

DR. LLOYD-PURYEAR: Sharon Terry.

(No response.)

DR. LLOYD-PURYEAR: Barbara Burton.

DR. BURTON: I'm here.

DR. LLOYD-PURYEAR: Oh, good.

DR. HART: This is Theresa. I'm here.

DR. LLOYD-PURYEAR: Oh; we called you.

CHAIRPERSON HOWELL: We have excellent representation on site and so forth. I might add that Dr. Bhutani and Dr. Johnson will be joining us by telephone today.

DR. BHUTANI: I'm here.

CHAIRPERSON HOWELL: Oh, good. Well, we will be looking forward to hearing from you during the discussion for hyperbilirubinemia, which we will begin at about 11:00 o'clock.

We also are expecting Ms. Diane Zuk and Dr. Matthew Park to join us tomorrow for the committee discussion on screening for critical cyanotic congenital heart disease.

Ms. Harris has some housekeeping notes. Alaina.

MS. HARRIS: Hello, everyone. Just a few housekeeping notes. When exiting our general session, the restrooms are down the hall to the left. The Altarum staff is Maureen and Rebecca. They are at the registration desk and can direct and assist attendees and answer any questions that may arise.

Please note that we are not able to provide wireless access in the meeting room, but the hotel does offer complimentary wireless in the hotel lobby, and I had heard rumors that you might be able to actually access that down here as well.

Continental breakfast and lunch is for committee members, presenters, and speakers, and that is in the Potomac Room. That's this level. If you go out and go right all the way to the end and then go to the right, we're in a room, and there's more food in there than what's available in the hallway. So you're going to want the good room.

For the committee members, organizational reps, and the speakers, we do have a dinner reservation

tonight. We're going to go to West End Bistro again. So if you would like to join us for that, please check in with Maureen and Rebecca and sign up for that so they can confirm our reservations. If you could do that before lunch, that would be great.

We are going to meet in the hotel lobby at 6:15 and walk over. So our reservations will be for 6:30.

Just a reminder for everybody: The subcommittee meetings are going to be this afternoon from 2:00 to 5:00. They are all on this floor. The Follow-Up and Treatment group is going to take this room. Laboratory Standards and Procedures will be out of the room and to the left in City Center Room No. 1; and Education and Training Subcommittee will be in City Center Room No. 2, which is also out here to the left.

Also, our HRT Work Group will meet today from 5:15 to 6:00 o'clock. They are going to be in City Center Room 2 as well, which is the room that's being used by the Education and Training Subcommittee. Just for everyone to know, that meeting is open to the public, as are all our subcommittee meetings this

afternoon.

If any of the presenters have changed their presentations after you submitted them to Altarum, please save the revised copy of your presentation to the laptop up here.

Finally, for committee members and organizational reps, you should have received a thumb drive that has a supplement to your briefing book materials. However, that also went out to you last night in your email, so under that password-protected site that information is there, too. But I see everybody is shaking their heads "No," so in the next hour you will get a thumb drive from Altarum with your supplement to the briefing book.

Thank you.

APPROVAL OF MINUTES FROM THE SEPTEMBER 2010 MEETING

CHAIRPERSON HOWELL: Thank you very much, Alaina.

The first order of business that we need to deal with is approval of the minutes from the September 2010 meeting.

DR. LLOYD-PURYEAR: Excuse me. Who just joined?

DR. CHEN: It's Dr. Chen. I was cut off and I just called back in.

DR. LLOYD-PURYEAR: Okay, thank you.

CHAIRPERSON HOWELL: Are there any objections or changes to the minutes of the September the 10th meeting?

DR. BOCCHINI: So moved.

CHAIRPERSON HOWELL: Joe is motioning and Tracy is seconding that. Those favoring that, raise your hand.

DR. BOCCHINI: Or say aye.

CHAIRPERSON HOWELL: Or say aye. Or you can raise your hands. That'll be good, too, but say aye also.

(Show of hands.)

We actually are looking at you. You didn't know that. But anyway, be that as it may, there seems to be consensus on that issue.

COMMITTEE CORRESPONDENCE

CHAIRPERSON HOWELL: There's a lot of

committee correspondence in your book. Let me -- the tab includes responses from the Secretary, letters to the Secretary, as well as other correspondence. I'd like to particularly have you look at the note from the Secretary dated September 23rd regarding our health care reforms. She recognized the need to align the efforts that we're talking about with the outcomes of the vulnerable populations and newborns and children, and she adopted the first three of our recommendations. Obviously, our recommendations will have to be dealt with as the health care program evolves, which is obviously, as those who are in Washington know, is a major source of discussion down the street under the dome.

The Secretary provided her response to the fourth recommendation in her letter concerning medical food dated December 14. In this response, she acknowledged the value of the information we provided to help inform the Department's ultimate decision on health benefits. As the letter states, the Secretary has the results -- until she has the results from the Department of Labor survey and the Institute of Medicine, she will

not make a determination about these particular benefits. She, however, has assured the committee that when she is able to, she will give serious consideration.

The other letters include her interim responses -- as you know, the Secretary is required to respond to this committee in no less, no fewer than 180 days after she gets correspondence. So some of the responses have been interim. There is an interim letter about the letter of emergency preparedness, as well as the residual blood spot documents, congenital cyanotic and congenital heart disease, and sickle cell disease testing.

Your briefing book also contains a letter from our committee to the Secretary, sent after the last meeting. The committee letters that we've sent to the Secretary since our meeting was: One about the retention and use of residual blood spots. It was sent on October the 13th. We also sent a letter to the Secretary about critical congenital cyanotic heart disease, that was sent on the 15th of October, and we also sent a letter to the Secretary about the revisions

to the sickle cell trait and disease screening, the NCAA athlete, that was sent on October the 11th. So we sent actually three letters within a period of several days to the Secretary.

Your thumb drive also contains files that supplement your briefing book. That includes the committee's response letter providing comments on the CLIAC report and the recommendations on the biochemical laboratory practices for genetic testing and newborn screening, and the responses from Doctors Frieden, Hamburg, and Berwick concerning committee recommendations. I don't think the committee has gotten a letter with three original signatures from such luminaries.

But, Coleen, can you comment about when the MMRW paper will be shared with the committee? Do you have that information?

DR. BOYCE: No, I don't. I apologize. I can find out for you.

CHAIRPERSON HOWELL: That will be helpful. That's referred to in the letter from the three folks that I listed.

DR. LLOYD-PURYEAR: Actually, the letter says it's going to be shared with HRSA, who will share it with the committee.

CHAIRPERSON HOWELL: Your briefing book does contain a response from the National Quality Forum dated November 29th, and Dr. Sara Copeland will be referencing this letter in the next session, which will provide the committee with an update on the National Quality Forum measures.

Sara, can you bring us the update on the National Quality Forum? You're on.

UPDATE ON NQF MEASURES,

SARA COPELAND, M.D.

DR. COPELAND: If you're ready for me. Good morning. Am I on?

(Slide.)

CHAIRPERSON HOWELL: Yes.

DR. COPELAND: Okay, good.

For those of you who don't know me, I'm Sara Copeland. I am a medical officer in the Genetic Services Branch.

At the last meeting, Alan Zuckerman presented

a little bit on the measures that have been submitted to the National Quality Forum and I'm just going to update you on where those have gone since then.

(Slide.)

So just to give you some idea, the National Quality Forum consensus process is where they call for the intent to submit, and then they call for nominations, then call for candidate standards, and then there's a consensus standard review, public and member comment, member voting, and then approval, committee decision, board ratification, and appeals.

This is what just recently happened. We're currently under public and member comment, just to give you some context there.

(Slide.)

HRSA submitted one measure, which was proportion of inference covered by newborn blood spot screening. NCQA, National Center for Quality Assessment, submitted one; and CDC submitted eight related to hearing. Of those, the HRSA measure was endorsed in a time-limited manner because we didn't have any data to back us up and so we need to prove that we

can actually -- yes, Denise?

DR. DOUGHERTY: Just a matter of language. I think it's not endorsed until the NQF board endorses it. Right now the Committee on Children's Health Care Quality Measures recommends these measures, and they're going out for public comment. And after the public comment, the NQF board decides whether to endorse them.

This is the current recommendation that's going out for public comment, which I think you said. But using the word "endorse" -- it's a recommendation to endorse.

CHAIRPERSON HOWELL: Denise, give me a little insight, or maybe Sara, about the board of this group. The "board" is referred to. Who is the board? What's the constituency of that board?

DR. DOUGHERTY: It's a broad constituency. Gee, we'd have to look it up and tell you who the members are. I think March of Dimes used to be on the board, for example. AHRQ is on the board. HRSA may be on the board now. But it's mostly private sector, professional societies and payers, insurance companies, and that kind of thing. It's a voluntary board. You

volunteer to be nominated, but I think you have to get elected by the membership.

We can look it up for you.

CHAIRPERSON HOWELL: Thank you.

DR. So, just to clarify, the recommendations are to endorse in a time-limited manner. They did not recommend to endorse the newborn blood spot screening from NCQA, which was -- this was more of a physician practice recommendation, which was the percentage of children who turn six months old during the measurement year had documentation in their medical record, and-or -- they recommended endorsement one, two, three, four of the CDC measures, and I'll get into those a little bit more.

So discussion of those that are recommended to be endorsed was the HRSA measure, which was proportion of infants covered by newborn blood spot screening and what percentage of infants had blood spot newborn screening performed as mandated by the state of birth.

The number of infants born will come from state birth certificates and hospital discharge records, and the details of each state mandate will define which

infants may be excluded. Unfortunately, at this point in time we don't have a really good way to link those together, so we're going to be working to do that.

(Slide.)

Then from the CDC, the recommended to be endorsed measures were: the measurement of hearing screening prior to hospital discharge, those who did not complete screening before discharge, the percent that had outpatient hearing screening, and then those that failed their screening that had follow-up at three months and at six months, the percentages.

(Slide.)

So next step. The draft of the committee's recommendation or draft report is posted and it's on the web site for review and comment by members of NQF and the public; and the end result, if it is endorsed, since NQS inception IoM, the federal task force, and major stakeholders have recommended that it be tasked with managing a set of standardized quality measures. In '09, NQF entered into a contract with the Department of Health and Human Services to establish a portfolio of quality and efficiency measures for use in reporting on

and improving health care quality.

So there is some benefit in having these endorsed and there might even be some teeth behind them as well. At this point in time, the federal government uses the standardized performance measures in its public reporting and payment programs, and NQF's endorsed measures are the measures of first choice by the Federal Government and private purchasers. So they set the stage for standardization of public reporting..

Just for an example, a previous measure was regarding aortic aneurism, and with the NQF endorsement decision they're deemed scientifically acceptable and suitable for public reporting. CMS has indicated these measures are intended for public reporting purposes and it's considering including these proposed measures for payment determination.

I wanted to know why NQF -- what the implications would be for having it endorsed, and it seems that this will have some implication in terms of payment.

(Slide.)

So if you need to contact me, there's my

information.

CHAIRPERSON HOWELL: I have a question. Go back to the aortic aneurism slide.

(Slide.)

And tell me exactly what happened? This endorsement has occurred and so in the real world what happens? I run a hospital; this endorsement does what for me?

DR. DOUGHERTY: Nothing.

CHAIRPERSON HOWELL: What?

DR. DOUGHERTY: Nothing. It's all voluntary. They endorse and they have this broad, broad group of stakeholders to encourage people to actually use the measures that get endorsed. It's a national consensus body.

CHAIRPERSON HOWELL: I'm still puzzled about aortic aneurism. What would you -- what are you endorsing, that you report them to somebody or that you find them when the person comes in the hospital, or what?

DR. COPELAND: I think this is a screening test. I'm not sure exactly what screening test it was

for aortic aneurism, but there was a consensus on measurement or monitoring.

Someone's raising their hand back there. They might know.

DR. OSTRANDER: I'm a family doctor. What it is --

CHAIRPERSON HOWELL: Oh, good. We need some wisdom.

DR. COPELAND: Come to a microphone, please.

CHAIRPERSON HOWELL: Come to a microphone. You can tell us.

DR. COPELAND: And say your name.

DR. OSTRANDER: I'm Robert Ostrander. What they endorsed was -- I'm from upstate New York -- the ultrasound screening for aortic aneurisms in men 65 years and older who have a history of smoking, with evidence that the incidence of that is high enough that it warrants screening so you can monitor and intervene early.

The effect has been, number one, that people are starting to adopt it separate from any punishments or rewards, just as a medical standard; and that the

insurance companies will cover this science this screening test as a medically necessary service. So that's what's happened because of this, so it actually has had some effect.

CHAIRPERSON HOWELL: So basically, you identify persons at risk because of age and personal habit and you say that it's appropriate if you're in practice to do screening for that particular problem. I'm sure Mr. Holbrooke would have been glad to have heard about this earlier.

Alan.

DR. FLEISCHMAN: Coming closer to the perinatal world, NQF endorsed five major measures, which were then adopted by the Joint Commission. The Joint Commission, the group that accredits the hospitals, has now added that to their standard package of measures around early deliveries and breastfeeding and other issues of importance to perinatal health.

So the National Quality Forum is highly respected. It vets the measures quite significantly. I'm just looking at a list of its board of directors, chaired by William Roper, with liaison members from all

of the federal agencies -- CMS, AHRQ, CDC, etcetera. A rather prestigious group and very highly respected.

DR. DOUGHERTY: I just gave Michele the link. If we wanted to see who all they were you could look at it, but it's probably not that useful at this point since Alan just summarized who the board was.

CHAIRPERSON HOWELL: That's helpful to me to get a little concrete feeling about what the implication of these acceptances of things that relate to our area.

Chris.

DR. KUS: I think the other part is measures that are specifically related to primary care docs or different things could be included in state reporting, and sometimes that is used if you consider pay for performance. That's a possibility. So in New York State our measurement of managed care includes some of those measures.

CHAIRPERSON HOWELL: Any other further comment? (No response.)

CHAIRPERSON HOWELL: Well, thank you very much, Sara. That puts us actually just a couple minutes ahead of time.

Our next session will be chaired by Jim Perrin from Boston. Jim's on the phone and he's going to go through with us the Evidence Review Workgroup report, the preliminary report on the candidate nomination of hyperbilirubinemia. Jim is, of course, joining us by telephone and we'll look forward to hearing from him.

DR. LLOYD-PURYEAR: Somebody else came on the phone. Can you let us know who it was?

DR. BOTKIN: This is Jeff Botkin. I was rejoining.

DR. LLOYD-PURYEAR: Okay, thank you.

Dr. Frempong is in Ghana. Kaf, are you on the phone?

(No response.)

Mike Skeels, are you on the phone?

(No response.)

CHAIRPERSON HOWELL: Jim, I think we've got our telephone situation settled. I think Michele in her next life will be a telephone operator. But anyway, let's hear about the hyperbilirubinemia -- oh, she confesses. She used to be an operator. And ATT has never recovered. But anyway --

(Laughter.)

Jim, are you there?

(No response.)

CHAIRPERSON HOWELL: Oh, my goodness. What happened to Jim? He was on the phone a bit ago. Could someone see if they could find Jim for us? Apparently Jim is not on the phone. He's been on all morning. As you know, we have had a longer discussion with Jim on the phone earlier. He might have stepped away since we're a couple of minutes early.

Is there anything else that we need -- that would be -- I don't want to go into the afternoon things. But let me bring up one little note that I was going to do before lunch anyway. I wanted to remind you, the last time that we had a meeting in this hotel we overwhelmed the restaurant upstairs. It's a relatively small restaurant and everybody went upstairs -- particularly it would be attractive today -- and the restaurant became totally overwhelmed, so that many of you were unable to return for the early part of the meeting because you were still waiting on your food.

At the registration desk outside, there's a

list of other places to eat in the area which might not take quite as long to get served. On the other hand, you'll have to go through the snow, so you'll have to kind of play that both ways because the snow has not been shoveled very effectively to have you leave the hotel block.

Jim, are you there?

(No response.)

Jim is not there. Does anybody have anything else they would like to discuss while we're waiting? Maybe someone could sing a song or something.

(Telephone tone.)

CHAIRPERSON HOWELL: Is that you, Jim?

(No response.)

DR. McLAUGHLIN: I just wanted to comment about the measures; CMS chooses NQF-endorsed measures for their physician quality reporting initiative, which fiscal years can report measures which then will give them a bump in their payment rate, depending on how good their measures reporting are. So NQF's measure endorsement does lead to higher payments for fiscal years in Medicare-Medicaid.

CHAIRPERSON HOWELL: Good. So that has a concrete reason.

Apparently Sara has something else to say?

DR. COPELAND: That's Kathryn McLaughlin. She's our newest project officer.

CHAIRPERSON HOWELL: Any word from Jim?

DR. LLOYD-PURYEAR: I just called him. He's calling in now.

DR. LLOYD-PURYEAR: Oh, he is joining. Jim, are you on now?

(No response.)

DR. LLOYD-PURYEAR: Who just joined?

DR. BHUTANI: This is Vinod Bhutani. I just rejoined.

DR. LLOYD-PURYEAR: Hi. Good.

Jim, are you on?

DR. JOHNSON: This is Lois Johnson. I just entered.

DR. LLOYD-PURYEAR: Who?

DR. JOHNSON: Lois Johnson.

DR. LLOYD-PURYEAR: Hi.

CHAIRPERSON HOWELL: Good.

DR. LLOYD-PURYEAR: We're waiting for Jim Perrin.

CHAIRPERSON HOWELL: We're waiting on Jim Perrin, who's been on the phone all morning, but seems to have gone out sledding or something around the hospital.

DR. LLOYD-PURYEAR: Jim, are you on the phone now?

DR. PERRIN: I'm on the phone. Hello.

CHAIRPERSON HOWELL: Oh, good. How was the sledding outside?

DR. PERRIN: It was great.

CHAIRPERSON HOWELL: Anyway, we are delighted to have Jim and he's going to lead the discussion on the report, the nomination for hyperbilirubinemia. On the phone we have Dr. Bhutani and Dr. Johnson, who are joining us also by telephone.

Jim.

EVIDENCE REVIEW WORKGROUP REPORT: PRELIMINARY REPORT ON THE CANDIDATE NOMINATION HYPERBILIRUBINEMIA

(Slide.)

DR. PERRIN: Thank you very much, Rod. We

appreciate the opportunity to make this report. I see we have the slides up there. I'm sorry I can't be with you.

CHAIRPERSON HOWELL: We have the slides up there.

DR. FLEISCHMAN: Can we make this a little louder?

CHAIRPERSON HOWELL: The answer is yes.

DR. PERRIN: Super. Can you hear me now?

CHAIRPERSON HOWELL: Yes.

DR. PERRIN: Great. So if I can have the first real slide, it says "Recent Progress and Activities."

(Slide.)

Just to bring the committee up to date on what we've been doing recently, and then we'll talk about where we are today.

As you know, at the meeting in September we presented the final report on critical congenital cyanotic heart disease, and Alex Kemper and Alex Knapp are in the process of putting together a paper relating to the review work that we did. There has been some

other work that the Advisory Committee has taken on with respect to the follow-up on that report and the AC recommendations arising after reviewing that report.

Today we're going to talk about neonatal hyperbilirubinemia. I just wanted to remind the AC that we're presenting today only the preliminary systematic review of published literature today. So there are undoubtedly questions that we are interested in and you're interested in that will now come through because we're only presenting what has been published so far.

A couple of recent publications: a paper in Genetics Medicine and a paper in the Journal of Pediatrics. Tomorrow there will be an opportunity where Ned and Rod will describe some of the work we're doing together to think through how to strengthen our evidence review process and make it even more beneficial to the committee in its decisionmaking.

Next slide, please.

(Slide.)

For the report today, the main workgroup members have been John Co here at the MGH, Alex Knapp, Danielle Metterville in our team at the MGH, and Lisa

Prosser, who has worked on the economic studies, from the University of Michigan. The slide then shows other members of our ongoing evidence review work team.

Next slide, please.

(Slide.)

The materials that we're including in the preliminary review -- and these should be in your packets or available on the download from the website -- are: the detailed literature review methods; summary of the evidence from our review; tables highlighting key data from the abstracted articles; and the bibliography that we include in our review.

Next slide, please.

(Slide.)

Neonatal hyperbilirubinemia, to provide a little bit of background for what this condition is and what we are trying to share with you, this is defined basically as elevated total bilirubin level in the newborn. It arises from a relatively wide variety of etiologies. It's a detectable risk factor for both acute bilirubin encephalopathy and kernicterus, which is a longer-term encephalopathic condition arising from

bilirubin toxicity.

The primary concern here really reflects the potential for neurotoxic effects of severe hyperbilirubinemia.

If I may have the next slide, please.

(Slide.)

The conceptual framework that we're dealing with is somewhat similar to what we've shown you in the past. Here there is a sort of continuum from neonatal jaundice to hyperbilirubinemia to acute and then chronic encephalopathic results of hyperbilirubinemia. The treatment, of course, is at the point of hyperbilirubinemia itself. It's not at a level of ABE or kernicterus.

If I can have the next slide.

(Slide.)

The rationale for review included these several comments, many of them arising from Dr. Johnson's nomination of the condition, but really reflect the fact that hyperbilirubinemia can lead to kernicterus, with permanent damage to the central nervous system and death. That's to say this is a very

serious condition with major results for the child and family.

Second is that early identification of risk factors for kernicterus, including elevated serum bilirubin, could allow interventions with lower risk.

Third is that measurement of bilirubin either through transcutaneous or blood drawing, total serum bilirubin measurement, is pretty widely available.

Fourth, that treatment is widely available to prevent severe neonatal hyperbilirubinemia, especially phototherapy, but also exchange transfusion.

Next slide, please.

(Slide.)

In our early work we put together a technical expert panel that helped us to define and refine our case definition. These included Doctors Bhutani and Johnson, on the call with us, Dr. Maisels, Dr. Stark, and Dr. Stevenson. Dr. Tom Newman also provided some advice prior to the actual phone meeting of this expert panel.

Next slide, please.

(Slide.)

For each of the conditions that we've reviewed at the request of the Advisory Committee, obviously an important early step has been coming up with a case definition. In this circumstance, it's actually been more difficult because we're talking about a couple of different conditions. In fact, I'm going to lay out three definitions for the committee's consideration.

First is neonatal hyperbilirubinemia, by which we mean clinically significant bilirubin levels in the newborn period, above 95th percentile for age in hours, and levels that may require follow-up and treatment.

The second case definition and perhaps the least consistent one in the literature is acute bilirubin encephalopathy, which is meant to be the variable acute manifestations of bilirubin toxicity early in neonatal life, and including somnolence, hypotonia, decreased Moro, and then potentially developing into an irreversible stage with external muscle group hypertonia.

Chronic bilirubin establishment, otherwise called kernicterus, is defined as chronic and permanent brain damage caused by bilirubin toxicity, characterized

by four clinical manifestations: movement disorder -- athetoid especially -- auditory dysfunction, oculomotor impairment, and a non-neurological finding, which is dental enamel hypoplasia.

Now, importantly, hyperbilirubinemia has also been associated with other longer-term neurologic dysfunction that we've listed before in kernicterus, especially auditory dysfunction, and we will address these associations also in this review.

If I can have the next slide, please.

(Slide.)

As with our earlier reviews for the committee, we've done this essentially in two steps, and we're reporting on step one today, which is the preliminary report, limited only to systematic literature published and reviewed that we've attempted to summarize the evidence as regarding natural history, screening, treatment, and economics of screening for neonatal hyperbilirubinemia.

When we present our final report to the committee at the next meeting in May, we will at that time have updated the literature review. We will have

consulted also with a number of experts and consumers relating to issues of neonatal hyperbilirubinemia and, where we can identify relevant unpublished data we will also try to summarize that for the consideration of the committee.

So again, I'm reporting only on the first half of the preliminary report today.

Next slide.

(Slide.)

As per our usual strategy, we carried out a systematic review of the literature. We did searches of databases. We also reviewed references from the nomination form and the bibliography of review papers. Three of our staff, Dr. Co and Alex Knapp and Danielle Metterville, reviewed all abstracts and independently abstracted a subset of the articles to assure consistent abstraction by our abstracters.

Next slide, please.

(Slide.)

The literature review led to our abstracting -- - examining about 2700 abstracts. 172 articles were selected for in-depth review and 99 articles met all

inclusion criteria for abstraction. That is a somewhat larger number than has been true for some of the earlier reviews that we've done for the committee and really reflects the fact that neonatal hyperbilirubinemia is a moderately common disorder and there's a substantial literature in this area, unlike some of the rare conditions that we've talked about in the past.

If I can have the next slide.

(Slide.)

The actual report includes more detailed tables such as this one, which describes some of the quality of the studies that we have reviewed in each of the areas, four major areas of review. But this gives you information about the total number of studies here. It's worth noting that there are only four studies that are experimental interventions here of any kind. There are a small number of cohort studies, a very small number of case-control studies, and, as per usual, the vast majority of studies that we reviewed are really case series. In this case, the case series may be ones that include a fairly large sample size, but still the large majority of studies are really case series.

By the ways that we grade the level of evidence, in general these are not high level evidence. We'll talk about that more in detail as we get into some of these in more specifics.

If I can go on then to the next slide.

(Slide.)

Let's start with description of the condition, and these are the key questions that we tried to answer or to examine whether the literature helped us provide some answers: How well is neonatal hyperbilirubinemia defined? When does it appear? What are the known risk factors?

What's the evidence available regarding the relationship between severe neonatal hyperbilirubinemia and kernicterus? How well characterized is kernicterus and when does it appear clinically?

Next slide, please.

(Slide.)

This provides first some information about the incidence of these conditions to provide a bit of perspective on rate. So newborn jaundice, babies who are yellow and have elevated bilirubin, are actually

quite common. 10 to 15 percent of newborns have newborn jaundice.

Bilirubin levels above about 25, however, occur in less than one in 100 infants, in fact more like one in 1,000 infants. Bilirubin levels of over 29 are even less common, as you can see, .01 percent.

Going to the next step and trying to examine literature regarding rates of kernicterus in newborns, the rates appear to be currently somewhere in the order of one to two per 100,000 newborns. So when you go from hyperbilirubinemia of any level, 10 to 15 percent, and then come down to rates of kernicterus, the condition that in general one may want to try to prevent, we're talking about relatively rare phenomena.

If I can go to the next slide.

(Slide.)

There is a little bit of evidence of change in incidence, both of jaundice and readmission rates for jaundice. These probably do relate to changing patterns of screening for bilirubin in different conditions. But if you look at the first one here, the California data, there were a number of factors that were associated with

here increased likelihood of readmission, i.e., readmission for hyperbilirubinemia, that included young gestational age or what might be called mild preterm deliveries, 34 to 39-week babies, smaller birth weights, being male, being insured, and being of Asian race. That seems to show as well in other studies, too.

So the next couple of incidence provide a little bit of information about changing rates of newborn jaundice and also changing rates of children with kernicterus. But again, this notion of somewhere between, in the past, maybe as high as 5 per 100,000 to rates now seeming to be on this order of one to two per 100,000. Whether we can associate that with changing patterns of identification, I'm afraid we don't have evidence to clearly show that.

If we can go to the next slide, please.

(Slide.)

Risk factors then for hyperbilirubinemia and kernicterus have some similarity, with prematurity and Asian race both being there. For hyperbilirubinemia, isoimmunization such as ABO incompatibility and hemolytic disease, low birth weight are all associated

with higher rates of hyperbilirubinemia. Kernicterus, you can see the list here. The early discharge one is of interest certainly in thinking through strategies for following children over time.

Next slide, please.

(Slide.)

The spectrum of severity has been described in a number of studies. We do summarize these studies in Table 5 in the larger report. Importantly, differences in study design limit our ability to compare these data in a meta-analytic fashion in any particular way. But they do describe a reasonable spectrum of manifestations.

In the next slide, I'm going to talk about the acute manifestations, after which we'll talk about the chronic manifestations.

(Slide.)

When I say about acute, we're really talking now mainly about events that occur in the first few weeks of life and typically include such things as behavioral changes in the newborn, but also include some symptoms of central nervous system involvement and

abnormal findings on MRI or both visual and auditory-evoked potentials.

Some of the studies, but not all of them, show associations between the severity of these symptoms and the total serum bilirubin level. Some studies indicate symptoms are transient and that they resolve, but others do not. Again, if you look at Table 5 of the evidence review it provides more direct information on each of these short and long-term outcomes.

Next slide, please.

(Slide.)

Chronic manifestations of hyperbilirubinemia. Seven studies showed significantly increased risk of abnormal neurodevelopment, especially gross motor, fine motor, adaptive social skills. Six studies showed that these neurodevelopmental issues appeared to resolve over time. None of these studies are particularly large. They all do have some real concerns about the quality of the evidence in each of these studies.

Auditory issues are really a little bit better described. There are three studies actually that do indicate a direct relationship between levels of serum

bilirubin above 20 and the risk of developing long-term hearing disorders.

Next slide, please.

(Slide.)

Kernicterus then. The evidence here is predominantly retrospective evidence that we have, rather than prospective evidence. The Pilot USA Kernicterus Registry, which has described now 125 cases, does demonstrate, for example, that this is a serious condition, with about 5 percent of the infants dying in the first year of life, some characteristic changes in MRI.

But of interest is no clear evidence that one has to achieve a particular level of bilirubin in order to lead to kernicterus. Indeed, kernicterus has been reported in apparently healthy term newborn without hemolysis and in some children whose bilirubins were not in fact particularly high. Again, the majority of these cases were children who did have high documented bilirubins, but there are exceptions to that rule.

Again, the next slide, please.

(Slide.)

The pilot registry does show again some of these contributing factors: G6PD deficiency, hemolytic disease, birth trauma, sepsis, dehydration, and infection. So there does seem to be some consistency in those as risk factors. Again, most children don't actually have those risk factors in the kernicterus registries.

So if I may go on then to the next slide, our last slide relating to description of the condition or conditions that we're talking about.

(Slide.)

These are expressions that remain a little bit unclear and for which we hope to get more evidence from our discussions with experts in the next phase of our work. One is the strength of the evidence on the relationship between severe neonatal hyperbilirubinemia and kernicterus, and when exactly do we have evidence about when kernicterus appears clinically?

(Slide.)

Let me move now to the second major area that we examined. We've described the condition, its prevalence --

DR. BOYLE: Jim, Jim. Can I ask a question?

CHAIRPERSON HOWELL: Jim, excuse me. There's a question. Dr. Boyle has a question.

DR. BOYLE: I guess for these two questions -- I was thinking there was a third one, but maybe the evidence is already there and there's not remaining questions, and that would be the relationship between acute -- well, I guess what you refer to in the case definition as acute bilirubin encephalopathy and chronic or long-lasting; do you feel like that, there's enough evidence there and that's not a remaining question?

DR. PERRIN: Well, no, I think we could include that. I think what we do have evidence on, Coleen, is the evidence for persisting neurodevelopmental and auditory outcomes. Again, as I said in the presentation, it's not extremely good evidence, but there is certainly some evidence that supports the association of hyperbilirubinemia and those longer neurodevelopmental outcomes other than kernicterus.

DR. BOYLE: Okay. I got I guess a little confused in your case definitions to start and in the

fact that you didn't sort of follow through with using those case definitions, but maybe there's a rationale for that.

DR. PERRIN: I think that's a super question. I think in fact we in retrospect, having done the literature review after we developed the case definitions, I think we would have wanted to expand the definition a little bit more of what we mean by chronic bilirubin encephalopathy, because obviously it includes not only kernicterus but also other neurodevelopmental findings, some of which are pretty non-specific, i.e., delayed gross motor, adaptive social skills. But the more specific one is auditory findings.

Now, if you look at the case definition of kernicterus, it includes auditory among the elements of that. So it might be that taking the word "kernicterus" off that definition of chronic bilirubin encephalopathy might be the better strategy here.

Would that sort of answer your question?

DR. BOYLE: I think so. Thank you.

DR. PERRIN: Any other questions before we move on to three?

DR. BHUTANI: Yes. Hi, Jim. This is Vinod Bhutani. That was a very great review and presentation. I just wanted to bring out the fact that, and I don't know if you addressed this, is that, looking at the incidence of hyperbilirubinemia and the acute bilirubin encephalopathy, the background of intervention was probably variable. That is, the use of phototherapy, which was based then on identification of children who needed phototherapy, was variable.

DR. PERRIN: Could we put this comment off until a bit later?

DR. BHUTANI: Sure.

DR. PERRIN: This is really not in the incidence-condition area, but it gets more into the treatment side, and we will be there in a few minutes. Would that be okay?

DR. BHUTANI: Yes, that would be fine, absolutely. Thank you.

DR. PERRIN: Thank you very much. Great.

If it's okay, I think we'll move on to screening now. If I can have the next slide, the key questions, screening: What methods exist to screen

newborns and how does timing, when in the prenatal period, what gestational age, threshold levels, other considerations, are important in helping to determine significant risk for significant neonatal hyperbilirubinemia? Then the third question: What's the predictive validity of using risk assessment nomograms to predict risk of developing severe hyperbilirubinemia?

Next slide, please.

(Slide.)

Additional questions in screening: What are the recommended follow-up and monitoring procedures for newborns found to have an intermediate risk level by bilirubin screening, an important question? What do we know about outpatient capability to handle follow-up visits for screen positive infants? Has there been population-based pilot screening? And what do we know of potential harms and risks associated with screening?

Let me stress again as we go through the next slides I'm going to be presenting information about again the published literature. We will be exploring these questions in more depth in the next phase of our

review in talking with experts, including some of the ones on the phone today, and hopefully we'll be able to provide even more information at that time.

Next slide, please.

(Slide.)

There are three major strategies for estimating the level of newborn bilirubin: visual assessment, transcutaneous bilirubin, a non-invasive strategy, and then blood-drawing, leading to measurement of total serum bilirubin.

Our report provides a good deal more information here than I'm going to provide at the moment, so I will summarize a little bit of it, to say first of all that in general the evidence for visual assessment would suggest that it is not a very reliable strategy for determining accurately total serum bilirubin. I'm not presenting that evidence, but it is in the evidence report. I'm going to spend more time on transcutaneous bilirubin and total serum bilirubin descriptions, as well as the work that's been done to develop nomograms that are hour-specific in predicting the development of severe hyperbilirubinemia.

If I can have the next slide.

(Slide.)

This is now screening using this total serum bilirubin and the question this slide addresses is whether total serum bilirubin screening is associated with subsequent significant hyperbilirubinemia. So if you go to column 3, "cutoff, timing," this is basically serum bilirubin is measured at different levels. You can see generally about 6, in some cases 9 or 12, milligrams per deciliter, at generally 24 hours, although some of the studies also look at 48 hours or in one case up to 72 hours.

The fourth column indicates the distal of this, i.e., the measurement of significant hyperbilirubinemia, in general measured here as greater than 17 milligrams per deciliter, at age over 24 hours of age, although it may be in some cases, some of these studies, later ages.

These studies are all done with healthy term infants here, and you can see that the sensitivity in almost all cases is quite good. The exceptions are really a population in the next to the last study here,

which used a different measure of cutoff timing that may in fact explain the difference in sensitivity here.

Sensitivity -- sorry. Specificity is quite high throughout. Positive predictive value is in the teens to 20s and the negative predictive value is very high, given the relatively low rates of high significant hyperbilirubinemia at 72 hours of life.

So this again now provides pretty strong evidence that TSB screening early on is pretty predictive of subsequent significant hyperbilirubinemia and that especially negative results are reassuring of the lack of likelihood of going on to develop significant hyperbilirubinemia at approximately 72 hours of age.

Next slide --

(Slide.)

-- is now looking, not at serum bilirubin, but looking at whether there is a good association of transcutaneous bilirubin measurement with concurrent total serum bilirubin values. It's not predictive. This is now associative, concurrent findings. This includes three studies that are among healthy term

infants and two studies that are with premature infants, the last two studies on the list here. Somewhat different cutoff measures here that you can see listed, from 14, 11, 18, 17, etcetera. The TSB comparison values, somewhat comparable to the cutoff values. Sensitivity is extremely high in all cases except the one premature infant study, the second value in the next to the last study. The specificity is also generally quite good here, varying from 40 percent, with one exception, a small study of premature infants, to as high as 70 percent, 80 percent.

DR. BOYLE: Jim. Jim.

DR. PERRIN: Yes.

DR. BOYLE: This is Coleen again. I guess maybe just let me understand if I'm interpreting column number 3 appropriately. So those measurements were taken at 70 hours, 4 or 5 days. I guess I'm just thinking of the relevance of this for newborn screening.

DR. PERRIN: I will get in the next slide --

DR. BOYLE: The next slide, okay.

DR. PERRIN: -- to the predictive value. But you're absolutely right. So this is really trying to

determine basically whether TCB and TSB measure approximately the same levels. So these are basically concurrent, concurrent sampling. So you could also view that as if TCB -- what we're asking here is is TCB an accurate measure of TSB.

DR. BOYLE: Okay.

DR. JOHNSON: Could I ask a question? What was your definition of significant hyperbilirubinemia at 72 hours of age? What percentile on the nomogram or bilirubin level per age and hours?

DR. PERRIN: I think our definition, the case definition, was greater than 95 percentile for age. Now, if you look at these studies -- and that's what I tried to say and may not have said it clearly enough -- the studies vary a great deal on what they define the hyperbilirubinemia.

So what we've reported here are what the studies actually used.

DR. JOHNSON: Could you give an idea of what you considered significant? I still am a little confused.

DR. PERRIN: If we went to the previous slide

-- (Slide.)

-- this is really looking at the question of whether these are children who had rates above 17. There's still a relatively wide variation. I think one can raise questions as to whether that is significant.

DR. JOHNSON: This is 17 even up to 72 hours?

DR. PERRIN: That's correct.

DR. JOHNSON: That's what I was trying to clarify.

DR. PERRIN: Right.

DR. JOHNSON: Okay.

DR. PERRIN: But most of these studies are -- yes, even up to 72 hours. But most of these are actually earlier than that.

DR. JOHNSON: Yes. It's interesting, in the collaborative project the number of babies who have a bilirubin of 17 -- this is pre-phototherapy age -- who went up to over 20 was very similar to the number in the nomogram who go up if they had a 17 at 72 hours of age.

DR. PERRIN: Thank you.

If I can go to the next slide.

(Slide.)

This is now screening TCB, and it says "TCB screening for subsequent significant hyperbilirubinemia." This is two studies, fairly large, 400 in one, 2,000 in the next. This is now looking at whether transcutaneous bilirubin screening is associated with significant hyperbilirubinemia, in these cases defined, in these two studies, as greater than 17 at greater than 72 hours of age.

You can see the cutoffs that were used in the third column, varying from 5 to 8 to 11 to 13 basically. You can see the sensitivity levels here and the specificity levels here, which are in general, by the way, pretty comparable, perhaps a little bit lower specificity, but not much, compared to the slide two slides ago, which was screening using total serum bilirubin rather than transcutaneous.

So pretty good sensitivity, pretty reasonable specificity. As before, the negative predictive value is extremely high and the positive predictive value varies from about 25 to 70.

DR. CALONGE: Jim, this is Ned.

DR. PERRIN: Yes.

DR. CALONGE: One of the things that as I go through this more times I don't have a sense for in the 461 how many kids actually met the definition. I think that number -- there is variation around sensitivity and specificity clearly by the different studies. I think looking at the variation across the studies makes me think about that variation, about meta-analyses, about confidence intervals around any of the measures, especially the positive predictive value.

Having a sense of how many kids it's based on would actually be quite beneficial.

DR. PERRIN: That's a great idea and we will try to provide that to you. We obviously have that information. I don't have it off the top of my head. It's not a very large number of kids. The numbers at 72 -- I'm sorry -- at greater than 17, 72, I can't tell you off the top of my head what the percentage, but it's not going to be 100 children.

DR. CALONGE: I just wanted to be cognizant of laboratory variation and other issues that would say that the stability of a positive predictive value that looks pretty good might not be very good. So the actual

confidence around that number, there's a variation that we just need to kind of always keep in mind, rather than take the number at face value.

DR. PERRIN: Absolutely right. Thank you. That's very helpful.

Let me move on to the next slide --

(Slide.)

-- which is really looking at the screening - risk nomograms. Doctors Bhutani and colleagues have been particularly critical in the development of these nomograms. I think it's really worth saying that this really reflects bringing together a series of data and trying to develop curves that are fairly predictive of children having an increased likelihood of developing severe hyperbilirubinemia.

Again, it can be defined in a couple different ways. The important things here really are again, you can really see these curves do vary. So if you use the percentile above 95th, which is more or less what we started out in the case definition, the sensitivity is about 50 percent, high specificity, etcetera. And you can see the variation when you include now a higher or -

- not really lower, but a higher inclusion level here and how the predictive values will change with that as well.

If I can go to the next slide.

(Slide.)

These are a couple of studies that really describe the use of these risk nomograms and show that their use in relatively large studies is associated with pretty good predictions of hyperbilirubinemia, here defined as above the 35th percentile, in both 48 and 98-hour cutoff points.

Similar issues as before; pretty good specificity and sensitivity here. So these are a couple studies about the application of the risk nomogram.

If I can go to the next slide, then.

(Slide.)

These are some summaries both of the materials that we have presented and then some of the things that are only in the full report. One is that underestimation of TSB level was the most common diagnostic error using just visual assessment. In general, the literature that we found would say that

visual assessment per se is not a very optimal method for defining hyperbilirubinemia or risk for subsequent severe hyperbilirubinemia.

The grading systems that exist for visual assessment don't seem to be helpful, did not prove accurate substantially.

The third bullet really is the TcB screening studies do seem to agree on the utility of using such screening, at the very least, to rule out subsequent severe hyperbilirubinemia and does provide at least a very high negative predictive value.

If I can have the next slide, then.

(Slide.)

The evidence would suggest that the interpretation of the risk of subsequent hyperbilirubinemia is possible using the hour-specific bilirubin nomogram using either TSB or TcB values; and data that we have not presented in the slides today, but are in our report, which is that multi-hospital university bilirubin screening was associated with a significantly lower incidence of hyperbilirubinemia and lower rates of hospital readmissions due to high

bilirubins.

The next slide --

(Slide.)

-- again are the remaining questions for screening. We will hope to bring you back evidence for some of these after we've had the opportunity to speak in depth with a number of the experts: What's the optimal approach for newborn screening? Do the use of risk factor assessments really improve prediction? Are they helpful? What follow-up practices should be in place, especially for newborns found to be in intermediate risk level by screening. Some of the children on the nomogram, for example, who are in the 40th percentile.

Do outpatient facilities, including clinical practices of different kinds, have the capacity to handle follow-up visits for screening positive infants? For example, how much TcB capability exists in community practice settings?

What are potential harms or risks associated specifically with screening? Can we find better evidence of population-based pilot screening?

What would be the effects of taking bilirubin screening to state-mandated screening?

And, I think of good interest to us all: What proportion of cases of kernicterus would be prevented by screening? We can actually do some estimates of that at this point.

That's now our review of the screening issues. We've discussed condition, we've discussed screening. We're going to go on in a moment to talk about treatment and ultimately talk a little about economics, for which there is some but not a lot of evidence.

DR. CHEN: I have a question.

DR. PERRIN: Please.

DR. CHEN: This is Dr. Chen. You're right, identifying early on that this is a different kind of condition than we've been used to talking about, in that it's fairly common in the usual practice of taking care of newborns at this point.

A couple questions came up in the screening sort of section. The first is that really it seems to me that one of the critical pieces is moving from whatever our usual practice, which I think you've shown

can be variable, to universal screening. That decrease in incidence to me suggests that -- is that decrease in incidence because you're screening more people and your denominator is then -- has changed? Or are you actually seeing a real effect of the screening and then subsequent identification and treatment?

DR. PERRIN: I think that the studies that we've reviewed all would suggest that the increased identification and the treatment of identified children has lowered the levels of bilirubin in children and diminished the likelihood of readmissions for high bilirubin levels.

Does that answer your question?

DR. CHEN: I think so. In my mind, it's just something that certainly in my community is just so commonly done. But it does seem like if it varies between a combination of screening strategies where you've got visual identification then leading to transcutaneous or serum testing, versus in some cases universal.

DR. PERRIN: Right, I think that's correct. So we do not have studies that sort of have compared the

effects of those, for example, two or three different strategies directly on rates of readmission. We did not identify literature that does that. But what I do believe the literature generally says is that in association with the increased screening one did find lower total rates of hyperbilirubinemia, severe hyperbilirubinemia, and lower total rates of readmission.

CHAIRPERSON HOWELL: That's a fairly important finding, and of course certain institutions have systematic screening programs.

Joe has a comment.

DR. BOCCHINI: At the same time, I think we're doing more outpatient treatment of elevated bilirubin levels with home phototherapy. So some of the decrease in admissions could be potentially related to outpatient treatments. So we probably need to look more at how many infants are being treated for hyperbilirubinemia, not readmission to the hospital for it.

CHAIRPERSON HOWELL: Yes, and of course the data would suggest that the actual incidence of kernicterus is declining.

DR. PERRIN: Right.

CHAIRPERSON HOWELL: Thank you very much, Jim.

DR. PERRIN: I think what we have troubles doing in looking systematically at the evidence is making a clear connection between one intervention and a particular outcome. We can merely provide you these associational data here, which is pretty compelling.

If I can move on --

CHAIRPERSON HOWELL: Excuse me just a sec. Chris has a question.

DR. KUS: Jim, just one question. Do we have any sense of how many newborns get at least one bilirubin test currently?

DR. PERRIN: Chris, I don't know that we've actually seen data like that. We did not ask a question that specifically.

Alex Knapp, do you remember any papers that addressed that question?

DR. KNAPP: No. We can go back and look in more detail and ensure that it's covered in the final, though.

DR. PERRIN: I don't know that. It's a really

super question, but I don't know, and I'm not sure that -- I don't remember seeing any papers that really talk about that specific an issue.

CHAIRPERSON HOWELL: I wonder if Dr. Bhutani or Johnson could shed some light on that question. Are you aware of data on that?

DR. BHUTANI: No. I think we have data on, obviously, the institutions that have adopted the screening and the use of bilirubin evaluation. The number of nurseries that have not adopted universal screening is probably about 40 to 50 percent. That's just anecdotal observation. But I've not seen any literature or data to that effect.

CHAIRPERSON HOWELL: Thank you very much.

Jim.

DR. PERRIN: Thank you.

Let's move on to the third area that we reviewed, which is treatment. Again, I'm sure we all see some of the overlaps of the discussions we've already had here.

(Slide.)

But the next slide lists our key questions

here: What are the methods to treat hyperbilirubinemia? What's their effectiveness? What's the relationship between outcomes and the timing of interventions? What's the availability of treatment? What do we know about harms or risks? And what do we know about whether treating neonatal hyperbilirubinemia reduces the incidence of kernicterus directly?

The next slide.

(Slide.)

The two major forms of treatment have been phototherapy and exchange transfusion. Indeed, exchange transfusion today is pretty much limited to a small population of children who very commonly have other medical conditions as well as hyperbilirubinemia. It's a relatively uncommon treatment today, but in the days prior to phototherapy, of course, exchange transfusion was substantially more common. But the treatment that is used today is almost entirely phototherapy in normal term infants who have hyperbilirubinemia.

If I can have the next slide.

(Slide.)

The evidence here is pretty clear. We provide

substantial tables in the full report, but to summarize the evidence: phototherapy does effectively decrease levels of total serum bilirubin in the neonatal period. A number of studies pretty strongly show that. The evidence here is really quite good.

The effectiveness does vary to a degree in the reported studies, depending on a couple of issues: age, gender, gestational age, although we need to go back and make sure that we know exactly how strong an effect that is. We have indirect evidence of the wide availability of treatment.

Some of the physical complications associated with the therapy include fluid loss, some temperature instability, corneal damage; and the two most common reported are really skin rash and diarrhea.

We could find no good descriptions actually of disruptions in parent bonding with their child, both actually initially or in the long term, relating to phototherapy. That isn't to say there's no effect; it's just that we were not able to identify literature that described that effect well.

The next slide.

(Slide.)

Treatment of exchange transfusion. This is mainly fairly old studies and I would not put a great deal of emphasis on this because again this is not a very common treatment strategy today. Adverse comments -- sorry. Adverse events are common here. Mortality rates exist, morbidity rates exist. But partly, of course, this reflects children who have gotten in the past and are continuing to get EcT. And there is some controversy even as to on which levels of bilirubin one should perform EcT.

Next slide, please.

(Slide.)

Outcomes of treatment. Getting back to the question of, first of all, the chronic bilirubin encephalopathy issue. The studies that we were identified -- and again, I want to stress that these are not large studies in most cases and the level of the evidence is fair here. It's not -- these are not extremely good studies in most cases.

They do provide mixed results regarding whether treatment is associated with a reversal of

neurological and developmental symptoms. Again, this is the chronic rather than the acute bilirubin findings here. Some of them do show no or minimal resolution after treatment. Others suggest that there is recovery from the early clinical manifestations of hyperbilirubinemia. I'd say that the evidence on the effect on long-term outcome is fairly limited here at the moment.

The next slide.

(Slide.)

Treatment, harms. I think it's more important to focus on the left side here rather than the right side, again because of the relative likelihood of using phototherapy rather than exchange transfusion for term infants. Fluid loss, temperature instability, etcetera; corneal damage, which is treated predominantly by blindfolding infants especially, or preventing access of the phototherapy to the cornea. The bronze baby syndrome was reported early in the use of phototherapy, but basically it's an extremely rare condition. We did not find literature about bronze baby beyond a few case reports basically. And there are behavioral changes

that are described with phototherapy, including crying and some poorer scores in orientation items.

If I can go on to the next slide.

(Slide.)

Within treatment I think there are a couple of remaining questions. First, the evidence about whether treating hyperbilirubinemia prevents kernicterus or other types of chronic bilirubin encephalopathy is marginal at best. There's not really excellent data in that area. We don't, frankly, know much about the availability of treatment beyond indirect evidence at the moment.

Are there questions that you would like to ask about the treatment side at this point?

CHAIRPERSON HOWELL: Alan.

DR. JOHNSON: I think it's important to point out -- and the data's not really available -- that duration of exposure to what we think are dangerous levels of bilirubin in relation to the time of treatment makes a difference in terms of whether or not there does seem to be a reversal, with clear evidence of acute bilirubin encephalopathy being associated with or

without the long-term sequelae.

Certainly there's not a lot of evidence on this, but the case reports that do talk about this reversal are I think very important. Of course, some of those were mentioned in the kernicterus registry. And in relation to the work of Dr. Thomas Boggs at Pennsylvania Hospital before and after the advent of phototherapy, there are very clear evidences of his diagnosis of acute bilirubin encephalopathy by someone who saw a lot of babies like this, being reversed and at four and seven-year follow-up being associated with none of the characteristic sequelae of kernicterus or its more minor manifestations.

So it's important to keep that in mind. The actual data available to show that is very limited, of course.

CHAIRPERSON HOWELL: Dr. Fleischman.

DR. FLEISCHMAN: Jim, it's Alan Fleischman.

DR. PERRIN: Hi, Alan.

DR. FLEISCHMAN: I think in this treatment remaining question area you may want to add: Does treatment, i.e., phototherapy, prevent exchange

transfusion? Those of us who had a lot of experience doing those procedures are rare and becoming rarer. One could conclude that it is possible that the risk of an exchange transfusion has gone up, of complication with exchange transfusion. But clearly that early treatment does prevent exchange transfusion. At least it used to.

DR. PERRIN: Alan, that's a great question. Those of us who remember doing exchange transfusions, painfully, often in the middle of the night --

DR. FLEISCHMAN: Always.

DR. PERRIN: -- are happy that we do them less frequently.

I'm trying to think whether we have good direct evidence of cause and effect here. We probably do not, but there certainly is a substantial amount of temporal evidence that the use of phototherapy replaced exchange transfusions dramatically. So I think we can try to address that and provide the evidence for it, but I think there would be pretty good agreement that this has happened.

DR. FLEISCHMAN: I think the relevant point, Jim, for me is if you don't intervene early and you have

a child with a more serious, already acutely symptomatic and higher level, you are more likely to have exchange transfusion occur. So the science could potentially cause earlier intervention.

DR. PERRIN: Absolutely correct.

DR. FLEISCHMAN: That's the point.

DR. PERRIN: Yes. We will try to address that. That's a very thoughtful question, comment.

CHAIRPERSON HOWELL: I would assume that virtually every place in the United States has access to phototherapy. That may not be correct, but I would think that would be fairly readily determined.

DR. PERRIN: Certainly our anecdotal information would strongly support that.

CHAIRPERSON HOWELL: Chris.

DR. KUS: Jim, what kind of evidence -- we've had the statement saying that kernicterus is less now. But what kind of evidence do we have to say that disease related to hyperbilirubinemia is less, including kernicterus? Do we have that information?

DR. JOHNSON: Well, certainly in the case of RH disease there's clear evidence.

DR. KUS: Right, okay. But I guess in what we're talking about --

DR. PERRIN: I think you're really asking a very complicated question, I think, which is looking for non-kernicterus long-term outcomes of hyperbilirubinemia, do we have evidence that that has decreased? Well, I think the problem to a degree, of course, is those long-term outcomes are predominantly hearing loss, for which we do have some evidence about changing rates of hearing loss, but that may also reflect other types of screening, of course, than bilirubin screening, and then other neurodevelopmental outcomes, which could of course reflect many, many other things.

I think it's a hard question to answer. I think kernicterus has the, if I can call it that, advantage of being clearly associated with bilirubin being laid down in the basal ganglia and elsewhere, and that therefore is somewhat easier to monitor, although even that's not all that easy to monitor in clinical variations of that.

The simple answer is I don't know.

DR. KUS: If you specifically use kernicterus, though, the feeling is that there's good evidence that that's decreased?

DR. PERRIN: We found moderately good evidence that that has decreased in some of the studies I reported on early about some of the statewide data bases, for example.

DR. KUS: Okay, thanks.

CHAIRPERSON HOWELL: Other comments?

(No response.)

Jim, do you have additional comments?

DR. PERRIN: Let me just go on and finish up quickly with the economics and then leave you with what we think sort of an overview of what our findings are.

(Slide.)

We did look at some economic issues. They're listed in the key questions there. I'm not going to go over them. The next page describes that there are several papers. Most of them are not good papers.

(Slide.)

The next slide, cost-effectiveness analysis, is the one relatively good paper that we found, the only

really relatively good paper in the economic area, which looked at an outcome of cost per case of kernicterus prevented, so it was looking at long-term outcomes in that sense. There are some issues involved with that in defining what the real costs are of kernicterus per se. But basically it suggested about 5 or $6 million per case prevented using TSB screening for children.

So that's one piece of economic evidence here, but we don't find much else in the literature. We will try to get more evidence about reported costs of screening and treatment when we talk to people. But the published literature is fairly limited in this area.

If I can go on to the first slide labeled "Key Findings."

(Slide.)

Which we'd like to provide a little brief description or summary of where we are. One question is does high serum bilirubin concentration lead to acute clinical manifestations. The evidence there is that when compared to controls neonates with increased total serum bilirubin did experience an increase in acute clinical manifestations. There are a series of case

studies here. The strength of evidence is, frankly, fair.

The advantage of TcB over visual assessment: fair evidence, but in general would suggest that TcB is substantially better than visual assessment.

(Slide.)

The next slide is the specificity and sensitivity of the risk assessment and pre-discharge scheme prediction. The evidence here is moderately good. We've listed here some of the numbers that were in the earlier tables.

We've already discussed the question of whether screening prevents kernicterus. We really can find no good evidence for that.

(Slide.)

Then finally, the last key findings slide is really that the effectiveness of early intervention for hyperbilirubinemia using the measure of later severe hyperbilirubinemia predominantly does show that it is effective in doing that.

(Slide.)

Let me stop at this point. Our next slide

really includes the people whom we intend to speak with. We would love to have advice from the committee on other people you would suggest that we contact.

CHAIRPERSON HOWELL: Thank you very much, Jim.

He summarized the data that they've accumulated so far and I think at this point we'd like to hear from the committee if you have additional recommendations as they move forward with their final report.

DR. BOTKIN: This is Jeff Botkin. Thanks, Jim and his group, for all the hard work here.

I have sort of a specific question and a more general question. I haven't heard much or seen much in the report about some of the heritable conditions that withdraw transferase deficiencies and I want to just make sure that those conditions are off the general table for discussion here.

It may well be that screening identifies those conditions and leads to a different treatment pathway, but it might be worth some at least brief comment about those conditions as part of this spectrum.

The more general question has to do with the

disease modeling we're talking about. It sounds like the assumption is that, irrespective of the etiology of the hyperbilirubinemia, it's the high bilirubin that's the direct cause of the adverse effects that we're concerned about. Of course, it may well be that, with the variety of etiologies of hyperbilirubinemia, that it's the primary etiology that's the problem and not the bilirubin per se.

So I wonder, in that context -- in my way of thinking, it might be something similar to, say, screening kids for fever. We know fever's associated with bad outcomes, but we would be kidding ourselves if we thought that detecting fever and reducing the temperature was the way to address that. It's the primary etiology that's the main thing we ought to be understanding and treating.

So I guess it sort of gets to a key question, and do we need a key question here, that asks whether there might be a targeted screening approach that would identify, say, hemolytic disease or intracranial hemorrhages or some other primary etiology for both hyperbilirubinemia and adverse outcomes that would get

us most of the way there to reduce the adverse consequences, but without the universal screening approach that we're talking about.

DR. PERRIN: Dr. Johnson may have some thoughts on this. I think the best evidence in trying to figure out what may lead to kernicterus or what might be the causes of kernicterus really comes, frankly, from some of the kernicterus registry data and their ability to look back on these children's records in their neonatal period and document in fact there were a variety of risk factors that were associated with these children's disease in most cases, but not in all cases. And that includes the fact that there are some children who did not have abnormally high bilirubins, not a large number but some.

So that gives us a little bit of the etiology side of this. But I guess I would say that at the literature side we did not find anything that would really address the question of whether a targeted screening approach would be more beneficial.

DR. JOHNSON: I don't think that a targeted screening approach could be done at this point, because

with the kernicterus registry, yes, babies who had chronic problems at the lower bilirubin levels, and that's the levels between 20 and 25, to a lesser degree between 25 and 30, yes, they tended to have a longer duration of exposure or they had associated infection. But those are only things you know about after the fact. You couldn't really have identified those with the predischarge screening.

One thing when we're talking about predischarge screening, if I could add, that I did not mention earlier, the question was raised about how many of the predischarge screenings were multiple, how many had more than one TSB level. I wanted, in that connection, to remind people that in the bilirubin nomogram there were no values included after phototherapy had been instituted, and in babies, primarily those with hemolytic disease, in whom jaundice was noted early or for some reason a TSB was felt to be needed. If the bilirubin level was worrisome at that point, a repeat level was done to determine the rate of rise of the bilirubin for that particular baby. If on the basis of that rate of rise it was considered

necessary to treat, that baby had phototherapy and occasionally, in cases of severe hemolytic disease, an exchange transfusion.

That small number of babies does not appear in the nomogram as it is usually presented. One of the things that relates to the number of bilirubin is the need for repeating a worrisome bilirubin level to determine the rate of rise in the particular baby.

DR. CHEN: This is Freddy Chen. I have a question. Dr. Perrin, on the slide with the questions that you're going to pose to these experts, I'm particularly interested in the one that says, what will be the effect of taking bilirubin screening from its current form to state-mandated newborn screening? One of those related questions that rises greatest for me is, for example, in the kernicterus registry, how many of these children were not screened at all? What's our potential for improvement?

DR. JOHNSON: A careful reading of that paper says that this was very, very high. Many babies were sent home very early, without any evaluation at all, but on the basis of what the bilirubin was when they came

back, quite soon because of the mom's concern, it had to have been very high before.

That's retrospective, taking back data. But bilirubin does tend to rise at a fairly regular rate, a certain rate of rise per hour, and there were a large number of babies who could have been predicted and needed to be reevaluated and not discharged, because there was absolutely no estimate of a risk of jaundice done before. Of course, that did happen much more in babies who were sent home within 24 hours of birth.

CHAIRPERSON HOWELL: Coleen.

DR. BOYLE: Just a couple things, Jim.

DR. JOHNSON: That was the main reason for saying we need to do universal screening. There's always the occasional, the baby who you wouldn't have predicted would be that high that early.

DR. BOYLE: Jim, this is Coleen. I just want to -- I think it's worth repeating what I had said earlier this morning, and I know you already know this, but I was going to reiterate that I thought it would be important to include. And I know that Tom Newman was engaged initially in the development of the case

definitions, but that's just not included within the hard copy report we got.

Again, I would encourage you to try to have a balanced perspective in terms of the working group that's providing consult to this area, particularly because it is such a challenging literature and it is a very different literature than what the committee, the evidence-based committee, has already taken on.

The other clarification I wanted was, on page 12 of the report, I didn't mention this earlier, but you said that you had sent a draft to an independent external review panel already.

DR. PERRIN: Yes.

DR. BOYLE: It might be helpful to just know who was on that panel.

DR. PERRIN: Sure. Alex, please check me if I'm wrong. Celia Kay at Denver. I'm just blocking on names.

DR. BOYLE: That's okay.

DR. PERRIN: Bob Davis at Atlanta.

DR. BOYLE: So these are people outside of the kernicterus world, really.

DR. PERRIN: Correct.

DR. BOYLE: That's what I really wanted to know. So that's great.

DR. KNAPP: Jeanine Cody, Celia Kay, Harvey Cohen, and Robert David.

DR. BOYLE: Okay, great. Then the other issue that I also mentioned is that several colleagues in my group had done a -- tried to replicate at least some of the body of evidence that you've created, and then I was going to send you those details. Also included in that is the economic piece as well.

CHAIRPERSON HOWELL: That will be helpful.

DR. PERRIN: Coleen, just to be clear -- and we will take the advice of the committee here -- we don't have an ongoing working group other than our regular evidence review group.

DR. BOYLE: Okay.

DR. PERRIN: The initial group was a group that we asked to help us specifically with determining the case definition. Insofar as that's been such a critical element in each of our reviews, we wanted to get some technical experts early on in that process.

Tom was actually not on that call because he was in Indonesia, I believe, at the time. But he did provide us advice prior to that call to help us figure out the case definitions. That is not an ongoing expert panel.

What we do in our next phase is we will have a variety of contacts through email and phone conversations with the people on the list on the slide, Coleen, "Next steps." Again, if you and other members of the committee have other people to suggest, we would be delighted to add them to our list. But that's really the next step at this point.

DR. BOYLE: Okay. Thank you.

CHAIRPERSON HOWELL: And Jane has a comment.

DR. GETCHELL: Two points. First of all, I'd like to know a little bit more about the cutaneous test, how it's performed, when it's performed, why it's performed, what does it cost, and so forth.

The other comment I have is really related to our discussions with CCCHD, and that is I would hope you would consider testing for hyperbilirubinemia as a standard of practice and not necessarily a public health

program.

DR. PERRIN: The first part of that, which is some of the characteristics of TCB, again all we've looked at so far is the published literature on TCB. We intend very much to try to answer the questions you've just raised about TCB and our next steps. We think they're critical questions. We have some gut feelings and anecdotes here, but we want to get better evidence than that to your set of questions.

I think the next question is really for the Advisory Committee's discussion. I don't believe we can provide -- I'm trying to think, what evidence would you like us to provide to help the committee with that kind of consideration?

(Pause.)

CHAIRPERSON HOWELL: There's silence around the table.

Unless there's some compelling information that we need to convey to Jim -- Coleen.

DR. BOYLE: This isn't for Jim. This is more for Jane. That was going to be part of the topic of our subcommittee meeting this afternoon. So you're welcome

to participate.

DR. LLOYD-PURYEAR: The subcommittee is going to be preparing for a larger committee discussion on that very topic, Jane, looking at point of service screening, public health role, etcetera. So it will be, hopefully, in May that we will address that.

CHAIRPERSON HOWELL: Chris, did you have a comment?

DR. KUS: The comment would be I think it's a discussion of the committee.

CHAIRPERSON HOWELL: Hearing no great material rising from the group, let's stop for lunch, and we'll resume at 10 minutes after 1:00, because we do need to allow that much time for folks to eat. Right after lunch, we're going to have a very exciting presentation that will be oversee by Jelili about the SCID program, which is moving along rapidly, and then the subcommittees.

We'll see everybody back promptly at 10 after 1:00.

(Whereupon, at 12:10 p.m., the meeting was recessed, to reconvene the same day.)