Transcript of Day One

Thursday, February 26, 2009

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Bethesda Marriott-Pooks Hill

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C O N T E N T S

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P R O C E E D I N G S

Welcome

DR. HOWELL: Ladies and gentlemen, let me welcome you to the 17th meeting of the Advisory Committee on Heritable Disorders in Newborns and Children. We are delighted to be meeting at the beginning of the new Obama administration, and hopefully, we can look forward to a lot of new health initiatives in genetics and newborn screening. The very first item on the agenda today is I would like to extend a very special goodbye to Dr. Piero Rinaldo. This is Piero's last committee meeting, and I think that everybody is aware of his important contributions. In addition to bidding him farewell, I would like to present him with a letter of appreciation from Secretary Leavitt and a certificate to go on his wall.

[Applause.]

DR. HOWELL: It is actually quite an impressive certificate, as you can see, and it is

actually signed. It is not a fake.

[Laughter.]

DR. HOWELL: I might point out, however, that Piero has agreed to continue to serve as a consultant to this committee. So we will be looking forward to his continuing input to this committee, and his input has obviously been extremely important. We will talk a little bit later about the new charter of the committee that, as the members all know, has just been barely signed in time to get us here, and in the new charter, it calls for an ex officio committee member from the Food and Drug Administration. The head of the FDA

has appointed Dr. Kellie Kelm, who is here today, and Dr. Kelm is a scientific reviewer for the Division of Chemistry and Toxicology Devices and In Vitro Diagnostic Evaluation and Safety within the Center for the Devices in Radiologic Health. She is also the lead reviewer and pre-market submissions, investigative devices and applications to the

clinical studies of chemistry, toxicology, genetic and newborn screening devices. Dr. Kelm received her Ph.D. from Johns Hopkins University. That means a lot to many of us in the room, and we are very, very pleased to have Dr. Kelm here today.

Where are you seated? Oh, you are right over here. Dr. Kelm, welcome to the committee.

[Applause.]

DR. HOWELL: We also have a new permanent member from the Department of Defense, Dr. Mary Willis, who is Chief of Pediatrics at the National Naval Medical Center, and she is not with us today, but she is ably represented by Dr. Brian Hall who is in the neonatal program here at the National Naval Medical Center. Thank you very much for being here. We have got a fat book today. We were talking at coffee this morning, and Tracy pointed out that was a cross-country book. It took from California to Bethesda to read the book and so forth, and I think that everybody else

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appreciated that some people were fortunate to have a day off, although their children had pink eye yesterday, in order to read the book.

[Laughter.]

DR. HOWELL: But there is one important letter in the book that we want to spend some time on. We have had a lot of discussion about the extreme importance of medical foods and their use in treating children that are diagnosed as a result of newborn screening, and there is tremendous variation from State to State. We have had a lot of input from experts in this area.

The committee that Coleen heads has been working for some time on a letter that I would like to have you look at today and have your input in, and I would like to have it approved. We would like to send it forward to the Secretary with specific recommendations about how to improve the national scene for medical foods. Coleen, would you please go through that letter that you worked so ably on?

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DR. BOYLE: In the binder?

DR. HOWELL: Yes, it is.

DR. BOYLE: What section is it?

DR. HOWELL: It is in the binder under Tab 5, and there is a lot of stuff under Tab 5.

It is toward the back of Tab 5, right at the pink sheets.

DR. BOYLE: Sure. I think I reported at our last meeting, at our last in-person meeting or maybe it was on the phone meeting, that June of '08 we actually had a subcommittee meeting, a work group meeting where we brought in experts to give us advice and guidance around the issue of reimbursement, financial reimbursement for medical foods. So, as Dr. Howell just mentioned, sort of the next steps for us in terms of a number of recommendations that came from that meeting was to put together a request to the Secretary based on the guidance that we received at that meeting. For those of you in the audience who don't have it, I will just walk you through the

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letter, itself. The letter summarizes the context of which this issue arose. It defines what medical foods are, and it uses the FDA definition of medical foods. It talks about the problem itself and the fact that there are over 12,000 children identified through newborn screening, a number of which require medical foods throughout their life. It summarizes some of the costs associated with medical food, specifically for contrasting infants with metabolic disorders and the cost for families relative to children who don't have an inborn error of metabolism. It talks about the patchwork aspects of trying to get financial reimbursement for medical foods, and it talks about the life-span issue, the fact that we are not just talking about children, we are talking about children, adolescents, and adults, so the life-span approach. Then it summarizes the recommendations

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from the June conference and June workshop in terms of the specific recommendations. That addresses issues relative to private insurance. It addresses issues related to the 60 percent of people who have private insurance but are not covered by State laws, sort of the ERISA issues. It covers issues relative to Medicaid and trying to harmonize those aspects across States, and then it talks about some very specific requirements. So that is really the summary of the letter, and what we are asking the Secretary is really to consider addressing this issue through changes in legislation and other aspects. DR. HOWELL: Are there any further comments or questions about this letter? The committee has had an opportunity to see this letter because it was sent electronically, some time ago. There have been a few changes in it. Do you want to comment about it?

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DR. BOYLE: Yes. We are going to make a change to the first paragraph at the suggestion of a number of people, and we are going to try to put this in the context of evidence-based health care reform. So we are going to rework the first paragraph to try to incorporate that issue there.

DR. HOWELL: Are there any questions or comments about this letter? We think that moving forward -- and again, a formal recommendation from this committee will be, we think, a very important first step for folks to work to get some regulations. It will make this a much more organized effort throughout the country. Any further comments about the letter? Can we have some?

[No response.]

DR. HOWELL: If not, can we have a motion from the voting members of the committee that we adopt this letter and we send it forward to the Secretary for his consideration?

DR. TROTTER: Second.

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DR. HOWELL: Any further discussion? We have a move and a second for the letter. Denise, you have a question?

DR. DOUGHERTY: Well, just a point of procedure. If we are revising the letter a little bit, shouldn't we vote on it maybe later, tomorrow morning or something?

DR. HOWELL: We can certainly do that and so forth. Would the folks who made a motion, would that be acceptable to you to delay until later, Tracy? We will come back and do that. The modification is going to be extremely modest, but I think that is very good. Okay, fine. Thank you very much. I hope that we can now get something quickly. I might point out the letter is very carefully couched, and a great deal of attention has been paid to the fact that if you recommend medical, if you recommend payment for diets in general, that could be a real problem because

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virtually every child in the country is on a diet for something. So the wording of the document is such that it would have very specific requirements for coverage and so forth. The other thing that we need to do, we need to approve the minutes, and the minutes are under Tab 5. We are still under Tab 5. Again, can we have a motion to approve the minutes? The members of the committee have had the minutes and so forth.

DR. DOUGHERTY: There is a typo.

DR. HOWELL: What?

DR. DOUGHERTY: The U.S. Preventive Services Task Force is called the "Preventative Services Task Force."

DR. HOWELL: On what page?

DR. DOUGHERTY: The top of page 8.

DR. HOWELL: The top of page 8. So noted. We will correct that and the name.

DR. DOUGHERTY: Okay. We have Ned as a second here.

DR. HOWELL: Well, we have both Ned and

Denise pointing out a typo. We would not want a typo there. We will fix that.

Becky?

DR. BUCKLEY: One more typo on page 9, and that hematopoietic, they have got it

"hermatopoietic," in the middle of page 9.

DR. HOWELL: Well, that is trying to be gender neutral, I guess.

[Laughter.]

DR. BOYLE: Okay.

DR. HOWELL: Okay. Any further corrections? I think it sounds better like it is, but we will correct it and so forth.

[Laughter.]

DR. HOWELL: Any further comment?

[No response.]

DR. HOWELL: We will need a motion to approve the minutes with those corrections.

DR. VOCKLEY: So moved.

DR. HOWELL: Second?

DR. TROTTER: Second.

DR. HOWELL: Favor?

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[Chorus of ayes.]

DR. HOWELL: Any opposition?

[No response.]

DR. HOWELL: Thank you very much and so forth. Now we will move along through this big, fat book. Under Tab 5, you will remember that the society, the committee, the other Secretary's committee had requested an education survey, and Dr. Puryear sent one to everybody here. That is available. The response that was sent from this committee to the other Secretary's advisory committee on genetics is here. Do you want to make any comments about that?

DR. LLOYD-PURYEAR: No. That is for your information. The Genetic Alliance also formatted their own survey to the committee members, and I guess you haven't done it yet, but Natasha is going to hand out the results of that survey to

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the committee members.

DR. HOWELL: Okay. We will get that survey. I think that we will vote on that at the same time we vote on the letter, but in your book today is the policies and procedures for the operation and development of recommendations for the screening of newborns children for radical disorders by this committee. It is under Committee Business. The committee bylaws have been slightly revised and will need to reflect the new charter and decision process, and we will need to vote on those during the course of this meeting. So be sure that everybody reads that. That is in the minutes. I think that many of you are aware that Dr. Betty Duke will be leaving. Actually, I think the 25th is her last day.

DR. LLOYD-PURYEAR: Tomorrow.

DR. HOWELL: Tomorrow is Dr. Duke's last day at HRSA, as the director of HRSA, and there

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is a new HRSA administrator that has been appointed, Dr. Mary Wakefield, who is one of the nation's top rural health experts, has been appointed to head HRSA. She currently is Associate Dean for Rural Health at the University of North Dakota School of Medicine and Health Sciences. She is a nurse with a Ph.D. from the University of Texas in Austin, and she is really a leading health care advocate. I have had an opportunity to talk with people who have worked with Dr. Wakefield, and they are really enthusiastic about her arrival. So we really look forward to her coming, and we anticipate that she will be a strong influence and very supportive of the work that we are trying to do here. The committee's charter has been signed on February 12th by Acting Secretary of HHS, Mr. Johnson. The charter will expire on April 24, 2013. It is slightly over a five-year, and the fifth year is from the enactment of the Newborn

Screening Saves Lives Act of 2008. There are a number of things in the charter that reflect that law that was passed last year. There are a few changes in this committee that I will point out. One is that by April of 2011, this committee will publish a peer-reviewed report on newborn screening guidelines that includes follow-up and treatment. The second thing is that we will add two new members to the committee, and these two people have expertise and backgrounds in the area of bioethics and infectious diseases. The nomination forms for these new members will be released by HRSA soon, I assume.

DR. LOYD-PURYEAR: By HHS, yeah.

DR. HOWELL: By HHS soon, so that there will be nominations for that, for these two new positions. The charter also alters the committee structure and does not include liaison members from the Secretary Advisory Committee on Infant Mortality or the Secretary's Advisory Committee

on Genetics, Health and Society. So those two liaison positions were removed from the new charter of this committee. The new charter does, however, encourage this committee to work with the other relevant HHS groups, needless to say, on reviewing scientific evidence and making recommendations for clinical prevention services. Are there any other housekeeping things that we need to do?

[No response.]

We are now going to adjourn into our subcommittee meetings, unless there are other things that we need to do. Is there any other general business before we go?

[No response.]

DR. HOWELL: There are two things now that we will need to vote on. When we come back, we will vote on the letter with the slight modification, the Coleen thing, and we also, however, will need to vote on the policies and procedures for this committee, which is the

operating procedure of this committee. Any further comments or questions?

[No response.]

Subcommittee Meetings

DR. HOWELL: Okay. We are off to the subcommittee meetings then.

DR. LLOYD-PURYEAR: So are you going to tell where these are?

DR. HOWELL: Oh, the subcommittee meetings and so forth, I do have a list of where they are. You know, I wonder if these microphones are very loud. Do you know?

DR. LLOYD-PURYEAR: You know, they are not.

DR. HOWELL: Who is in charge of AV and the sound? Because I don't think these microphones are very loud. Do we have someone who is doing it?

DR. LLOYD-PURYEAR: Yes.

DR. HOWELL: Who?

DR. LLOYD-PURYEAR: The Marriott, but I

am looking for staff. Excuse me. We need some help.

[Breakout Session.]

DR. HOWELL: Ladies and gentlemen, we have had some very, very active discussions in the breakout session. We will look forward to hearing about those later in the meeting and so forth.We are now going to move to an area in which there has been an enormous amount of activity, and we are going to have an update on the American Health Information Community's Newborn Screening Use Case, and our presenter is Dr. Alan Zuckerman. Alan is a consultant to the AHIC Personalized Work group and heads and chairs many other things. His home base is at Georgetown here in DC. He is going to tell us about the progress of the Newborn Screening Use Case and the companion resource guide that he has recently presented to our meeting that is in October. This case originated from the subgroup

on newborn screening of the American Health Information Community, AHIC Personalized Health Care Program, and was approved by AHIC in 2008. It is now being developed by the Office for the National Coordinator for Health Information Technology within the U.S. Department of Health and Human Services. It will be made available to software developers to use as a guide to develop software that will meet the standards and specifications. Alan is involved in numerous things, which I won't go through because it will take the rest of the morning, but Alan, let's move along with your presentation. He is going to later introduce his sidekick who is sitting there, who also

will present from NLM. Alan? It is hard to tell when the microphones are on, I might point out. Here comes a microphonologist. Good.

[Laughter.]

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Update on American Health Information Community's Newborn Screening Use Case

DR. ZUCKERMAN: It is very exciting to be coming back here when the use case is actually under development and when the prospects of bringing it into implementation the next two to three years is so great. I have with me Dr. Clem McDonald, who is the Director of Lister Hill Center at National Library of Medicine and also the Chairman of LOINC, Logical Observation Identifier Names and Codes, which will be an important part of the presentation we are having. We are currently passing out to many of those who want it some materials some of the materials that he developed with our work group for bringing newborn screening terminology into modern data standards. Again, the use case and the coding document were published in December. You can all download them. I do have copies. I can show you they are discussed.

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The standards harmonization is now taking place in the Health Information Standards Panel, HITSP. They are meeting weekly, had a big person-to-person meeting last week, and it is a very open and engaging group. All of you are invited to participate, and if you can't participate directly in writing the Interoperability Specifications, there will be opportunities for public review and comment. It would be extremely important to keep them from narrowing their focus or from leaving out needs of those working in the field. Last week, we also did a webinar with APHL to get the newborn screening labs. We need to prepare for using the electronic newborn screening lab reports, and both will be specified in the use case. We also hope there will soon be document for the use case that will deal with privacy issues under HIPAA and CLIA and State law, particularly dealing with sharing newborn screening results with non-ordering providers and

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sharing results across State lines. But today I am hoping we are going to focus on the transition from the Personalized Health Care Work Group that ended its tenure in December into the National Library of Medicine, UMLS, Unified Medical Language System as a site where newborn screening terminology should be maintained. Just to review the components that will be coming forward within the use case itself when it is completed in June, some of it deals with the initial screening and electronic lab reports, and that begins with an order that collects data on birth history in the newborn. There is a consult and referral document based on existing standards that will be available for cases with confirmed diagnoses to summarize the usual screening and confirmatory testing and serve as emergency information forms for families. There is a section of the use case dealing with public health reporting and

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registries, and an area of particular interest will be how quality measurements and follow-up will be addressed through reuse of methods that are being developed for the quality use case and the use of templates for quality measurement. So HITSP is not developing something new and different for newborn screening, they are identifying the suitability of existing quality measurement tools to collect data from EHRs and collect data in the field in this context. There also are context-specific information distributions, methods for getting things like the sheets and other resources out. The basic timeline is that the use case

is expected to be accepted by the Secretary through the new Health Information Standards Panel, when that is constituted around December 2009, after a year of trial use to be recognized, and currently newborn screening is on the road map for July 2011 to enter into certification and commercial products. HITSP has changed their overall timeline

a little bit, so that we may have two public comment periods instead of three as in past years, and June is currently the target for when the draft specifications and the requirements design and standard selection will actually take place. Again, we hope as many people as possible will participate in the review. As I said, the coding and terminology guide is out there. The online version is still there, but the big change since your last meeting in October is the LOINC code revisions that came through in 2009 incorporating the recommendations of the AHIC work group on newborn screening requirements. What I want to speak further on that is clarification of the meaning of the ACMG codes and other plans that are emerged from revisions to SNOMED and integration into UMLS. There are dataset development activities for reporting newborn screening results -- they are on the way at HITSP -- that hopefully will lead to some national standardization for how we

issue initial reports. There are also the long-term follow-up datasets, such as the work from the subcommittee here, and again, there will be ample opportunities over the next six months for public comment on the scope of this work. Again, this is a brief view of our online version of the terminology, but now we have already moved most of that into LOINC. It is important to remember coding and terminology for drivers of modern standards, newborn screening has special needs, and there are three key applications of coding. One is to enable an unambiguous electronic result ordering and reporting. It is essential for quality insurance in defining the outcome datasets, and it is essential for population research and program evaluation. The ACMG Codes have been quite a challenge for us. The 29 test panels were just filled, as you know, out of a list of over 80 conditions, but they are essentially acronyms and

labels of convenience. They are being used extensively, though not always consistently, by the National Resource Center, by our National Newborn Screening Information Centers. But they are not a formal vocabulary like ICD-9 fills. And one of the goals of involvement of NLM will be to adjust the granularity of these acronyms or what the States are actually testing and trying to follow up with a diagnosis in SNOMED and ICD-10 and other reporting tools, so that the method by which a diagnosis is entered on a patient's problem list or reported out to other agencies will match what the genetic screening community feels is the appropriate way to cluster group into conditions. So it will take some time to get SNOMED adjustments to match these conditions. We currently have over 100 conditions in the coding guide, with the primary and secondary targets, other activities that the States are doing. As an interim, using the medical subject

headings for literature searching will be a rapid way of adjusting and facilitating literature retrieval around this same set of unique concept identifiers. Again, at HITSP, they are trying to develop the fields and value sets for both ordering newborn screening tests with the additional observations to be gathered before the test is done and the initial results. The LOINC codes that have been developed were designed to allow both a qualitative scoring of what issues were screened for, as well as separate reporting, if labs choose to do so, when the individual quantitative measures are analyzed. We are still working on a final clarification of everything needed for hearing screening. We involved the people from CDC. We now have LOINC codes to report newborn hearing screening on the standard in our optical documents. The ACMG Codes are still going to be

with us, but they will formally become short names and abbreviations for more formal terms in SNOMED and other diagnostic vocabulary, so that we can generate standard consult and referral documents listing the issues identified in a standard way. Long-term follow-up is a more complex issue and critical for following outcome, and this essentially involves defining quality measures, some of which are patient-based, some of which may be practice or population-based and have codes for the various observations that will be gathered. As was shared with the subgroup, the use of service-oriented architecture is a strategy that will allow these templates imposed to extract data as needed through other clinical records often in a de-identified way to get at the critical measures for long-term follow-up. I just wanted to make the advisory committee aware of some new provisions in Reauthorization Act that calls for, under their

quality measures, looking at an electronic health record format for children. Clearly, if this is going to be interoperable and allow parents and caregivers to view and understand the extent to which care of children is received as clinically appropriate and of high quality, newborn screening has to be a foundational component. A standard national child health record needs to begin with ordering a newborn screening and collecting birth parameters and should carry the newborn screening results forward in this context. Again, as we migrate to NLM, we are beginning with the kinds of LOINC codes with the terminology guide today, and the final interoperability specification that will be coming out in June will provide guidance to laboratories and registering reporting for appropriate codes and quality matters. Finally, the reason Dr. McDonald is here is to really facilitate this integration into our

National Unified Medical Language Service. We need input from the advisory committee, so that all the necessary conditions that are under discussion and evaluation here are properly represented in the standard terminologies and codes. We are going to begin with the work that was done through the AHIC work group, but there are additional conditions under consideration. They need to be headed. The granularity and precision of these codes needs adjustment, and once we have this integration to UMLS, perhaps by next summer, there will be the ability to standardize the way these genetic conditions are represented in electronic health records and to synchronize this with laboratory reporting, literature searching, and research data that will be used for decision-making. Of course, all of this has to operate in one central way, and it is hopeful that this committee would become the filter of repress for new terms needed for a variety of clinical

purposes. So let me stop here and take questions and comments, but first, perhaps let Dr. McDonald make his own series of requests in letting NLM provide the seed. DR. McDONALD: Hi. I am Clem McDonald and I am from NLM, as Alan has just mentioned. For those of you who don't know, we produce about 2 billion hits a year worth of scientific literature, but there is also close to a billion hits a year for consumer information on MedlinePlus and a couple hundred, many hundred thousand access this for genetic home references, all of which come out of NLM. But what we have committed to do is to be sort of the larder for this information that codes the structures and to facilitate and inform, provide information about how to make best use of it, particularly in terms of messaging. I heard just today there is an HL7 implementation already up. We would like to

promote that or explain how people could get to it and use it themselves, so to help with this communication which will be necessary to use this information most accurately. We have passed out to the panel this list of what the codes are actually in this first round of newborn screening. I have more. So, for those of you in the back, we will leave the stack up here if you want to get them. I am ClemMcDonald@mail.nih.gov. Everybody has got that same ending. So it is not hard to remember that, and if you have questions, you can ask me. We would actually like to invite ourselves to be a late connection to this committee. You are the expert panel and could help us keep this up to date, and we would welcome whatever you want to do.

DR. HOWELL: Thank you very much. Are there questions of Alan or Clem about the program? It is obviously an enormous opportunity to have newborn screening emerge as a foundation in the health information technology

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push that is becoming a national effort, and so it is great to have them here and so forth. Are there comments? Coleen.

DR. BOYLE: Just a quick question, maybe a clarification. You mentioned the quality use case and its application for long-term follow-up. Could you just elaborate on that a little bit?

DR. ZUCKERMAN: Yes. This was one of the 2007 use cases. Currently, CMS, AHRQ, and the National Quality Forum are working on getting practical implementations out. This was an effort, high priority of the AHIC, to be able to do, in effect, automated records review of electronic records to extract quality measures. For example, there are LOINC codes for all the ETIS measures. There are a variety of tools that have been developed, but they are in the process now of getting several quality measurement targets illustrated, so that you can send a template to an electronic health record in a practice and get back the data that you need

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for quality measurement. The hope is we are going to be looking at this in HITSP as being suitable for newborn screening. The more concrete examples of measures and the types of information that come out will be needed. HITSP has a component for data collection forms in a standardized XML way, which you can enter data on the Web and report it back or in which you can pull data from an electronic health record. The hope is that we are not going to have separate systems for research and clinical care, that the clinical care systems will be automated, will also meet research and quality measurement needs.

ATTENDEE: [Speaking off mic.]

DR. ZUCKERMAN: Within HITSP, we have both the identification protocols, and we also have something called pseudo-anonymization where, when needed by selected individuals to go back and get more data, you can re-identify a person

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of interest. This was developed for biosurveillance and other public health activities under control. So all of these tools will be part of the newborn screening use case and available, so that data that is reported out will be either de-identified or pseudo-anonymized if there are reasons why you may need to re-identify at some point in the future. Of course, the policy issues that go with that, early, separate but need to be addressed, and will be identified.

DR. HOWELL: Mike?

DR. WATSON: I am in the you-can't-hit-a-moving-target part of this thing where there was AHIC, then there was the AHIC successor, and then there is something that succeeds that, that is a private-public partnership of some kind, and then the HIT part of the stimulus bill goes back to two HHS-based structures. I am trying to figure out who we

talk to because we are moving some of these languages along fairly quickly.

DR. ZUCKERMAN: The only thing to be sure is that transition is definitely going to happen, and that under the bill, which is still being worked out, because that was discussed extensively last week at the Health Information Standards Panel, the priority-setting will take place in two separate committees. There is an HIT Policy Committee and there is an HIT Standards Committee, and these are both going to be under FACA, and they have details of their bylaws and rules that are being worked through. But I think one of the important things that will happen is that the policy committee will try to both identify what we should be doing and looking at the value and the intent to implement. The value cases that have currently been going to the current AHIC successor that hopefully will move into these two groups will try to do that.

The Standards Committee is not going to replace the Health Information Standards Panel, which does the day-to-day work of harmonizing standards or the standards development organizations like HL7. It will provide a review step on the usability and the intent to use these standards, so that the work that is underway at HITSP today will hopefully be among the first set of standards going to this standards panel for a broader review on suitability. One of the few things that is in the legislation, very clearly spelled out, is that in December 2009, there will be an initial set of standards designated by the Secretary. It will have some significant weight in acceptance, and some of those will incorporate existing recognized standards, and some of them may allow other approaches or make modifications. So, of course, one of our goals is to see what is ready in December 2009 in the area of newborn screening because this will provide some

significant constraints on the use of certain types of funds and on certain time frames to migrate to these new standards.

DR. HOWELL: Do you know who to talk to?

Talk to Alan.

[Laughter.]

DR. HOWELL: He can probably get through all these very complex abbreviations.

DR. ZUCKERMAN: It is hoped that there will be a smooth transition between these organizations and a clarification of their roles

and mission.

DR. HOWELL: Thank you very much, Alan and Clem, for that presentation and so forth. For those of you who have not seen the

list that Clem mentioned, you should certainly look at it, and I would hope memorize it during lunch.

[Laughter.]

DR. HOWELL: It is most complex list. Let me make a few comments before we go to lunch and so forth. Let me remind any of the

presenters, if you have changed your presentation from which what you forwarded in, please be sure to load it in the laptop before then. This evening, at the Agio Restaurant at 6:30, which is off the main floor lobby in front of the hotel, committee members and members are invited to join our group at dinner. Now, there are some very complex things. Number one, please bring cash instead of credit cards. The restaurant cannot reconcile a check with more than two credit cards. I guess the biggest number to divide is two, but anyway, the bottom line, there is a preset number, and the total cost is $46 per person plus tax and gratuity. So bring a lot of money. There is an ATM in the lobby.

[Laughter.]

DR. HOWELL: Beer, wine, and liquor are additional and so forth, but anyway, hopefully, a large group will bring your money and join us at dinner tonight at 6:30. So, hearing no further comments, let us

go the lunch, and we will return quite promptly at 12:45. We got a busy afternoon.

[Luncheon break.]

DR. HOWELL: Ladies and gentlemen, we need to get the show on the road here. So can we get everybody to have a seat as we proceed? We have got a very full afternoon agenda. We have been working for some considerable time on the decision criteria and process work group, and after our conference meeting on the telephone, Dr. Calonge and Nancy Green agreed that they would work on the criteria and process work group. Ned has agreed to distribute the document, showing the changes, which he has done, so the members would have a chance to read the new document, et cetera. So it would be my hope today, Ned, that if you would be good enough to go through this with the committee again, that we can go ahead and finalize and adopt this report. It seems that it has been worked on extensively. It is

nicely aged and of fine quality, and so, hopefully, we can get it done.

Ned?

Decision Criteria and Process Work Group

DR. CALONGE: I very carefully didn't put my name on this presentation because there are so many people that worked on it, too many to name, and I don't have a 45-second clock like the Academy Awards, but what I would like to do today is kind of get approval for the process, recognizing that there are some edits to the final document that we still have to work through, but I honestly believe that we are ready for adoption. I think our analytic framework and key questions are set. There are still some minor editing of the introductory sections that make this decision process fit into your operating procedures as a whole. There is still a little bit of debate among committee members about how much discussion of the decision of certainty of net benefit needs

to be in the body versus an appendix. There have been some issues brought up about some fine-tuning of the decision matrix, and I will own the fact that the issues on study design and quality appendixes, which were drafted very early on and since we were working on the main body of the report, we haven't really gone back to. We need some additional work just to fine-tune those. So what I would like to concentrate on is the heart of the process itself, the key questions, so we can improve that process. The decision matrix, we may have to spend some discussion time on today to clarify, and then for me, the rest is really minor editing. I think there really are no new concepts to bring before you or to have you wrestle with. So this is an analytic framework, and the original analytic framework that looks like this came from Dr. Russ Harris in the U.S. Preventative Services Task Force, and this has

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been adopted for use specifically for newborn screening. What an analytic framework does is give you a process in which to work through in order to get from your evidence report, your systematic evidence review report to a recommendation at the end, and the questions, the numbers refer to key questions. So the issue is you have a general population of newborns and children, but newborns and children have testing for a condition. The overarching question would be whether or not that testing leads to improvement in morbidity and/or other outcomes. The fact that we may not have an overarching study says can we actually put together a chain of evidence that gets us to the same answer, so does testing lead to the diagnosis of the condition, does treatment of the condition lead to improvement in morbidity, mortality, or other outcomes. Now, inherent in this is also diagnosis

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without treatment leading to a broader potential group of other outcomes, and I think that is something we all need to wrestle with, but we recognize that treatment is still a very important issue. Then once we are able to establish that testing leads to diagnosis, leads to improvements in health outcomes, are there harms associated with testing, diagnosis, and treatment? And can we balance the harms with the benefits and make a recommendation to the Secretary? Finally, we have specifically in, I think, our charter and our charge to look at the cost utility of screening and treatment, and that is why that is added on the end. Any questions about the analytic framework?

[No response.]

DR. CALONGE: So I am going to quickly just go through the key questions one more time and see if we have questions about the questions.

So the overarching questioning: Is

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there direct evidence that screening for the condition at birth leads to improved outcomes for the infant or child to be screened and/or for the child's family? Now, usually what you would see as adequate evidence in the adult prevention world would be randomized control trials of randomized to invited-to-screen versus not-invited-to-screen going all the way out to improved-health-outcomes in terms of morbidity or mortality. We recognize that it is probably rare that we will be in a condition where we have that level of overarching evidence, but I think we want to ask the question to set up the rest of the framework. So then we move on to Key Question 2, which really talks about the condition. Is there a case definition that could be uniformly and reliably applied? What is the clinical history and spectrum of disease of the condition, including the impact of recognition and treatment?

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So this says you cannot actually screen for something that you can't define, and we should be able not only to define the conditions that we are looking for, but to find them reliably with a good case definition, so that we are always talking about the same thing. Key Question 3. Is there a screening test or screening test algorithm for the condition with sufficient analytic validity? A lot of time has been spent on

trying to explain what analytic validity is compared to clinical validity. I think because we are in an area where the screening platform, the technology, the screening algorithm is all key to the uniform acceptance and use of the test across 50 States for all of the birth cohort of our country, that we have to pay attention to does the test actually do what it is supposed to do in terms of measuring the actual biochemical things we are trying to measure. This really talks about reproducibility. It talks about validity at reaching the target,

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separate from what the clinical validity or does it actually predict the condition. Key Question 4. Has the clinical validity of the screening test or algorithm in combination with diagnostic tests or testing algorithm that determine and is that validity adequate? So this is a two-part question that says do we actually have sufficient evidence to conclude what the clinical validity is; that is, how often or how well does the test actually translate to the condition we have concerns about, and then number two, is this level of clinical validity sufficient to justify testing. That last question gets into the tradeoffs against false positive versus false negatives and the performance of the test in picking up a condition of concern. It also gets to the issue of a spectrum of condition. So we know the more we test, the better we are able to actually describe the complete clinical spectrum of a condition from

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very severe to not as severe. So I think buried in this question is we want to pick up disease that we need to intervene in, not necessarily conditions we don't need to intervene in. So that is both false positives, false negatives, and in the adult world, we call it watching out for over-diagnoses, diagnosing things that don't need to be treated. They are really there, but they don't need to be treated. So that is Key Question 4. Key Question 5. What is a clinical utility of the screening test? So, finally, this is the core of the issue. Does screening lead to more benefits than harms? That is where we want to be, and that is the definition of clinical utility. So we have separated No. 5 into what are the benefits associated with the use of the screening test. Again, I would say here what we have not done in this document is wrestle with the complete list of important outcomes that might be

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associated with testing. So the Genetics Advisory Committee has a published list, and we kind of looked at that. I think that the advisory committee is going to have to wrestle with how we look at those broad outcomes and how we weigh those because that is an important issue. Then what are the harms

associated with screening, diagnosis, and treatment? Those are both from false positives, false negatives, diagnostic tests for confirmation, ELSI issues, labellinglabeling, anxiety, interference with the parent-to-child interactions. We also need to think about a broad potential list of harms in order for us to weigh those. Key Question 6. How cost effective is a screening diagnosis and treatment for this disorder compared to usual clinical case detection and treatment? Again, this is one that doesn't actually talk about whether or not benefits outweigh harms. This just says how much does it cost to

get those benefits. Again, I think that we have included this question not necessarily as a decision-making point for the advisory committee, but as a point that we are charged with describing in our recommendations. So, after we go through questions, we need to do three steps in weighing the evidence. We have to evaluate the study quality, determine adequacy of evidence for each key question, and determine adequacy of evidence across the key questions. How do we evaluate study quality? Well, while study design is up there, the real issues are what are the threats to internal validity and what are the threats to a generalizability. That is the study quality question. Is the study of sufficient quality that we know the outcomes can be associated to the factors under study, and then do we think it will have the same impact in populations other than the populations studied? That is really all there is to study quality.

So then, once we have study quality, we try to determine the adequacy of evidence, and here definitions that we are asking you to adopt of adequate evidence is the observed estimate or effect is likely to be real rather than explained by flawed study methodology. The advisory committee concludes the results are unlikely to be strongly affected by the results of future studies. So that would be adequate evidence. Inadequate evidence would be everything else. The observed results are more likely to be the results of limitations and/or flaws in study methodology, rather than an accurate assessment, and subsequent information is more likely to change the estimate or affect enough to change the conclusion. So we tried to make it pretty black and white. We either have enough adequate evidence, or we don't. These are six critical appraisal questions that the task force has adopted. There

is nothing magic. Any epidemiologist would be able to come up with the same list, but these are looking at adequacy. Do the studies we have reviewed have appropriate research design to answer the key questions? Do they have internal validity? Do they have external validity? How many studies are there?

How large are they in order to answer the key question? This gets to the issue of precision of evidence. Are the studies consistent, and are there additional factors supporting the conclusions? This last one, I just want to point out is very important criteria because I think it actually assists us in looking at contextual issues in judging the adequacy of the evidence. So the last step, once we have weighed the evidence, is translating the evidence into recommendations. So the three questions that show up in the matrix and give us our final answer are what is the magnitude of net benefit, which is benefits minus harms; are the benefits

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of screening, diagnosis, and treatment minus the harms significant? The second question is: What is the overall adequacy of the evidence? Again, we have already gone through that. Does it meet the standards for having adequate quality? Then finally, what is our level of certainty? Now, I would like to say that evidence-based medicine is so regimented that you could look at something and say yes or no, but ultimately, along the path, there are judgments that we need to make. We have to make a judgment about study quality. We do that by looking at criteria. We have to do a judgment about the adequacy of evidence, and we do that by applying criteria. Then ultimately, we have to make a judgment about our level of certainty that we are right, that in making the recommendation we believe overall addition of this condition to the core set is going to result in improvement in important health outcomes.

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Finally, that leads us to the decision matrix. I realize this is very small for folks in the back, and I apologize, but here are the categories for the recommendation, our level of certainty, our magnitude of net benefit.

DR. LLOYD-PURYEAR: Excuse me, Ned.

DR. CALONGE: Yes, Michelle.

DR. LLOYD-PURYEAR: If you guys don't have this printed out, it is in Tab 15, and it is in back of your --

DR. HOWELL: Sixteen.

DR. LLOYD-PURYEAR: I am sorry, 16.

DR. HOWELL: It is printed out at the end of Tab 16, for the members of the committee.

DR. LLOYD-PURYEAR: It is 16.

DR. HOWELL: Sixteen, right at the very back of 16.

DR. LLOYD-PURYEAR: The standard operating procedures, and it is Attachment C within those policies and procedures.

Sorry.

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DR. CALONGE: That's all right.

DR. SKEELS: Hello. This is Mike Skeels in Oregon, and I am looking through my tab and I don't find it. Is that in the ones that were

sent out early?

DR. LLOYD-PURYEAR: Yes.

DR. HOWELL: It was in mine that came.

DR. LLOYD-PURYEAR: It was sent out --

DR. HOWELL: Yeah.

DR. LLOYD-PURYEAR: -- many, many weeks ago for your review.

DR. SKEELS: Okay. Which tab is it, 15 or 16?

DR. LLOYD-PURYEAR: Sixteen.

DR. HOWELL: Sixteen, right at the back end of 16.

DR. SKEELS: Thank you.

DR. HOWELL: It is after the legislation, Mike.

DR. SKEELS: Okay, thanks.

DR. HOWELL: Thank you, Ned.

DR. CALONGE: I think I actually have

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the categories here. So the way the matrix is supposed to work is we decide our level of certainty and our magnitude of net benefit, and if we have sufficient certainty and a significant net benefit, we would recommend adding. So let us just go through the categories separately. Well, you know, it would be great if you can leave them up, but I will go through it. So Category 1 is the committee has sufficient certainty of significant net benefit to recommend adding the condition to the core panel. So this would be we get to the end of our process, and we put the level of certainty here and the magnitude of net benefit here, and we end up with a recommendation. Now, there has been some confusion about Category 2, which is the committee has sufficient certainty of no net benefit or of net harm to recommend not adding the condition to the core panel. So the question is how is this different from not adding it when there is insufficient

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evidence, and the difference is there could be situations where we actually have evidence of no benefit, which is different from no evidence of benefit. So I think this is a category we have to be able to capture and say that when we actually look at the evidence that is out there, we are sufficiently certain that at least at this point in time, that adding the condition to the core panel is not warranted. We would actually make a recommendation to not add it.

DR. VAN DYCK: Could you go back to that previous slide and read that again?

DR. CALONGE: Committee has sufficient certainty of no net benefit or of net harm to recommend not adding the condition to the core

panel.

This is the phrase that I always joke will be on my headstone. Evidence of no benefit is not the same as no evidence of benefit. So

this isn't an insufficient rating. This is a

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"sufficient" and "don't do it." In task force language, this would be a "de-recommendation." An example of a de-recommendation would be screening for hepatitis C in a low-risk

population.

DR. HOWELL: I think that note is very important and very clear.

DR. CALONGE: Sometimes I can be that way.

The next category, the evidence is insufficient to make a recommendation. However, there is compelling potential for net benefit. Committee wants to make a strong recommendation for additional study, such as pilot studies to fill in the evidence gaps. So in both EGAPP and in the U.S. Preventive Services Task Force, this is looked at as an I-optimistic or an I-hopeful. The evidence is insufficient to meet our criteria, but you know what? It looks pretty good, and we think if we had a little bit more experience, filled in the evidence gaps, did some pilot

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studies, we think we would add this condition. We are optimistic. So what we need is a strong recommendation to fill in those evidence gaps, and I am hoping that I am setting enough of that difference that you understand that Category 4 is different. Category 4 is we don't know. We simply have not enough data. There is not evidence. We don't have enough evidence of potential net benefit to lead us to want to make that strong recommendation regarding pilot studies. This could be a condition for which there is currently no treatment, and we don't have evidence that there may be other benefits that could be realized through early detection. So this is traditionally the insufficient and "I don't know" category, or this is the insufficient and "I think a little bit of work would get us there." Hi, Nancy.

DR. GREEN: Can I just ask you for a

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clarification? If you can go back to No. 2, with your permission, please? This is very clear, no net benefit, but it does leave the question open about inadequate net benefit, like there might be minuscule -- some net benefit but at such a cost, how everyone defines cost. So could you address that for a moment, please?

DR. CALONGE: Well, it is a great point, and I will tell you it gets subsumed in the actual culture of an evidence-based group. When you do look at benefits that are so small and at such a great expense that it is near zero -- and I think that is where things end up in this "don't do it" because of that category -- let me tell you, I actually think we will use -- at least looking across the conditions we could add -- I believe we will use this seldom, but potentially not never, and the reason is if it costs too much now, that is what it costs now, and could you conceive of some time in the future where economies have scaled, improvements and

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other issues, where that cost ratio might say, you know, this is probably worthwhile. I will tell you, though, for the extremely rare -- and I don't know. I can't even tell you what that number is -- extremely rare and high-cost issues, I think the committee will wrestle with that, whether we are ready to pull the trigger and say it should be in Category 2, and we should. I think that is exactly an appropriate way to be. We will have to be very reserved, I think, when we say we think we have sufficient evidence to don't do this because it is hard to go back on that, I keep saying. I am certain we shouldn't do this. So I have been told by people who have heard me talk before -- I know the task force -- that we need a little bit of fine-tuning of this matrix in order for those points to become clear, and I am happy to. Michelle and I will work, and Nancy together and the rest of the committee will work

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together to try to clarify these four categories with words that look more like the ones I have tried to put together in slides, but what I hope we could vote on is this is the way we are going to do it, and you go off and do the editing because we are fine with it.

DR. HOWELL: Thank you very much, Ned. Are there questions from the committee about this report? The group has worked on it a long time, and I think it is extremely well done, frankly. Brian?

DR. HALL: Thanks. I know I am coming late to this, so pardon me for that, but I just have two questions about timing. One is in the framework. It is not explicit where the idea of diagnosis at a particular time being earlier than it would be otherwise is made, and I don't if it would help people perhaps to point out where that is occurring in the framework.

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The second issue is I assume that there is an assumption on all of these cases that we are talking about within the current screening timing again, that it is happening in newborn screening at whatever time that is done, because that may make a difference for some tests that may not be as good if they are done on premature infants, for example, right away. So I think that there is that assumption there. I just wanted to point that out as a clarification.

DR. CALONGE: Well, I think that is a good point. The analytic framework that we kind of prepared is what we call a "generic analytic framework." Nancy is here, and Jeff can tell too, that you have to modify this on the basis of the peculiarities of the condition you are looking at, but you are right. In the text, the testing for the condition, the diagnosis of the condition, and

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the treatment, it is in the treatment part. There is the concept that we want to assure that early detection makes a difference compared to clinical detection, and it is in the text.

DR. HOWELL: Further questions of Ned? Piero.

DR. RINALDO: Ned, a couple of comments. When I look at this matrix, I wonder if really the order should be one, three, four, two, because it really is in a sense how positive is the outcome. It is a bit confusing that you put sort of the best outcome first, the worst, and then sort of the intermediate scenarios.

DR. CALONGE: I take that as a very useful comment, and I will change it.

DR. RINALDO: The other question I have is about the Key Question No. 6, and I think you made a disclaimer that this will not be somewhat evaluated very strictly. What concerns me a little is at the end, compared to usual clinical case detection, because, certainly, there are conditions where

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sometime the onset is sudden death. So you may say that doesn't really cost in a cynical way. I remember 10, 15 years ago, the discussion about MCADD, and there were people stating why should we be screening for this condition where in many cases we don't save any money, because when the

disease becomes apparent, the patient is dead, which, obviously, is totally a ridiculous statement, but is that the comparison? It might be possible. So how you going to handle early mortality in this context?

DR. CALONGE: So that is actually in the phrase, believe it or not, "cost effectiveness." "Cost effectiveness" is not "cost benefit analysis." It is saying what utility do I get, at what cost, and the way you take in prematurity is you say how many potential life years do I save and what is the cost for a potential life year. One of the things that occurs with early mortality, because you have such a long number, a large amount of potential life years, it ratchets

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down the cost effectiveness to make it look pretty good. So, if I prevent a death of an infant who has a life expectancy of 75 years, I buy a whole lot more for my money than when I do colon and rectal screening on a 65-year-old and buy he or she 10 to 15 years. So I want to assure you that, though it is imbedded in that phrase, "cost effective," if you look at the section and you look at what Scott Gross and others have done, you kind of understand that that is in there. Cost effective depends on the utility.

DR. HOWELL: Jeff?

DR. BOTKIN: Ned, I wonder if the analytic framework accounts for multiplex platform testing. So you are looking for five, but you get results on 20. Does this assume that each condition stands on its own, or is there any influence of the fact that you are getting information about conditions that you may not be initially targeting with the test modality?

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DR. CALONGE: So my understanding in working with leadership at HHS and Dr. Howell is that this is a condition-specific recommendation, so that the systematic evidence review and the judgment and the process will be around the condition, not the test or the test platform. Hope that helps. Would you say that is correct, Dr. Howell?

DR. HOWELL: I think that is fair.

DR. CALONGE: And it took me a long time, Jeff, to stop putting "test" in there because that is what I was used to saying, "test," and after being beat about the head and shoulder by Michelle for a long time, I now say "condition." I have got it down now.

DR. HOWELL: You have got big shoulders.

That's great.

[Laughter.]

DR. HOWELL: The committee has had a chance to look at this in the past, and they have seen it electronically. We have seen some

conditions.

Becky?

DR. BUCKLEY: Just one minor question. Looking at the decision matrix here, the head of Column 3, level of certainty, I think it is not entirely clear whether that level of certainty pertains to your recommendation or whether it pertains to the evidence. Maybe you should qualify that too by indicating what level of certainty.

DR. CALONGE: This is the way I would put that, Becky -- and maybe it just needs to be in the matrix -- we have sufficient certainty of significant net benefit.

DR. BUCKLEY: Okay.

DR. CALONGE: All right?

DR. BUCKLEY: Yeah.

DR. CALONGE: Because that is really what we are doing. We are looking at ourselves. I am turning to Denise and saying I am sufficiently certain this is the right thing to do.

The way I like to talk about certainty is that it is your risk of being wrong, and what we want to do is, I believe, in our recommendations is minimize our risk of being wrong. The flip side of that is to be certain, sufficiently certain.

DR. HOWELL: Mike, had a comment?

DR. WATSON: Yeah, just a question. I understand why, at least the vast majority of reasons why you would look at every condition independently, but when it comes to cost of a laboratory test, when you are doing the cost-effectiveness analysis and you have got maybe 10 conditions from tandem mass spec and you put on another one, your cost is incremental, not $25 for a tandem mass spec test.

DR. CALONGE: I think that is exactly right, and I think that our cost-effective methodology allows us to account for that. So we would not look at adding a condition to the core 29 that was a tandem mass spec condition and say in order to screen for

this, we have to start tandem mass in every setting where there is not one. Does that make sense?

DR. WATSON: Yeah.

DR. CALONGE: We would say since we already have it in all 50 States, we would add analyzing those analytes in that pattern to what we current do. So then the only cost is the cost of confirmation or retesting, confirmation testing, if there is required a diagnosis, and then the counseling and treatment that would follow up with that.

DR. HOWELL: Further questions or comments? I would hope that the committee would feel comfortable in moving ahead and adopt this because we have been talking about it is long time, I think it outlines what we really would want to do.

Is there further discussion?

[No response.]

DR. HOWELL: Could we have some generous soul make a recommendation?

DR. TROTTER: I move that we accept Ned's committee's recommendations as our concept.

DR. HOWELL: Dr. Buckley seconds it. Those in favor of that say aye.

[Chorus of ayes.]

DR. HOWELL: Any opposition?

[No response.]

DR. HOWELL: Did anyone abstain?

[No response.]

DR. HOWELL: It is unanimous. Thank you very much, Ned, and you are going to polish up some of the wording a bit, and we will see a final document then.

DR. CALONGE: That is right. The hope is to submit and publish. We have to decide. We may only publish the appendices online. So the idea would be to publish the main document in paper and the appendices online.

DR. HOWELL: I would hope it certainly would be published, so that it would be available, because it is an important document for this meeting.

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Thank you very much. That is a very nice document and so forth. Now we are going to move ahead, and we are going to have a report. This is the final draft report on the candidate nomination of severe combined immunodeficiency, and we would like to welcome Dr. Ellen Lipstein from Harvard in Boston. As you know, Dr. Lipstein is in the Center for Adolescent and Child Health Policy at Mass General Hospital, and she, of course, is working very closely with her colleagues there and Jim Perrin on this review. As you know, we had an excellent preliminary report presented by the Evidence Review Committee at the November webcast meeting, as you will recall, and a lot of discussion. Now we look forward to hearing this final report, and it would be our intention that the committee will take action on this recommendation today. I will make a formal notation that Dr. Buckley, because of her involvement and expertise

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in this area, will remove herself from the committee decision, but we will look forward to her to making any comments during the public comment section that she would like to, so thank you. Dr. Lipstein? Evidence Review Work Group: Final Draft Report on the Candidate Nomination of Severe Combined Immunodeficiency (SCID) DR. LIPSTEIN: Good afternoon, and thank you to the committee for this opportunity to present our work group's final report on newborn screening for severe combined immunodeficiency. Before I get started, I want to just give you a brief overview. Today, I will be providing an overview of the SCID report, which was submitted to the committee last month, and also to update you that, while completing this report, our work group has also begun to evaluate the evidence related to screening for Krabbe disease in work that is being led by Alex Kemper. I would like to acknowledge the work of

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all of the members of our group who assisted in preparation of this report on SCID, and in particular, Aliex Knapp, our able project coordinator, and Dr. Perrin, who is unable to be with us today but is the chair of

the work group. To begin, I would like to provide a very brief introduction to SCID. As many, if not all, in this room are aware, severe combined immunodeficiency is actually a group of disorders characterized by the absence, both humoral and cellular immunity, due to defects in T cell production and function. Additionally, some subtypes have defects in B or natural killer cells. Mutations in at least 17 different genes have been shown to lead to SCID, and due to the absence of both humoral and cellular immunity, as protection from transplacentally acquired maternal antibodies wane, infants with SCID develop severe infections from both common and opportunistic pathogens. With that background, let me move to the

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reason that SCID was nominated and reviewed for consideration on the panel of recommended disorders for newborn screening. As I alluded to on the previous slide, without disease-specific treatment for SCID, SCID leads to death in early childhood from infection. Disease-specific treatment, primarily in the form of bone marrow transplantation, has been shown to decrease mortality and morbidity for affected children. Additionally, there is some evidence that earlier treatment, especially before the onset of lung infection, may offer greater benefit. The final reason for review at this time is that methods to screen infants for SCID, most commonly using quantitative polymerase chain reaction or PCR, for T cell receptor incision circles, small pieces of DNA specific to T cells, have been developed. The written report submitted in January contains the elements listed here. Today, I hope

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to highlight the methods we used, summarize the evidence, and leave you with a list of areas where key evidence is lacking. In the most general sense, a review of the evidence consisted of two related steps. In the first, we conducted a systematic literature review, which I will describe more fully in the coming slides. This was done in order to summarize the published evidence. However, we recognize that in a rapidly changing field, key evidence may not yet be published. For this reason, we contacted key investigators in the field in order to obtain unpublished data for assessment and inclusion in the report. Based on the previously developed template for evidence review, we sought to evaluate the evidence under five specific topics. Namely, we evaluated evidence concerning the incidence or prevalence of SCID with an emphasis on U.S. population studies, the natural history of the disorders, specifically the timing of clinical onset of disease, severity of disease,

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and variation by genotypes. With regards to testing, we considered evidence on the methods of screening, including accuracy of the screening methods, diagnostic testing, and the risks and costs of both screening and diagnostic testing. We reviewed the evidence regarding treatment of SCID including methods, efficacy, timing, availability, and risks. Although we considered evidence on all of these topics, we emphasized the data related to screening and treatment. Finally, as mentioned before, we developed a list of areas in which we feel critical information is needed. For the literature search, we searched Medline using a 20-year time span, using the National Library of Medicine, medical subject heading, severe combined immunodeficiency, combined with subterms including epidemiology, incidence, prevalence, disease progression, neonatal screening, genetic screening, diagnosis, and therapeutics.

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In order to capture literature which was not yet assigned medical subject headings, we conducted a keyword search using the Ovid In-Process and other non-indexed citations database. This search strategy resulted in 725 abstracts, of which 60 were ultimately included. The excluded studies included those not written in English, basic science publications, opinion pieces, case series with fewer than four patients, and studies that did not address one of the key topics I mentioned on the previous slide. This table shows the study design of the included studies. The two listed as other design were epidemiologic studies utilizing retrospective record review in one case and a telephone survey in the other. Perhaps the most striking aspect of this slide is that nearly two-thirds of the included studies were case series. For each of the 60 included papers, we assessed the quality of the study in two

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different ways. The first was by study design. This part of the quality assessment is fairly analogous to quality assessment used for other evidence review processes. Specifically, we assessed the quality of the study within design categories. For example, a list of criteria was a variable for assessing cohort studies, and a different list was used for assessing case series. The second quality assessment was by what we termed "study goal." For example, the type of evidence desired for a treatment study was different than the evidence desired for a natural history study. By way of example, I have listed here the three options for the quality of a study about sensitivity and specificity of screening. In the second quality assessment, a single study may have been assessed multiple times. For instance, a screening study may have information on both sensitivity and repeat specimen rate.

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As I proceed through this report, I will provide a summary of the second sort of quality assessment by study goal for each topic area. After completing the literature review, we contacted experts in the field. These experts were identified through the literature review, discussion with our work group, and recommendations from other experts in the field. We strove to include individuals from varying areas of SCID research and advocacy, including newborn screening, treatment, and family advocacy groups. For this report, information obtained specifically through such contacts is presented for each category after a presentation of the published literature. This slide indicates the experts whom we contacted directly or to whom we were referred by other experts. An asterisk indicates that the individual responded to our inquiry. We initially contacted individuals via e-mail, sending an introductory letter, a written open-ended survey, and a conflict-of-interest

form. After receiving the written response, we arranged telephone interviews with those individuals from whom we desired clarification or further details. Those who did not respond to our initial e-mail were sent a follow-up e-mail. With that explanation of our process, I am going to move on to the actual evidence review. I want to start by mentioning that as I present evidence, my goal is to highlight our finding, rather than provide comprehensive details on all portions of the evidence report. For this reason, those of you who have seen the written report will note that the tables shown on these slides highlight fewer studies and less detail from each study than the evidence tables in the written report. This slide is the first one demonstrating the way in which we assess the quality of a study by its so-called goal; in this case, description of the natural history of the disorder, specifically the correlation between disease phenotypes and genotypes, and the

incidence of SCID within the U.S. population. With regard to incidence, published literature suggests an overall incidence around one in 100,000, based on clinical and laboratory referrals. The Chan and Puck estimate for SCID incidence in the United States is based on the assumption that all children with X-linked SCID had samples sent to a single laboratory, and that these samples represent half of all SCID cases in the United States. A higher incidence has been estimated among Navajo and other Athapaskan-speaking Native Americans due to distinct genotype in that population. The evidence regarding the natural history of SCID corroborated the information I presented earlier by way of introduction to the disorder. Specifically, most children are diagnosed after they have had recurrent infections or after particularly severe or unusual infections. Additionally, some present with failure

to thrive, chronic diarrhea, or persistent oral candida. It is especially common for children with SCID to have recurrent pulmonary infections. Although the exact timing of such infections may vary slightly, most begin in the first few months of life as transplacentally acquired maternal antibodies wane. Some children are diagnosed prior to infection, but this primarily occurs in families in which an older sibling or other relative is affected with SCID. As noted here, without specific treatment for immunodeficiency, children with SCID will die from these infections. Although there are some phenotype and genotype variations, these differences do not significantly affect these main findings related to infection and subsequent early death. Now I am going to move on to the evidence related specifically to screening. As you can see from this slide, there is little published literature that met criteria for inclusion in this review.

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We found the total of four studies, none of which were from a population-based screening program. Several screening methods have been proposed within these four studies. These include the use of whole blood to assess lymphocyte counts and the use of dried blood spots to either use quantitative polymerase chain reaction to look for T cell receptor incision circles, TREC, or enzyme-linked immunosorbent assay to measure a specific interleukin. This is the first of several evidence tables I am going to present. I apologize for the difficulty of reading the slide, but we want to provide a sense of the evidence to those people who have not had a chance to review the full report, although, again, I want to comment that these tables are meant to highlight our findings rather than be a comprehensive overview. For all the tables I present today, we have listed the studies in chronologic order with the newest study at the top.

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In this table, we present the four studies in the review which relate to newborn screening for SCID. For studies which did not include sensitivity or specificity, we completed those calculations using data available in the paper. The first and last study on this table utilized white blood cell counts in small studies comparing children with and without SCID. Both papers found persistent lower white blood cell counts among children with SCID than among other children. The Chan and Puck study, shown here, utilized quantitative PCR to measure TREC among children with SCID and on anonymized dried blood spots which were assumed to come from children without SCID. They demonstrated the ability to amplify TREC DNA from the dried blood spot in that there was no detectable TREC in the children with SCID. Finally, the McGee study proposed a two-tiered approach in which interleukin-7 is

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measured from dried blood spots and TREC is measured only in those samples where IL-7 was elevated. As most in this room are aware, newborn screening for SCID was an area in which information from experts was crucial. There are currently two State population-based SCID newborn screening studies being conducted. Massachusetts began their study the 1st of February, and Wisconsin has an ongoing study which began in January of 2008. The Wisconsin program and specifically Drs. Mei Baker and Ronald Laessig have shared their current screening data with this evidence review work group. Here we show the overall results for children screened in Wisconsin during 2008. The percentages in parentheses are the percentages for that subgroup. In other words, 0.308 percent of premature newborns had an abnormal result. All samples within their program are tested for TREC. Those with less than 25 TREC

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per microliter are repeated in duplicate from the same dried blood spot and beta-actin is measured as a control at that time. This occurs for approximately 1.5 percent of the samples. Based on this process, an abnormal result is defined as less than 25 TRECs per microliter, a sample from which they were able to sufficiently amplify beta-actin. In full-term infants, this leads to a recommendation for confirmatory testing. An abnormal result in a premature infant leads the program to carefully track the second newborn screening test as it is standard practice in Wisconsin to obtain a second and third newborn screening card for premature infants. Inconclusive results are those in which there was less than 25 TRECs per microliter, but insufficient amplification of beta-actin. In those cases, a second newborn screening card is requested from full-term infants. Overall, approximately 0.2 percent of children required a second newborn screening for confirmatory

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testing. Here you see the detailed outcomes for children with both abnormal and inconclusive results from Wisconsin's first year of newborn screening. The left column shows the outcomes among abnormal results. Most children were ultimately shown to not have any disorder, particularly among premature infants, and although several had other types of immunodeficiencies, they have not yet detected any children with SCID. In the right column, you see the results from the inconclusive results. Again, most children have normal results on repeat newborn screening. At this point, I would like to move on to the evidence related to treatment for SCID. There are three methods for treating the underlying immunodeficiencies associated with SCID. Most of the research and clinical treatment is in the area of hematopoietic stem cell transplant, but two other treatment

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modalities are being studied for children with specific subtypes. Those with adenosine deaminase or ADA deficiency enzyme replacement has been studied. Additionally, gene therapy using viral vectors has been

investigated for both X-linked and ADA-deficient SCID. Most of the evidence I will present relates specifically to transplantation. Here you can see that, although 47 of the 60 articles we review were related in some way to treatment, the vast majority of those fell into the lowest evidenced tier, as they were case series. Because so many were case series, we subdivided the case series by size and placed more emphasis on the studies which contained larger groups of patients. This slide presents three of the large case series which provide some assessment of the treatment efficacy. I want to pause at this point and comment that for those of you who are detailed readers or experts in the field, you will note

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that there is sufficient variation in protocols between transplant papers with specific areas of controversy, including the need for matching between donor and recipient, use of pretransplant myeloablation, and the specific T-cell depletion techniques. I will comment a bit about these later, but mostly these are issues of maximization of treatment efficacy, which are better addressed in a different setting. The points I would like to highlight from this table are that overall survival following transplant was fairly good, and patients consistently had good, long-term T-cell function following transplant, but less commonly had good B-cell function, meaning many patients continue to require treatment with intravenous immunoglobulin. Also, at least in the van Leeuwen study shown here, death following transplant was associated with having had a lung infection prior to transplantation.

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This table highlights some of the larger studies that provide data on the long-term outcomes following transplantation for SCID. These studies evaluate patients approximately three to 10 years after transplant. All of them found persistent, relatively stable T-cell function, that many patients continued to have some degree of B-cell impairment, and that survival has improved over time. Poor outcomes were associated with lung infection prior to transplant, lack of T-cell reconstitution following transplant in chronic graft versus host disease. The Antoine study found that SCID phenotype was not associated with differences in survival, although the Haddad study found that children with B-negative SCID -- in other words no innate B cells -- had worse outcomes. Additionally, the Antoine study showed that in children receiving both matched and unmatched transplants, the survival improved over time.

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One of the key questions in evaluating the evidence for newborn screening for SCID is whether children detected via screening have better outcomes than other children. Because there is not published data on outcomes of children detected via screening, we instead grouped the studies that compared children treated within the first few months to those treated later. In all of these studies, the infants who received early treatment were primarily identified because an affected family member led to early testing for SCID. The first and last studies on this slide compare children who received early treatment with those who received later treatment, one in a cohort design and the other in a large case series. In both cases, the infants who received earlier treatment had higher rates of long-term survival. The next slide will expand upon Dr. Buckley's study, which is shown here. The middle study is a smaller case

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series of children who were all treated early in life. It is included because it provides a snapshot of more detailed outcomes in addition to survival. Specifically, most of the children in this study had normal neuro

development, although the degree of immune reconstitution was variable. As an extension of her case series of 89 children highlighted in the previous table, Dr. Buckley provided us with further information on survival among children with SCID treated by transplants. The graph on the left is a Kaplan-Meier curve showing projected survival among the 48 children treated in the first three and a half months of life, and on the right is shown the same curve for 113 children transplant after three and a half months. As you can see, the one of the right shows a longer decline in survival with the plateau being reached at a lower level. Because definitive treatment of SCID

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typically by transplant requires specialized treatment facilities, we saw evidence on treatment availability within the United States. However, there were no published evidence on this topic. Conversations with experts reveal than an informal survey conducted by the NIAID Rare Diseases Workshop identified 34 centers in the United States and Canada that currently perform transplantation for SCID. Others with whom we spoke reported 15 major and 34 minor centers in the United States and Canada currently performing transplantation. These numbers and information provided by advocacy groups suggest that treatment may be more accessible in some areas of the country than in others. With regard to potential harms of screening and diagnosis, no studies were identified which provide any evidence about specific harms related to screening or diagnosing SCID.

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In the area of treatment, many studies about transplantation note specific harmful treatment side effects, such as graph versus host disease. However, two studies met criteria for inclusion in this evidence review, specifically because of their focus on harms from treatment. The first shown here highlights the risk of autoimmune hemolytic anemia associated with transplantation. The second relates to gene therapy, which we have not discussed previously, due to the small number of studies in patients treated under research protocols. However, we want to note that this paper discussed the development of leukemia in four out of 10 patients treated with gene therapy for SCID. Three out of four of these children were successfully treated with chemotherapy. Our literature search uncovered one cost effectiveness study for inclusion in this review. In this study, McGee, et al., compared universal and targeted screening approaches and conducted

98 the analysis from a health care system perspective. They found an 85 percent likelihood of screening being cost effective using acceptance threshold of $100,000 per quality-adjusted life-year gained. Several of the experts with whom we have contact provided us with sample treatment costs from small numbers of patients at their individual institutions. Similarly, we obtain estimates of screening costs from several researchers. This information suggests that while the screening costs used in this study are similar to current screening costs, the treatment costs may be underestimated compared to current costs. After that rather whirlwind tour through the evidence, I would like to summarize our key findings from the evidence review as follows. SCID incidence is at least one per 100,000 newborns in the United States. Population-based screening trials are underway, but none have been completed to date.

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Without curative treatment, newborns develop severe infections leading to early death, and treatment most commonly with hematopoietic stem cell transplant decreases morbidity and mortality associated with SCID. Finally, there is some evidence that supports the benefit of pre or early symptomatic treatment

compared to later treatment. As I mentioned at the beginning of this presentation, there are several areas in which this work group felt critical evidence was still needed. In general, with regard to screening, it is difficult to ascertain the accuracy of screening because currently there is no systematic method of case finding for cases of SCID. Pilot screening programs, such as those in Wisconsin and Massachusetts, should serve to systematically identify cases in their screened populations. Additionally, a newly consortia of treatment centers may facilitate systematic case findings, particularly in unscreened populations.

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Regarding specific areas of screening evidence, current data regarding the accuracy of SCID screening are limited, although early data from Wisconsin suggests a low false-positive rate. No data exists regarding the accuracy of screening methods other than quantitative PCR for TREC in population-based protocols. The feasibility of screening is also not clear. Wisconsin's experience suggests screening is feasible and the work in Massachusetts will lend more evidence to this topic. We are not aware of any evidence regarding the ability of other newborn screening programs to offer SCID screening. Finally, there is no data describing either consumer or physician acceptance of newborn screening for SCID. With regard to treatment, there are areas in which the work group felt critical evidence was lacking. In terms of the value of early treatment, the studies that exist show

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improved outcomes for children treated earlier, but these studies are limited in scope and number. As noted a few slides earlier, the data on cost effectiveness is also limited, and further studies utilizing measured costs and utilities are needed. Finally, there is no data on the adequacy of treatment facilities within the United States. Current data does not address possible variation and treatment success among centers. Moreover, the number of centers within the United States and their ability to provide treatment for SCID is unclear. Future data from the U.S. IDNET and CIBMTR consortia may provide evidence regarding treatment availability and comparisons of varying protocols. With that, I want to thank you for your attention, and I am happy to take questions.

[Applause.]

DR. HOWELL: Are there questions of Ellen before we move on to the public comments

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that we have scheduled?

Coleen?

DR. BOYLE: Hi. Thank you. That was a wonderful review of a very complicated report. This came up in our November call, and that was the issue on the Kaplan-Meier graph and whether or not those were somehow confounded by the recency of treatment among those who were treated early versus those who were treated later. Did you explore that at all with them?

DR. LIPSTEIN: We were unable to get the database for that.

DR. BOYLE: Okay.

DR. HOWELL: Any further questions of Ellen?

[No response.]

DR. HOWELL: Well, if not, thank you, Ellen. That was a very nice presentation. Why don't we then move ahead with the public comments that we have scheduled. The first one on our schedule is Jennifer Puck, and I am not sure that she is on the line on not.

Jennifer, are you there?

DR. PUCK: Yes, I am here. Can you hear me?

DR. HOWELL: We can hear you well.

Thank you very much.

Public Comment on SCID Review

DR. PUCK: So I am very pleased to have the committee considering this condition which I believe I was the first nominator for, and I don't want to talk very long because I think there is some exciting new data coming from the Immune Deficiency Foundation and SCID Family Group.

However, I just want to remind people that we all know about David the Bubble Boy who made SCID famous by being born and placed into a germ-free environment, but we don't often think about David's older brother who was born with SCID and not recognized early and died. His brief life was the tragedy that made the recognition of David the Bubble Boy possible. I think this is a theme that is

recurrent. Most families have only a sporadic occurrence of SCID. So they are not expecting it, and people don't think of it because infections are very much the rule in young babies. So it is often not discovered until it is too late. I think newborn screening is a terrific opportunity to save babies from the family of the Bubble Boy on, and that is really my only comment. I am enjoying listening to this discussion. Thank you.

DR. HOWELL: Thank you very much, Jennifer. With those comments, we will move to Dr. Baker who I think many of you are aware is the Science Advisor to Newborn Screening Program, University of Wisconsin in Madison. Mei?

DR. BAKER: Thank you.

DR. HOWELL: Good. And you apparently have some hot new information.

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DR. BAKER: Well, I think Ellen already presented ours already. Well, SCID is a group of immunity fact that block normal T-cell development, and it is uniform better early in life unless patient undergo successful endogenic stem cell transplantation. SCID is ideally suitable for newborn screening for several reasons. First, it is estimated to one in 66,000. Two, effective treatment is available, and early identification and intervention result in significant improvement of survival, and three, confirmation tests are readily available. A proposed newborn screening test for SCID involves -- quantitate the number of T-cell receptor incision circles, TREC, using a newborn screening specimen. TREC results from the productive rearrangement of the T-cell receptor are found in normal native T cells, which are consistent, absent, or very low in all SCID patients.

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With funding from the Jeffrey Modell Foundation, the Children's Hospital of Wisconsin Foundation, the Children's Research Foundation, and the Wisconsin State Laboratory of Hygiene, a scientist team in Wisconsin has optimized a use of a real-time quantitative PCR to quantitate TRECs for screening SCID in newborns The method is amenable to current existing newborn screening programs. We also have developed reporting and a follow-up album. We began to implement the screening test on all newborns in Wisconsin in January 2008. We will continue our screening pilot study with grant support from CDC received in October 2008. As I said, Ellen had did a good job in reveal our data, and one thing I would like to add on is we had opportunity to test five different SCID baby samples, which is blinded to us, mixed with other samples. One is from our consultant, and four is received from Dr. Buckley. These five samples repeatedly, except

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one, all comes zero TRECs. The only one showing TRECs, which actually will be past our cutoff value is SCID baby after transplantation. So I think it is another evidence showing the assay is working.

DR. HOWELL: Mei, give those numbers again. You said how many? Excuse me for interrupting. How many babies did you screen that were mixed with your other sample who had indeed SCID?

DR. BAKER: Which is four. One is from our assay development stage, and we have the one baby which is blind to us. Well, actually, I should have said five because this come in with other samples. We don't know who is who.

DR. HOWELL: Right.

DR. BAKER: Dr. Buckley has sent four samples to us, mixed with other samples together, and the code didn't reveal to us until we report out the results.

DR. HOWELL: Thank you.

DR. BAKER: We are very excited that

post the transplant, the babies didn't show TRECs. So our experience, I mean in 2008, just summarized by Ellen, indicates that screening all newborns for SCID is feasible in a State newborn screening laboratory with a minimum screening false positives. Quantitate the number of TREC on newborn screening dried blood spots identify infant with primary immunodeficiency, and you notice I said "primary immunodeficient," not just say SCID, because through our program we did identify a baby with a neutrophil migration defect. The gene mutation has been identified, and I believe this is the second case in the whole world. The baby underwent successful bone marrow transplant and is doing very well, and we do believe this baby without newborn screening, we don't know if he still here. Well, thank you.

DR. HOWELL: Thank you very much, Mei.

We are now going to move and hear from

Barbara Ballard who is the parent and the administrator of the SCID Network for Families. MS. BALLARD: Thank you. I would like to thank the committee for this opportunity to represent the families of children with severe combined immune deficiency. My name is Barbara Ballard, and I am the mother of the boy with X-linked SCID. I am also the administrator for a group of SCID families dedicated to supporting one another in this journey we call "SCID Row." It was 25 years ago this week that David Vetter, the Texas Bubble Boy, died. Despite being diagnosed as a newborn, it took doctors years to offer any treatment other than a plastic bubble because transplants were only an option if you had a matched donor. There were no donor registries, and half-matched transplants would not be available for more than another decade. Today, bone marrow transplants are the standard of care for the majority of SCID patients.

An effective method to diagnose SCID from a simple blood spot now exists. SCID families, passionate to improve the rate of diagnosis, have given their children's very blood toward improving the rate of diagnosis. Let me talk a moment about quality of life for those children who are lucky enough to be survivors of this disease. Specifically, I would like to talk about those children who were not diagnosed as newborns but who had to be sick before a doctor could diagnose the problem. My son Ray is one such child. Ray is now 15 years old. Born seemingly normal, he thrived for several months until he caught his first cold. Within days of first entering my pediatrician's office with a child that I thought might have a virus, he was in the PICU and on a ventilator with PCP pneumonia. He spent four and a half months on a ventilator, had 13 chest tubes, and was trached. He received his first bone marrow transplant at a year old while on the

ventilator in the Duke PICU. An enteral virus ultimately caused severe GI damage. His GI tract never fully recovered, and he remains fed by enteral and parenteral means. Infection and graph versus host disease caused his first graph to fail, and he required two additional booster transplants. He managed to come off the ventilator. His trach was eventually removed, but he has severe lung damage and scarring, which significantly limits his ability to participate in normal childhood activities. All the infections had to be countered with multiple antibiotics, antivirals, and antifungals. Ultimately, we learned that one of the antibiotics used to save his life had also left him deaf. My son's medical costs maxed out a $2-million insurance policy by the time he was five years old. Though Ray survived when many have not, his life will continue to have many costly challenges which could have been

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prevented. Benefits of early diagnosis would have been a life without these ongoing costs and challenges. My son is not alone in having long-term medical complications resulting from a delay in diagnosis. He is one of many. As the administrator for a support group of SCID families, I can tell you many similar stories. It is for all of these SCID children, surviving and lost, that I speak to you today. Modern viruses are becoming more of a risk, even to the general population, and the best way to battle them has been the development of live virus vaccines. It is now considered safe to give live Rotavirus vaccine to an infant that is only six weeks old. How is a pediatrician to know that a six-week-old healthy infant has SCID unless there is a mandatory test for newborns? It is unconscionable that the administration of a live vaccine to children as young as six weeks has been approved without first providing a method to

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identify those children for whom this vaccine would be devastating. The responsibility to protect these children who are most at risk of injury from these vaccines now lies with you, the members of this committee. As more live vaccines are developed to protect the general population, it compounds the risks to our undiagnosed SCID babies and compounds your obligation to protect them. There are those who would argue that a false-positive test for SCID would be too dire for the family involved. I disagree. When I asked the SCID families their perspective on this argument, these families were overwhelmingly shocked to learn that there was more concern for a family with a healthy baby who might be asked to repeat a test than for a family with an undiagnosed SCID baby who might not learn of that diagnosis until after they have buried their child. SCID is a disease which cannot be seen

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or identified at birth without a blood test. Children with SCID are born looking and acting seemingly normal. A simple and reliable test for SCID now exists. We can easily identify affected children before they contract their first cold. Without this early diagnosis and the now-standard medical treatments, the damage caused by infections allowed to ravage the bodies of these children will cause irreversible damage and very often death. How many children must suffer with a diminished quality of life? How many children must die before you say it is too many? We have the technology. We have the science. We now need the prudence to step up to the plate and make this test a standard of care. Thank you. DR. HOWELL: Thank you very much, Ms. Ballard.

Now we are going to hear from Marcia Boyle who is president and founder of the Immune Deficiency Foundation.

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MS. BOYLE: I want to thank the advisory committee for allowing me to present some very new data that we are very excited about. I just want to indicate that since 1995, the Immune Deficiency Foundation has been conducting surveys of our patient population to understand their outcomes, their treatment, and their experiences, but we initiated it just in January, so the results are hot off the press, the first National Patient Survey of Families with SCID to better understand their experiences with diagnosis and treatment. This survey was conducted, again, in January, with 124 eligible families, a total of 156 SCID cases in these households as a basis for analysis. Of this group, 59 children or 38 percent are deceased. It is a true tragedy, since we know SCID is curable if diagnosed and treated early. Indeed, 30 percent of these children were not diagnosed until after they died. The survey demonstrates the early onset

of SCID systems with a median age of eight weeks at symptom onset and a median age at 24 weeks, at diagnosis. Unfortunately, the age of diagnosis is three times the age of symptom onset. The current average delay in diagnosis after symptom onset can be the difference between life and death. Eleven percent of the diagnosed SCID children never received treatment for the condition because they had either died or had become too little. No one reported that a child was not treated because treatment was not affordable or available. It is late diagnosis, not the cost of availability or treatment, which is the barrier to care for these children. I think you have seen some data from the Duke study that found a 96-percent survival rate for children treated by 3.5 months. In our national survey, we found only 23.7 percent of patients were treated by 3.5 months, less than a quarter.

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Our data confirms the Duke data with a 91-percent survival rate for those treated by 3.5 months. Furthermore, we find the average age at treatment in weeks was 29 weeks for those who are still alive compared with 58 weeks for those who are deceased. This is a significance at the 95-percent confidence level. Without treatment, SCID are fatal. The survey demonstrates that very early diagnosis and treatment is the real key to survival, but without newborn screening, this is not available for the great majority who lack a family history. If disease is recognized only as a result of infection, it is often too late for effective treatment. Hence, screening at birth can mean the difference in a life measured in many years rather than in weeks. In this survey, there is a 62-percent survival rate. Since 69 percent is considered in school a failing grade on school tests, then 62 survival rate is a catastrophic failing grade in

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American health care. I want to thank you for a vote to save lives and end unnecessary suffering, and given what Barb Ballard very eloquently pointed out to you, it is not just life and death. It is the quality of life and the cost of lack of newborn screening that is also at risk here. I also want to comment on my comment that it may not have been SCID that was identified, but in that this newborn screening in Wisconsin actually has identified other primary immune deficiency diseases is huge to our patients. So thank you very much.

DR. HOWELL: Thank you very much, Ms. Boyle. So we have had a good bit of new information this afternoon. I wonder if Dr. Buckley would like to make a comment in this public session. Obviously, she spent her career in this area, and she might have some additions to make.

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DR. BUCKLEY: Well, thank you, Dr. Howell. I just would like to answer Coleen's question, if I may. If you would turn under Tab 9 to page 14 and to the slide that Dr. Lipstein earlier showed you, I think you can see on the X axis that the years post transplantation both bill out to over 25 years. We have two papers that we have submitted that are not yet published, one on the long-term follow-up of these patients, and in that study we compared those who were transplanted under three and a half months of life versus those who were not transplanted until after that time. There were two things. The median survival was the same in those treated before and after three and a half months, if that answers your question. The second thing was that there were fewer problems. There was a much higher survival rate, and more of these patients were considered

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healthy by their families in those who had been treated under three and a half months of age. Then the only other comment I wanted to make is about the leading cause of death in these patients. It was mentioned that lung disease or pulmonary disease is a leading cause of death, but really it is the viruses that kill these children. It is CMV, EBV, parainfluenza 3, the chickenpox vaccine. We have had several patients who received the live chickenpox vaccine who came to us with clinical chickenpox. So I think that we have to worry about the live vaccines. In third-world countries, they receive BCG on day one of life, and I am sure that in those countries that very few of the SCID babies survive. But I think it is the live vaccines, the exposure in day care to these community viruses, and then certainly the fact that they really go quickly downhill from there. The median age at referral to our institution for a transplant was

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six and a half months. I will stop there.

DR. HOWELL: Thank you very much, Becky. Anne, would you like to make a comment?

DR. COMEAU: Yes. Thank you. With just 4,000 specimens under our belt -- I am not going to talk about rates of positivity, but I think that we are comparable to what Mei is seeing, and we have now identified one baby with in utero exposure to teratogen who does not have thymus. We have another baby who is being worked up right now for possible SCID. So, certainly, I do believe that this is something that is possible to do at the State level. I would like to make the comment that like we have used for CF, I think that both Mei and I have participated in training of other State programs, and I would say that this would be a very helpful exercise to train other State programs in the technical capacity for SCID screening.

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That was through the NNSGRC, those kind of training workshops. I think if you want to move this quickly, even at the pilot program, such training workshops are very helpful.

DR. HOWELL: So you have had two positives, is that correct, one with the congenital absence of a thymus?

DR. COMEAU: Yes.

DR. HOWELL: And the second one, I missed the problem in that baby.

DR. COMEAU: That one has zero TREC on repeat screenings and is now being worked up by flow. The data on it is just too early just to say what this second baby is, but 4,000-specimen sampling error, it might be just a false positive, but certainly, the first baby was not a false positive.

DR. HOWELL: Thank you very much. Bob, are you lined up there to speak?

DR. VOGT: I am, and more importantly,

Nancy is behind me.

[Laughter.]

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DR. HOWELL: Okay.

DR. VOGT: I just wanted to reiterate something that Marcia mentioned, that Mei mentioned, about what has happened in Wisconsin. There has not been a classic SCID detected to date in Wisconsin. I have just been doing some probability calculations back there to find we are somewhere in the window of, I think, about halfway, we might have expected by now, with 50 percent, depending on what you want to guess at for prevalence and all that. So we really don't know what that means, but it is not surprising that a classic SKID, quote/end quote, has not been found. What is more important for this committee is to realize that in finding the DiGeorges, that is a higher bar for this test. The second thing -- and I think this is not part of the evidence-based review, and I think it should be -- is that if you do a test, you ask what are you actually measuring. We have gone round on this, what are we

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measuring. I used to say profound T-cell lymphocytopenia, but that is not true because what is really being measured is profound recent thymic immigrant T-cell lymphocytopenia. Now that is a hard thing to get a handle around, but that is what you are measuring. So the question that should come out in an evidence review of a newborn screening test is what might you detect, regardless of what the condition that was nominated -- this is my opinion, of course -- what might you detect with this test and how important are all the conditions that might be detected that way. I think if you mix that into this discussion, you would go somewhere from pigeon-hole number two and a half or three and a half, depending on how you reorder them, to one and a half or two and a half. So we are just delighted by the experience in Wisconsin, first of all, because of the low hit rate, the fact that this is not going to inundate the newsroom. That is maybe the most

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important operational thing. But as far as what this test can do in detecting significant clinical immune deficiency, we have got a winner here and in the first year of effort. It is going to continue. Anne's most recent findings just open up a whole new door. Here is, in essence, I guess, an iatrogenic situation that has emerged from a TREC test. We still have no idea why this neutrophil mobility defect came, that had only been reported one time previously ever and is associated with a very specific genetic mutation, why that gives a TREC deficiency. Nobody knows that. We are opening up a whole new window to biology here, and I don't know if that can be folded into an evidence-based review, but I think it is an important aspect of this for the committee to consider. Thank you.

DR. HOWELL: Thank you very much, Bob.

Nancy?

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DR. GREEN: Thank you. I just have a brief addendum to Ellen's presentation since I sit, in some capacity, on the evidence review group, and that is that I would like to point out there was some disagreement in the committee about the magnitude of potential benefit from early diagnosis through screening and treatment. So Ellen presented that there was limited evidence, and as I just would like to remind her and just to bring up that there was some disagreement about that from the committee. Thanks.

DR. HOWELL: Thank you very much. Ellen, would you like to comment about that? The answer is no, and I would assume that the disagreement was on the side of the one group that felt that there was limited evidence and the other felt that there was a bit more evidence. Is that right?

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DR. LIPSTEIN: Yes.

DR. HOWELL: Okay. Thank you very much. Mei?

DR. BAKER: Could I say one more?

DR. HOWELL: You may say a word. If you get close to the microphone, you could say two.

[Laughter.]

DR. BAKER: Well, because Bob mentioned the DiGeorge, I just want to mention that in our first-year experience, we did identify three DiGeorge's syndrome. This DiGeorge is a subgroup that have assignments. I think it would benefit that the kids be identified at birth. So that I think is a good thing.

DR. HOWELL: Thank you very much. Is there further discussion? Actually, any public comments? Because we will now go to a formal discussion that will be led by Professor Vockley. Is there any public comment before we go to Gerry?

[No response.]

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DR. HOWELL: Gerry, you want to take over this discussion?

DR. VOCKLEY: I am not sure.

[Laughter.]

DR. HOWELL: Gerry's slides, for the committee members, are under Tab 6.

Committee Discussion and Decision on the Nomination of SCID to the Recommended Uniform Screening Panel

DR. VOCKLEY: All right. What I decided to do, since we do have limited time here, I would run some slides out that sort of followed the review and the logarithm that was presented earlier by Ned. So here is our decision matrix. I am not going to repeat that because you already heard it. Here are the key questions, and it is a small font, but we are going to go through them one by one. I would like to try to get the discussion to center, in turn, on individual questions.

Then, finally, this is the analytical

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framework. We will come back to this at the very end, as well as the chart as we try to sum things up.

DR. LLOYD-PURYEAR: I don't think there are any slides.

ATTENDEE: There are at Tab 9.

DR. LLOYD-PURYEAR: Tab 9?

DR. HOWELL: Mine is, indeed, under 6, so be of good cheer.

DR. VOCKLEY: They were distributed earlier.

Key Question No. 1 -- and this wording is right from the document -- this is the overarching question for evidence review. Is there direct evidence that screening for the condition at birth leads to improved outcomes for infant or child to be screened or for the child's family? As the original document points out, if so, it is a done deal. If not, then you go to the other pieces. So we can start there. My assessment

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was that we don't have the killer argument here that we need to just stop the discussion and vote.

DR. RINALDO: Gerry, I was really impressed by the comment about the morbidity and mortality related with live vaccine. The harm related with that of undiagnosed children can really be seriously affected. We are talking about here the harm on no screening. Has that been weighted? I don't know if there is a consensus that this is a no. I don't know how we need to proceed with each question, but from what I heard today and read before, I personally do not agree with a no.

DR. HOWELL: Comments from other members of the committee about the no? Duane?

DR. ALEXANDER: I agree with Piero. I cannot quite bring myself to saying no to this question. I think the evidence is scattered. It

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has not yet come systemically from the two sites where the definitive work is being done because they have not gotten enough numbers yet. I think the evidence that has come from the Duke program that Dr. Buckley cites and others, not to mention the evidence, the clear indication that live virus vaccines can be death-dealing to these kids if they have not picked up at a newborn time means you can't say no to this question.

DR. HOWELL: Ned?

DR. CALONGE: I would point out that what you are doing is putting together a chain of indirect evidence, and that there is nothing wrong with saying no to the overarching question. The question is, is there a population-based, invited-to-screen, not-invited-to-screen or itemized-control trial that proves better health outcomes? The answer to that question is no, there is not. So the direct-evidence question, answering no is okay because that is the answer.

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It doesn't mean you are going to end up with don't add this condition. It means we ought to look at the other questions. So, again, if you look at the document, it says what is a direct-evidence study, and the best study would be a randomized control trial of invited versus non-invited to screen, which we are never going to have, and that is okay. I think that we can easily get to weighing the evidence and coming up with the matrix question without having a randomized control trial. We have to be okay with that. DR. RINALDO: If I can make another comment, one could argue that actually we had a screening test for the last, at least, 26 years, and that was the birth of a first child with a disease that suffered, obviously, usually died or suffered terrible damage. We have heard examples of that. So I argue that the second case in that family -- and I believe there is a fair number of them -- that was by risk, diagnosed at birth and

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received treatment early, I believe that is a core of the cases that shows a 90-percent-plus survival because of early intervention. So that is perhaps a convoluted and painful way to screen to wait for a first death in a family, but you have a population that was in a similar situation of children that would benefit and would be picked up without any known risk by screening.

DR. CALONGE: It still comes down to what the definition of direct evidence is. Cervical cancer screening has no randomized control trial. There is no direct evidence, but it is an A recommendation from the U.S. Preventive Services Task Force, high certainty of significant health benefit. But there is no randomized control trials, and the definition of direct evidence is a RCT. I would be nervous about an evidence-based group redefining direct evidence, especially when you don't need to. So that is my nervousness, that we would be the only group that

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I know of that would say direct evidence is not an RCT.

DR. RINALDO: You are saying let us see what happens next?

DR. VOCKLEY: Let us look at rest of the key questions. Any other comments?

DR. HOWELL: Any further comments? I think that the point that Ned is making is the fact that there is a no and that there hasn't been a newborn screening test. I mean, I agree that the death of a child is one kind of a test. That has identified infants in the newborn period, that just hasn't been done, but that would not necessarily preclude this committee from making a very positive recommendation at some point in time.

DR. VOCKLEY: Right. Jane, go ahead.

DR. GETCHELL: I just wanted to make a comment. When you added the words "population-based evidence," I was okay with the no because I agree there is not. What we need to focus on here is it is

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going to be a population that we are going to be screening in State programs. So I like that.

DR. VOCKLEY: The other piece is that where this statement refers not only to the outcome but also to the tests that is under consideration. So, while it is true that having a second affected child is a way of screening, it is not the way that is being proposed here. This is one of those questions where if you can't answer yes by definition, it becomes no, that maybe is no or it is positive that there are good things going on, but we are not there yet, as Dr. Alexander said. So there are only two possibilities here. There is more wiggle room in the rest of the guide, the key questions. DR. RINALDO: Okay. If I can make one final comment. If a question is asked that the answer is always no, then just get rid of a question.

[Laughter.]

DR. HOWELL: Go to your next slide.

[Laughter.]

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DR. HOWELL: Because I know what is on your next slide.

DR. VOCKLEY: Anticipating this reaction, I did add a second bullet point. Key Question 2. Is there a case definition that can be uniformly and reliably applied? What are the clinical history and spectrum of disease of the condition, including the impact of recognition and treatment? You have all got my slides. So I don't even have to do those for you. I will just put them up. Comments?

DR. DOUGHERTY: In Ellen's slides and presentation, I am trying to gage the "more research is needed" versus yes here, and the evidence review concludes more research is needed, but more research is always needed. So how do you get to yes from the evidence review?

DR. VOCKLEY: Well, I can comment on my reasons here. I read the evidence review. I pulled out the data that I thought were

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pertinent, and I disagreed with the conclusion of the evidence review. So I am accepting their data, but I don't think they hit the right answer.

DR. DOUGHERTY: We should probably discuss that.

[Laughter.]

DR. RINALDO: Gerry, another question. I remember last November, I went to a meeting and I heard two presentation, one by Dr. Puck, who I hope is still on the line, and one by a French researcher. There was this comparison between bone marrow transplant and gene therapy. I left that discussion with impression that gene therapy is far behind. So I see where your conclusion is treatments are similarly and highly effective. I am wondering what is the basis for that. Maybe, Jennifer, if she's on the phone, I hope you can comment.

DR. PUCK: Yes, I am on the phone. Can you hear me?

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DR. VOCKLEY: Yes, go ahead, Jennifer.

DR. PUCK: Can you hear me? I am on the phone.

DR. HOWELL: Yes, go ahead.

DR. PUCK: Okay. So gene therapy for SCID, for X-linked SCID has been stopped in this country because of the severe adverse events that occurred frequently with the original gene therapy construct. People are now looking at safer vectors to provide XSCID gene therapy, but there are no active trials of that at this time in the U.S. So that would be considered strictly experimental. The ADA form of SCID is one that has had more success with gene therapy, and there are trials ongoing in the U.S., as well as Italy for that, and also in England, but, again, this is a highly experimental form of therapy. So it is not mainstream yet by any means. DR. HOWELL: Okay. So there seems to be some concern about the "equally effective," including general therapy.

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DR. VOCKLEY: The "equally effective" was actually meant to modify the forms of SCID and not the therapy. I think it would be quite reasonable to throw out the gene therapy. It was just there to round out the menu, bone marrow transplant and in ADA, enzyme replacement therapy are effective.

DR. HOWELL: Ellen had a comment.

DR. VOCKLEY: Ellen?

DR. LIPSTEIN: I just wanted to clarify that in the evidence review, we were not intending and we did not make any specific recommendation. What we were trying to say was that the treatment is effective, that the improvement for early treatment, the evidence there, there is some evidence but not as complete as overall treatment for particularly using transplantation for SCID.

DR. VOCKLEY: Ned?

DR. HOWELL: Thank you.

Ned?

DR. CALONGE: So there is nothing like

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being faced with your own methods to make you wrestle with your own methods. So I would just go back to Key Question 2. The real reason this is in the analytic framework is to answer the question, do we know what we are looking at. Do we know? Is this a spectrum of conditions that is poorly described, or is this a set of very tight, easily defined conditions of which we know a lot about? So the treatment issue is just that we have described what happens before and after. It is not making a judgment about efficacy of treatment. It is just saying has this been around long enough for us to know that this is SCID and this is the condition we want to test for. This gets on with that last comment. My desire would be that we not necessarily jump ahead to the conclusion, that we work through the questions the way they are put forward, because I think the answer to this one for me is yes, that we know what the condition is

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and we have a good description of what it does and some description of what it does with and without treatment. That doesn't necessarily say we weigh automatically to get to a net benefit, but it does say at least we know what we are dealing with it. It is a well-described condition. It has been around for a long time, looks like it is fatal if you don't treat it, looks like you can treat it and not have it be fatal, and I think

there is adequate evidence that I could conclude that. DR. VOCKLEY: There will be a discussion on one of the other questions about efficacy of treatment. Anne?

DR. COMEAU: Very quick comment. Yes, there is a good case definition, and yes, this case definition applies at the time that the newborn screening result or diagnosis would go forward, so one doesn't have to wait three years for the case definition to apply.

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I think that is very important to know whether or not the diagnostic methodology is applicable at two weeks of age, at 30 days of age. I still say yes, but I think that that is key to this question.

DR. VOCKLEY: All right. Chris, go ahead.

DR. KUS: When I read it, it is Key Question 2, but there is two questions. That is confusing to me because it really is that first question that you are answering. That other one is really just asking for information to help you answer that. Is that right?

DR. VOCKLEY: Basically, yes.

DR. KUS: Yes.

DR. VOCKLEY: Jim?

DR. HANSON: Just two cautions that I want to express. One is that the DiGeorge sequence is not a single entity, and it is not as tightly defined as has been implied here. There is a great deal of variability among those children, and the ones who come to attention are

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the more severely affected cases. They are not etiologically uniform either. I would be a little cautious about asserting the tightness of that definition. The second is what about females with X-linked immunodeficiency disorders? For most X-linked disorders, females have a wide range of expression of their symptomatology. I don't know what it is, and I am sure Dr. Buckley does, but I don't, and I would be surprised if there is not some variability in the phenotype there.

DR. HOWELL: I am sure Dr. Buckley knows the answer to that.

DR. VOCKLEY: Go ahead, Rebecca.

DR. BUCKLEY: Yes. The carriers of X-linked SCID do not have any clinical phenotype at all. They are normal. They use a good X.

[Laughter.]

DR. VOCKLEY: Let me remind you of Michelle's beating about the head and neck of Ned on test versus condition.

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The test might pick up other conditions, but we are talking about SCID right now. So we have to keep that clear. All right. Question 3. Is there a screening test or screening test algorithm for the condition with significant analytic validity? I said no, and I based that on the fact that we still don't have a SCID baby that is been diagnosed by newborn screening. This is proposing specifically with TREC quantitation, that we don't have that. That is how I interpreted what we were asking with this question.

DR. RINALDO: A comment. Mei, do we know of any false negative?

DR. BAKER: Wisconsin, no. Well, actually, we just had a meeting, and there are no clinical reported cases.

DR. RINALDO: That is the nature of populational screening. So the fact that is no positive in 70,000 doesn't mean it could happen tomorrow when the estimates -- and we are still

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below, I think. Bob made the comment earlier. I think at this point, you can ask, really look at that in the perspective of no false negatives and a comfortable rate of false

positive.

By the way, what is the number, false-positive rate?

DR. BAKER: That is 0.02 percent.

DR. VOCKLEY: Pauline?

DR. RINALDO: 0.02 percent.

DR. VOCKLEY: Okay. Barbara?

DR. HOWELL: Why don't you call on the people? Barbara, go ahead.

DR. BURTON: Okay. Well, I just wanted to say to that, isn't it significant that you had the cases diagnosed on the blinded specimens that I thought were infants sent in by Dr. Buckley? I find that very compelling because, in the eyes of the screening laboratory, they were just like any other specimen. So, to me, that is cases that were detected. That is proof to me that the test

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works. As somebody who doesn't work in the SCID area, I find this very convincing.

DR. VOCKLEY: Yes. We didn't have that going into to making my slide. Fred, did you want to make a comment? I thought you were raising your hand.

Okay. Ned.

DR. CALONGE: So, a couple things, because I must have misheard, but I thought somebody had 4,000 tests, two positive tests, and one sounded like a false positive. That sounds like 50 percent.

DR. VOCKLEY: Yes.

DR. CALONGE: But I realize that is only 4,000, and it is not a false positive yet and all those other issues, but I just got to tell you, that sounds like 50 percent.

DR. VOCKLEY: All right.

DR. CALONGE: That just came up because of the 0.02 percent.

I wanted to talk about Key Question 3

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real quickly, that we wrestle with this issue about analytic validity, and it is more critical to the implementation of the test than it is to whether or not you recommend adding the condition. So let me tell you how that works. If you have evidence of clinical utility, who cares about analytic validity? It must have analytic validity for you to get clinical utility. Does that make sense? You can't have clinical utility if the test isn't detecting something that is what you want to detect and treat. So that is a really important point. So, before we get too hung up, the whole issue about clinical validity has to do with can all screening programs do this in a reliable and valid way. So that is why it is an important question, not that it breaks the change of evidence.

DR. VOCKLEY: Hang on a second, Anne. Jane, can you comment? Go ahead.

DR. GETCHELL: Yes. Where it says no

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data yet in a State program, again, without the quality control materials, a proficiency program, we are not going to want to get into it. So I think that has to be addressed as an important part of this. I haven't heard anyone say that there are quality control materials available.

DR. VOCKLEY: All right. Anne, go ahead.

DR. COMEAU: Analytic validity is different than what you started to answer which I think was clinical validity.

DR. GETCHELL: Right.

DR. COMEAU: Analytic validity. Can we find TRECs? Can we quantitate them? Can we see when there are zero TRECs? The analytic validity of this test is really pretty good. However, given analytic validity, in order to measure it very well, one needs really good quality control materials, and those don't exist. The kinds of quality control materials that can be sent around to all the State

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screening programs do not currently exist. They ought to be able to exist, and Mei and I are making do with what we have, but this is different than clinical validity of finding kids who have SCID, so analytic validity. Mei and I are running different tests. Mine is a multiplex, and hers is a singleplex. So there are two different tests being run now too. How do hers and my tests compare? She might have a better test than me. I might have a better test than her. They might be equivalent. We don't know that yet. They still can be great tests, but that is what analytic validity in Question 3 is asking. Is there a screening test? So I will answer for you. I think so, but I don't think we have proven it yet, and without the materials, I don't think that we have proven it yet.

DR. VOCKLEY: Go ahead, Fred.

DR. CHEN: Thanks. I agree with that last comment, and I

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also think that what is throwing me on your particular slide is that the pilot study data information on the slide, actually for me it applies more to Question 4 about clinical validity rather than the analytic validity thing. So I would like to come back to that piece of it when we discuss Question 4.

DR. VOCKLEY: Okay.

DR. VOGT: A quick comment on the QC materials. Jane and Anne are absolutely right. Jennifer is now making a large pool of CD3 lymphocyte-depleted material that will be used for distribution, centralized through our program in the Newborn Screening Branch at CDC. This material should have been available a year ago. We should have done it ourselves, and that is my fault that it is not available. It is a "don't let the perfect be the enemy of the good," how close are you to really looking at SCID likeness and so on. As with the LCDs, we can easily make leukocyte-depleted and added-back materials and get calibration curves.

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That minimally should have been done a year ago, and that is my fault. The fancier version of T cell-depleted and ultimately TREC-depleted in the face of mature, T cell-present materials is a tougher nut to crack. Eventually, we will get there. So the questions of analytical validity are important. Each laboratory has established within lab, analytical validity. I think that is a fair statement to make, and that is the basis for the experience so far. In six months, we will have the interlab experience pretty well documented.

DR. VOCKLEY: So let us go to Question 4, which is the clinical validity of the screening test for screening algorithm in combination with the diagnostic test or test algorithm. Has this been determined, and is that validity adequate? I am just throwing this up as a straw man, guys.
[Laughter.]

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DR. VOCKLEY: This is my take on the evident report. This touches on the point that Anne just made, that while DNA testing for TREC seems most robust, we don't even yet have two labs that are doing the same test in a public health setting. Then the issues that we have already touched on about population screening, cases being identified, and there is no data on variability of clinical expression, if that is a concern or an issue. Comments? Go ahead.

DR. CHEN: Yes. The point about the pilot studies is that you do have two ongoing pilot studies that have not identified a single case of SCID, and that, in fact, that we are discussing the condition SCID. I think it would be very difficult, challenging for this committee to act positively on something where your pilot data is ongoing and you don't actually have a confirmed case.

DR. VOCKLEY: Anybody else?

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[No response.]

DR. VOCKLEY: This was just a subpoint in the document from the process group, and that we really do have good diagnostic testing here. So, once you identify a potential, it is easy to sort out whether or not it is a false positive or a true case. Ned, did you have another comment?

DR. CALONGE: It was a question about the evidence. The evidence we do have is in clinically detected cases, the sensitivity is very good. That is correct. Right? Is there evidence that you would have a TREC-positive test and not the -- is there a possibility -- I don't think there is any evidence -- that you would be TREC-positive but not have SCID?

DR. HOWELL: Well, if you are TREC-positive, you would not have SCID. That is a sure thing. Gerry?

DR. VOCKLEY: I just said there is no

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evidence of it.

DR. HOWELL: I think a number of the cases that Dr. Buckley referred to were not clinically diagnosed. They were diagnosed because of family history, and at the time you saw them, they were not symptomatic, so that they did not have clinical symptoms, so they were not, quote, "clinically diagnosed." They were diagnosed because of a family history. Is that fair?

DR. CALONGE: Again, it gets to the issue, but we are certain that their trajectory would have been of a SCID's phenotype. We have a high degree of certainty that their clinical trajectory, if they were transplanted -- I am just trying to figure it out. I am just trying to figure out where, if there is a gap, how big that gap may be. It gets to Fred's issue. I am kind of comfortable in the sensitivity data for kids who we know had SCID, but I am really not comfortable -- and I want to be more comfortable -- is if my test is abnormal.

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DR. RINALDO: I am sorry. You are asking a positive predictive value, basically. I have another question, and that for everybody, for Jennifer Puck, for Dr. Buckley, and for Mei and Anne. How many retrospective analyses have you collected with being able to do -- like you know a child has SCID, and you were able to go back to restore procedural specimen, so going back and pulling out cards. I would like to know how any of them were retrieved and what was the outcome, and particularly, how many were tested in a blinded fashion, so that the testing lab did not know they were looking at the SCID. Can anybody give us a brief summary of this? Because in the early stages, like we are, I think we are putting far too much weight on the fact that you still don't have the perspective hit. You have to do it, and certainly, the honesty of what you are doing depends on the knowledge of lack of false negatives.

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But the question here seems critical. How many actual specimens, newborn samples, have been retested in a blinded way after, after a variable period of storage?

DR. VOCKLEY: Jennifer, do you have an answer to that?

[No response.]

DR. VOCKLEY: Uh-oh. Did we lose her? Rebecca?

DR. BUCKLEY: So am I allowed to answer that?

DR. VOCKLEY: Yes.

DR. BUCKLEY: Okay. We published in the year 2000, all of the pretransplant samples that we had stored in my liquid nitrogen freezer. These were not blood spots from the State lab, but they were the pretransplant samples, and they had no TRECs.

DR. RINALDO: What I am asking is actual specimens, pull out of a storage facility of a State newborn screening lab after that.

DR. BUCKLEY: No.

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DR. RINALDO: So this has never been done, and if not, why not? Like California has 24 years.

DR. BUCKLEY: Yes.

DR. VOCKLEY: So, Piero, Jennifer's original paper did that and reported on it.

DR. BUCKLEY: Yes.

DR. VOCKLEY: I am thinking that the number was 17, but it may have been 12, and I don't know why I am mixing those two numbers up. The answer to your question about were they tested blindly, I don't know the answer to that.

DR. PUCK: Hello? This is Jennifer on the line.

DR. VOCKLEY: Oh, good.

DR. VOCKLEY: I thought you were not there, Jennifer. I'm sorry.

DR. PUCK: I can tell you that by now, I have tested 24 actual recovered Guthrie cards, and for the last eight of them, this has been a collaboration with Fred, Laurie, and Marty Kharrazi at the California State Department of

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Public Health.

They have sent me SCID patient Guthrie cards that I have identified, and they have also sent the two on either side of it. So I get five spots to test at a time, and I am blinded as to which is which. I have unerringly picked out the SCID samples in this kind of approach. Furthermore, I picked out a SCID sample even though the patient was a partial SCID who was actually not diagnosed until nine years of age and had been misdiagnosed and just given gamma globulin as a common variable immunodeficiency. I have no SCID cases where I have ever found TREC and have always found them in these blinded cards. Furthermore, I have got 1,000 anonymous spots from California, and only one of those in which we cannot find TREC. So that is what my current false-positive rate would be, and the false negatives are zero.

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DR. RINALDO: Which happens to be consistent with Wisconsin findings. This is, I think, exactly why we are talking about this newborn screening translational research network of the repository expression, because we could actually answer this question in a very conclusive way in a matter of days, if not hours, if the thinking that is going on now about creating this repository to facilitate the validation of new assays. So, unfortunately, that is only beginning now, but I submit to you as a screener -- and I am one of those guys that actually do spend a fair amount of time looking at several hundred samples a day for some type of screening -- that I think this is a heck of a good test. You are now going to answer it differently, two, three years from now.

DR. VOCKLEY: Fred?

DR. CHEN: I am just going to comment that what I am hearing is a very different discussion about how this test works when you

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test a known group or even a blinded group of blood samples from patients with SCID. It is different thing than testing 100,000 samples, looking for one case of SCID, and that is population-based screening. I think it is a fair argument that you could do it retrospectively. I think that is an interesting argument that we could think about, but it is a different story than when you have 10 samples and five are SCID and five are not SCID. The fact that you are finding one positive in 1000 is concerning to me when there really should only be one in 100,000. I just think there is something about the fact that we are talking about population-based, statewide, universal screening that requires the thinking to be a little bit different than the discussion that I am hearing. DR. BAKER: I just want to say the screening rate, I want to make clear. Our experience after 70,000 samples, in a full-term, the rate is a 0.002 percent. For

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the premature babies, which would different algorithm, is at 0.028. So, together, it is 0.05. It is not 0.2.

DR. CALONGE: So I did see that the difference between premature and full term, and so you have just explained it is a different algorithm. What is the source of that difference? That would imply a relatively high relative risk of prematurity associated with SCIDs compared to non-SCIDs. DR. BAKER: Well, sorry. The screening algorithm is the same, and the recommendation fall off a little bit different. The difference is the premature babies, most that we see is from NICU. When we had the first specimen, TREC is low. Since we have every other week, repeat in place that go to a flow, we said let us look at the second specimen, and in 99-percent samples, we cleared a second one.

DR. CALONGE: Okay. So you are saying TREC is low because of prematurity, and that you have to keep following up, and that is why you

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are taking any low TREC as a positive test. So that is why it is higher in the premies because they are low because they are premies?

DR. BAKER: At that point, I don't want to draw this conclusion. Actually, we have an ongoing study on that. Sampling and IV, how you -- because we know a lot of premature babies, the sample is not from heel stick. So it is a lot of these issues.

DR. VOCKLEY: Let us go on to Key Question 5, which I have sort of teased out three different subsections. What is the clinical utility of the screening test or algorithm? What are the benefits associated with it and what are the harms associated with it? The last one was easy. There were none

identified, and it is hard to anticipate any. We deal with the same issues related to false positive, false negatives with every screening test. So I don't think there is anything unique to the SCID testing. I think we just have to accept that we don't have a lot of data about

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that.

The first two bullets, are there any comments?

Ned?

DR. CALONGE: One of the problems I have is I am learning about these things every time I come, and that is okay. I mean, I am just the evidence guy.

[Laughter.]

DR. CALONGE: The issue I would ask about the harms is I would like to know the likelihood ratios of the diagnostic tests and needed to actually look at the diagnosis of SCID. I am assuming the post-test probability after applying a diagnostic test to a screened-positive child is 100 percent because otherwise there is a harm. You would transplant somebody who does not have SCID, which from where I am sitting does not sound very good. So I don't have that post-test probability in front of me. I don't know enough about the condition to say that the post-test

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probability of diagnosing a screened-positive child is 100 percent.

DR. VOCKLEY: Coleen? We are just going to go around. We got a bunch of hands up here.

DR. BOYLE: My question was very similar, not as sophisticated, but very, very similar. And the same thing with treatment. The evidence-based review did talk about harms from specific treatments. I think those clearly cannot be minimized.

DR. VOCKLEY: Mike?

DR. WATSON: I am trying to get at a sense of the value of the non-SCID primary immunodeficiencies that get detected. I dread going to the secondary condition list as a benefit, but several DiGeorges, where they are 50 percent are familial -- it is in the definition of the condition, I guess, that the problem of what you are screening for comes in, which leads you to have primary and then conditions that are

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part of the differential from a positive result. DR. VOGT: If I my comment briefly on that, the term "SCID" is of historical evolution, and it is not true. In terms of molecular pathology and cell biology, it is not a combined defect. It is a defect in a single arm of the immune system. The phenotype is expressed as a

combined defect. That was a surprise to me. I did not know about this stuff. That happened between graduate school and when I came to CDC. So back in the days when it first became obvious there was cell-mediated T-cell immunity and B-cell-mediated humeral immunity, SCID was seen as a combined immune deficiency, but the molecular and cellular pathogenesis of the disease is not a combined. It is a T-cell deficiency, and since T cells are required for affective immune responsiveness, the net effect. It was in contrast to DiGeorge's which was uniquely T cell and Bruton's which was uniquely humeral B cell.

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Those distinctions are not useful anymore in this discussion, at least I don't think so. I am responding merely to the question, has there ever been a case of a negative TREC or an extremely low TREC that was a valid analytical result in which the baby did not have SCID, and I guess I would say by definition, no. I mean, if there are no recent thymic immigrants in the bloodstream of a newborn, that newborn has some kind of severe immune deficiency. I think that is fair. Rebecca, is that fair?

DR. BUCKLEY: Well, not exactly.

[Laughter.]

DR. BUCKLEY: This gets back to the DiGeorge issue. There are complete DiGeorges and then there are partial DiGeorges, and it would be the complete DiGeorges that you would pick up by the TRECs. So you may pick up a complete DiGeorge or you may also pick up an Oman syndrome.

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Oman syndrome is a leaky SCID where there is one or two clones that are there, but these are all CD45RO positive that contain no TRECs. So you may pick up either an Oman syndrome or a complete DiGeorge, but you are not likely to pick up anything that does not need treatment.

DR. TROTTER: But you can clarify those, post screen. Correct?

DR. BUCKLEY: Yes.

DR. TROTTER: A hundred percent of the time?

DR. BUCKLEY: Very easily, it is clarified post screen.

DR. TROTTER: Which was the question.

DR. BUCKLEY: Yes.

DR. RINALDO: If I can comment on that, Ned, you implied that there is a risk to go from abnormal screening to a transplant, which I don't think is a realistic risk; in other words, just doing a simple lymphocyte count. You made a comment about you are

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concerned about somebody getting transplanted by mistake. I would like to know what Dr. Buckley thinks, but I don't think it is of something that should be considered.

DR. CALONGE: So you don't think it is worth asking the question?

DR. RINALDO: It is always worth asking

a question, but sometimes you have to admit that

maybe it was not the smartest question.

[Laughter.]

DR. VOCKLEY: Anne? Go ahead, Anne, and then Chris.

DR. COMEAU: In the context of possible harms of transplant, this is incredibly minimal, but I think it is a possible harm. Currently, the screening pilots are being done in centers where the flow cytometry is good, reliable, and quite sophisticated. That being said, the flow cytometry test requires a couple mils of blood and to do a couple of mils of blood and a couple of mils of blood for a CBC and differential, depending on

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how good the flow cytometry is. So, when you have babies, low birth weight babies, not necessarily the 600-grammers, but other babies that will be referred for flow cytometry there is a fair amount of blood that needs to be taken. I think it just has to be on the table.

DR. VOCKLEY: Not clinically significant. We can do that. Chris?

[Laughter.]

DR. KUS: In the treatment of patients diagnosed, there is risks with the transplant, just to be clear. So saying there is none identified just doesn't fit.

DR. HOWELL: But we should also remember the fact that the benefit is spectacular. There is a risk, but let us not forget the benefit. It is just enormous. The other thing is let us emphasize the fact that the false-positive rates that we have heard about are very low, and so I think that

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that is true, but the thing is that we should move along.

DR. VOCKLEY: This is probably where I really wanted to make the second bullet here. My take on the evidence review is I would have fallen in line with Nancy Green's interpretation, that I think the evidence that early diagnosis and treatment is compelling or spectacular or whatever you want, I think that that is the issue that drives this. I think that the ability to treat these kids is so good that what we are doing is we are trying to decide whether or not we can accept slightly incomplete preliminary data at the screening level. That is really where I think we come down on this, and so I think that the treatment data really cannot be underestimated for the importance in this discussion. Cost effectiveness. If you really want to talk about it, we can, but we did go on to the diagnostic algorithm. All right. So here is the algorithm

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that Ned presented earlier. We don't have the slam-dunk screening. It has been proven to be effective and, in concert with treatment, to give us a cost-effective and life-saving protocol. However, now we go to these other segments, and here we go. Do we have enough information? Do we have enough information

on the treatments of the condition? I put that in a big yes because I think, again, that is really a driving component here. It is compelling. Can we diagnose the condition? Yes. Do we know the harms of the testing? We have had a little bit of discussion about that, but I think that the answer is probably yes. Do we know the harms of treatment or other interventions? Again, we have had some discussion, and although I ignored it, I think that we heard how much a lifelong odyssey with treatment of this disease costs. It does not take too many patients like that to pay for a screening program. So this has

not come to a conclusion, except to say that I think that we have the information that we requested going into this kind of a discussion for a decision. Yes.

DR. BOTKIN: I had a question about 5A, and maybe it goes back to Key Question 5, and it is sort of a systems question, whether there is been any discussion of availability of resources. If you go to a population-based screening you are identifying kids, what sorts of resources are available to assure those kids are making the jump from the diagnosis to the transplant piece. If those are not readily available for costs or expertise of those sorts of things, then that is going to be, obviously, a challenge for a program.

DR. BUCKLEY: Ellen presented that in her talk, that there are at least 35 centers in the United States that can do these treatments. In the Immune Deficiency Foundation survey, it indicated also availability of

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treatment was never a problem.

DR. HOWELL: Mike?

DR. WATSON: I think I read it the same way you read it, and it is that first number one in the screening place. One of the criteria we established for this, for even accepting something for further review, was that -- I think it was that a pilot should be going on, a pilot should be done. I don't remember what the nuance there was, and I would really hate to get stuck in a loop. We have already had a number of things come before us that were obviously premature. This is perhaps a little premature in that the very first step of a big population screening for a really rare disease has not been completed yet, but I tend to agree with all your other assessments.

DR. VOCKLEY: Piero?

DR. RINALDO: Well, I look at this

picture, and I recall the earlier conversation

that answer to Question 1 will always be no.

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DR. VOCKLEY: Yes, it will.

DR. RINALDO: I think there was disagreement in the evidence review group, and I suspect there is disagreement around this table that the answer to Question No. 3 is no. I would say that with these two considerations, it seems to me this is a strong yes.

DR. VOCKLEY: Well, here was my summary. There are strong reasons for screening. We have gold standard diagnostic tests. We have compelling treatment for data that drives this issue. There are questions concerning the screening, and so, as I said before, what I think we are all wrestling with is that we are very close. We have a condition that will benefit from screening. We have babies that will be saved. Are the inadequacies or the holes that are still left in the screening data enough to put us into -- and I just show this to remind you

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what our categories are. Are the uncertainties yet the screening data enough to put us down into the let us just get that last little bit closed and we will all feel more comfortable about moving forward, or are we in fact in Category A? Jana?

MS. MONACO: I think for me, from a parent perspective, I would rather still see slight imperfections in the screening being conducted than allowing these babies to obviously come aboard and be born with it and not detected, and then they end up in everyone's clinic anyway with the lifelong problems. With the screening, then there is much more focus on it, and I think you are going to see the numbers. You get a focus in order to perfect those imperfections.

DR. VOCKLEY: I should emphasize that this should have had a question mark added. This is at the end of it. This is not a recommendation. This is a question.

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Piero?

DR. RINALDO: If we believe the one in 100,000, and usually these are underestimates, and let us say that we give it a C and say come back in a year, in this year I would say 40 children will be born in the United States with SCID, and 35 will die. I cannot live with these statistics.

DR. HOWELL: Further comments around the table? Jane?

DR. GETCHELL: If I can comment. I am simply not comfortable at this point with the screening test, that it is ready for prime time, for distribution to State programs. Once this body makes a recommendation, then it kind of is up to the State programs to figure out a way to implement the test, to pay for the test, to put it out there. I just don't see that States are ready for that or that the test is ready for that either. There is no QC materials. There is no PT for it. I don't think it is ready yet.

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DR. VOCKLEY: Barbara, then Fred.

DR. BURTON: I just want to say that it sounds to me like the issues of concern that have come up will be very quickly resolved with broader implementation of this. I think that having heard the discussion, there is absolutely no doubt in my mind that I would want my children and grandchildren screened for the condition, and I think that the rest of the kids in the nation would have that same benefit, should have that same benefit. So I agree 100 percent with what Piero has said.

DR. VOCKLEY: Fred?

DR. CHEN: I think my organization is represented here because we do have to worry about the other 99,999 kids who don't have SCID out of every 100,000. I really feel like our discussion of clinical utility is incomplete. I don't think we have heard about the potential harms. I don't think we have really considered them seriously.

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The Rotavirus vaccine, if you are going to put that side by side and put that as a potential benefit, that has an incidence of one in 90 in this country as Rotavirus. I don't think this is a situation where we are weighing sort of one vaccine versus one newborn screen, but I feel uncomfortable with the level of discussion we have had about clinical utility, and I don't think that that is been fully flushed out.

DR. VOCKLEY: Okay. Duane?

DR. ALEXANDER: I think it was clear from the statement I made earlier that I really believe that this is a test that is going to work. The problem that I have is the credibility of an organization recommending moving ahead with full-blown newborn screening when the systems that are in place to do it have not yet found one case. Those are going to come, but I think we lose our credibility as a committee if we recommend national newborn

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screening when the systems have not found a case yet. I reluctantly would go along with C, although I think we are going to get the A. I would say that I am going to be talking next about the Newborn Screening Translational Research Network. It is possible to expand the pilots that are going on now and

add more sites and try to get this answer much quicker than we can with just two sites. We have this existing site saying that they can train people. We have places that are set up to do this, and we have the dollar resources to put into getting this answer quickly. It would seem to me that this is a high-priority activity to try and get an answer as quickly as possible because everybody here in this room believes the answer is going to be "Yes, we can do it." We just can't take that step, I think, without having yet found one case in the screening programs.

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DR. HOWELL: Alan?

DR. FLEISHMAN: I agree with Dr. Alexander, and I think that it is incumbent upon us as a committee to define carefully in a list what it would take in order for us to say yes, to ask our evidence-based committee not to do a new evidence-based analysis but an incremental addendum, and to report back to us sequentially at each of our meetings so that we could be told where are we with this process in a regularized fashion. The danger would be that we go back to the beginning for a full review, and we cannot tolerate that.

DR. VOCKLEY: Nancy?

DR. GREEN: I think that those recommendations from Drs. Alexander and Fleishman are very important, and I would certainly concur. I think one of the additional aspects, looking in a new months, whenever the next committee meeting is, at the existing data from both Wisconsin and Massachusetts will be very instructive. Perhaps we will find a case or

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learn other things. I think revisiting early and often is a good idea. But the discussion also has touched but not fully focused on one important aspect which is that the Wisconsin and Massachusetts programs are topnotch, and they are doing this in a research context. I don't know if the other State programs can take this on. That may not be a reason not to implement, and it may be that this particular disorder, the technology for this particular disorder precipitates a serious discussion at the committee level of assistance to States or to regions in setting up high-quality screening, because it may be that the States, each of the State programs don't reach this level of technical proficiency for a long time. That would, I think, be a heartbreaker for all of us who think that this is close to being ready.

DR. VOCKLEY: Chris?

DR. KUS: Representing the State and Territorial health officials, I totally agree

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with that idea. Really, I think the idea of thinking about this in a planful way, not going back to the beginning but saying what does it take to move this along -- because Piero's comment was very compelling, but I would suggest that if we recommended today to add this, in a year from now it would not be in all the States. We would not save all the kids because we did not plan for how to do it in a qualitative fashion.

DR. HOWELL: Unfortunately or fortunately, we need to move along, and I think that most of us share Piero's passion for moving this along and I think Duane's concern about being really very sure where we are. I think one of the things is that I certainly don't want to get in the mode of having a report at our next and our next and our next meeting. That gives me hives, frankly.

[Laughter.]

DR. HOWELL: I think that most of us feel that this is really ready for prime time, and there are a few things we want to do, but not

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subsequent meetings. I think we need to come up with a recommendation that would satisfy the voting members of the committee about what we should do. I think it is C at the current time, but I think it needs to get up to A in a hurry, and I think we need to figure out what is the best way to do that, frankly. Do we have a recommendation that we do that?

DR. RINALDO: Can I make just one final comment? I hope that we also learn from past experiences. It took 15 years to implement tandem mass spectrometry nationwide, which is a joke, because everybody had to reinvent the wheel. After the thirty-seventh pilot study, I was actually embarrassed to see that people were still saying, "Well, I am not sure. I have to do it myself." So it would be the catalyst needed. Until this condition is on a recommended panel,

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the States will have no drive, no desire to expand. I understand, and in the end, all the arguments that I heard actually do have a variable component of common sense, but the reality is that change is slow. Frankly, it would be a shame that this thing drag. Right now, almost 20 years after the first State started doing a newborn screening by MS/MS, there are still two States that are not doing it -- 20 years. So, in 20 years, if there will be States and no screening for SCID, that will be, in part, our failure.

DR. DOUGHERTY: With the committee's new charter, we are supposed to make a recommendation to the Secretary. I don't know on the last two votes we have had, that a letter has gone to the Secretary.

ATTENDEE: Yes, it had.

DR. DOUGHERTY: Oh, okay.

DR. LLOYD-PURYEAR: Yes.

DR. DOUGHERTY: Okay. It is not in the

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correspondence. So I don't know. Okay. So I think there is an opportunity but it --

DR. LLOYD-PURYEAR: What is not in the correspondence? You have seen the letters to the Secretary. Is it your Blackberry? Remove your Blackberries and cell phones away from your microphone.

DR. DOUGHERTY: Okay. Okay.

[Laughter.]

DR. HOWELL: That was Michelle's Blackberry.

DR. DOUGHERTY: Okay. That is the problem. I mean the question is what is in the recommendation, and I think the recommendation should include the need for more studies. We all know whose going to implement it, but I am talking about the correspondence, not on the charter, the recommendation to the Secretary.

DR. VOCKLEY: Yes.

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DR. HOWELL: Let us have a recommendation from the committee that we can vote on and move along here about what we need to do.

DR. DOUGHERTY: My question is: What is the recommendation that we do?

DR. HOWELL: That is my question too.

[Laughter.]

DR. HOWELL: So we have the same question. We can send a letter to the Secretary, whoever that may be, and if they can find someone. I think they are looking for someone outside, if you want to volunteer.

[Laughter.]

DR. HOWELL: Let us have a recommendation that would capture what I would feel is the urgency to get this on the panel along with some plans to do something. Duane, would you like to make a recommendation?

DR. ALEXANDER: Recommend that we

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consider this in Category C at the present time, but recommend that necessary steps be identified and taken as quickly as possible to get the necessary information to reconsider it, to move to Category A as quickly as possible.

ATTENDEE: Second.

DR. HOWELL: Is there discussion of Duane's motion? It is been seconded here, and I think Denise was thirding it and so forth.

DR. RINALDO: Well, these days, as from the periphery of a country when we hear to what happens in Washington, we often hear that there are not much details in proposals. So I really think we need to be more specific about the steps that would be the transition between the current recommendation and what I think there is consensus. Otherwise, if we leave it generic and unspecified, I will be very troubled by that.

DR. CALONGE: I wonder if we could vote on the current recommendation with a promise to think about this overnight and fill in the specific gaps of what the committee would be

comfortable with, just to revisit quickly tomorrow. Otherwise, I think the laboratory ends and the people who are doing the screening should be able to say what they are going to be able to produce for us by the next meeting or the next month's phone call or some other issue. I understand your need for specifics and a time in that is not 20 years. I think we are so far beyond the issue that it is going to 20 years to get there. We are new now. This is a different age, and I don't think we should necessarily be painted with the activities that took us so long to get here.

DR. HOWELL: If it is acceptable to the group, why don't we do this? We have a move and a second. Why don't we vote on Duane's thing? And then we will have a promise that some group that I will appoint after we go to coffee break will come back in the morning with a list of specifics that will be tied into this motion.

DR. RINALDO: Can we wait to vote until we know what specifics, maybe tomorrow?

DR. HOWELL: I would vote on the motion today, with a promise that we will revisit it.

[Motion passes.]

[Break.]

DR. HOWELL: Ladies and gentlemen, there has been so much exciting stuff on the agenda. We are running a little behind time, but I am delighted that we have Dr. Duane Alexander, who is director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and who is obviously a member of this committee, and he is going to talk about several important programs going on at NICHD, the Newborn Screening Translation Research Network and some stuff about the novel technology program that is under the institute and also make a few comments at least about the National Children's Study. Duane?

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DR. ALEXANDER: All right. Thank you. Thanks for the invitation to give you an update of where we stand with this.

It has taken on an added importance, I think, with the discussion we just had for the last hour and a half, but it also relates to discussions that we had the last couple of meetings when we have considered other conditions for addition to the standard list of conditions routinely screened for. The Newborn Screening Translational Research Network was one component that evolved from the NICHD's initiative in newborn screening that we started about four years ago. This is a new contract that we have just awarded. It will support activities of not just the NICHD but of HRSA, the CDC, and AHRQ as well, and along with some of the work from this advisory committee. It is the third component of NICHD's newborn screening initiative that we started about four years ago. Other components, the first was to increase the number of conditions that we screen for by developing new tests, using to the extent we can the same platforms, so that we keep costs

down and are able to screen for multiple disorders at once, and encourage uniformity among the State screening programs. This was funded by a request for proposals from contracts. We funded two contracts

that have been working in using different techniques, including tandem mass spec, microarray chips, Luminex beads, and micro fluidics in developing new screening test methodologies. These contracts are expiring, and we will be issuing new solicitations for continuing those activities as an open competitive process. The second component was to develop and test new treatment approaches for disorders that are potentially screenable but not being done because we don't yet have an affective treatment. This, we have issued a program announcement for several times requesting grants from investigators interested in pursuing new methods of possible treatment for people with these rare disorders.

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NICHD has funded 12 grants from this program, and other institutes have funded another five. I will be reporting to you about those later in this talk. The third and the major focus of this presentation was to build a research infrastructure that would be large and potentially even national in its size and scope to facilitate introducing new screening tests and treatments in a research mode, to gain knowledge as fast as possible from as many subjects as possible, so that no potential data would be lost when we are working on these rare disorders. We only had five major objectives here. First, we wanted to provide a material resource for investigators, like blood spots, for helping them in developing new screening tests. Second was to provide sites, like States or regions, for piloting new tests when they were ready in a controlled program. The third was to provide sites with gathering standardized information on the natural

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history of untreated disorders, genotype, phenotype correlations, also looking at standard treatments and their outcomes as a basis for comparison when new and better treatments came along. A fourth objective was to provide sites for testing new treatments in a research context, and fifth, possibly setting up a registry by disease with all the privacy protections necessary built in of affected individuals for future treatment studies and for natural history studies. When we looked at how we might do this, the national ready-made resource to do it was the National Regional Collaborative Network in newborn screening that has been supported for some years by HRSA. This is semi-structured group that provides services but does do some research and compares data on testing and was coordinated by the American College of Medical Genetics. So, with this group already in existence and no other

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group really set up to do what we wanted to do, we made the case successfully to award a sole-source contract to the American College of Medical Genetics to serve as the coordinator for this Regional Collaborative Network to carry out the research projects that would come along. This contract was awarded in September, and it has been operational since then. The statement of work in the contract was pretty specific in setting up 10 things that we wanted them to do, first establishing a network of State newborn screening programs to get information from State labs and registries; second, developing and implement and refining a research informatic system for investigators and policy-makers that would be consistent with this network. We would be able to link researchers with potential subjects for trials and provide liaison between researchers and registries and link grantees with technology validation sites. Third, we wanted them to be able to establish and administer an efficient and

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reliable repository for residual filter paper blood spots. You have heard these referred to today. You are very familiar with those. Those are the basis for the whole program, and they are in high demand but obtainable sometimes with some difficulties by investigators who want to use these to document whether their proposed now screening test works. Fourth, we wanted to provide expertise and support to researchers about the regulatory requirements for their work, things like uniform consent, IRBs, and the variations in these between States and then localities. Fifth was to facilitate research on developing new methods and technologies by maintaining close contact with the scientific and research communities,

then facilitating research on screened and treated patients to determine the effectiveness of treatments and long-term outcomes. We also wanted them to be able to have the capacity by statistical leadership and

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clinical trial design expertise for individualized needs of researchers who wanted to come to them and use that resource. We also hope that they would facilitate timely dissemination of research findings, and that they would establish a research steering committee with expertise in it from health care professionals, public health people, ethicists and scientists that would make recommendations about the proposals that would get access to this research network. Finally, these researchers, in conjunction with their institute program officer would nominate research projects for consideration by the network to get access to this program. This was funded for five years for a total of about $13.5 million. This may not seem like a lot of money for a Cancer Institute or Heart Institute project. For NICHD, this is pretty substantial funding. We have the capability of augmenting

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that with other funds, such as the economic stimulus funds, when they become available. So this, then, was the activity that we have had underway just now for a short period of time. They have made progress. Their report to us of what they have accomplished indicated that they really have established this organized network. There is a steering committee that is been formed as a coordinating group for the contract with a number of work groups to carry out aspects of the project. The steering committee will discuss how these work groups will interact with each other and with them. The first meeting is scheduled for April 6th and 7th. The work groups of both States, laboratory officials, and the clinical centers have been developed to create these networks, and their first meeting is scheduled for June. Progress has been made in developing the informatics and communication system. The

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coordinating center is looking at possible options for doing this. One they are looking at is caBIG. It is the National Cancer Institute project, the Cancer Bioinformatics Grid to serve as a model and possibly a resource for doing this. An IT research working group has been established and also is going to be meeting in June. They made progress in developing this virtual repository of residual and dried blood spots. This is part of a meeting, this April 6th and 7th meeting, and there is been a working group set up on biospecimen repositories. They have also been successful in developing recommendations for model-informed consent and research policies, looking with our committee on the session that we will be having here at this meeting on IRV issues. That is part of what they have been doing, and their work group on bioethics and legal issues also is going to be meeting in June.

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They have made some progress in developing laboratory and practice standards and guidelines related to newborn screening. They have developed care plans for each of the conditions that are already included in the newborn screening programs. These are not practice guidelines. They are care plans, and they reflect current practices of people providing these services which often have a lot of variability in them. They had a meeting in Denver, February 20th and 21st, to discuss a national consensus on these care plans for metabolic diseases that are really the framework for many of these new activities. They are ready to receive requests for blood spots and request to do pilot studies from this committee. That is about all I want to say about the translation and research network. I am going to give you an update on the other two components.

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First, the technology development in newborn screening. We had two contracts for this; one, the University of Washington, working primarily on lysosomal storage disorders, developing methods for detection of Fabry, Pompe, and mucopolysaccharidosis 1 in newborn screening samples. This has had a lot of delays, primarily due to IRB concerns and considerations, and so they have made some progress, but not as much as they had hoped to do during their time of funding. The second contract with was the New York Department of Health, with Ken Pas, looking at novel technologies. They have developed a new multiplex buffer for assays for thyroid, cystic fibrosis, and congenital adrenal hyperplasia. With SCID, they have developed and optimized an IL-7 assay and tested it using dried blood spots for the newborn screening programs, and they are now testing it in their program. They are also looking at genotypic

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multiplex assays using Luminex B to raise for biotinidase genotyping, and this work is progressing. The second component was the program announcement with review for newborn screening treatments. This announcement has attracted a lot of response. As I said earlier, we have funded 12 of these from NICHD and five from other institutes. One of them was developing a novel treatment for heritable gamma hydroxybutyric acidemia, another pharmacologic chaperon therapy for mouse Gaucher disease and also working the therapy of Gaucher disease. Another project looked at n-carbonyl glutamate in treating hyperammonemia, any of the urea cycle disorders, work at the Children's Research Institute at Children's Hospital in D.C., another looking at optimizing drug-like compounds for treating spinal muscular atrophy. Another project has been looking at augmented phenylene clearance by muscles as a

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novel therapy for PKU, and another on innovative therapies and clinical studies for classical galacticemia. Another project has been trying to stimulate SMN2 exon 7 inclusion with short RNAs as a treatment approach for spinal muscular atrophy, and another looking at novel therapies for global and cell leukodystrophy and one in therapeutic opportunities in spinal muscular atrophy at the University of Utah. So you can see there is a very wide diversity of the kinds of topics that are being pursued by investigators here in this program. In addition to those NICHD ones, the Deafness Institute has funded one on restoration of hearing in connexin mutant mice, a genetic disorder, and another on gene therapy for Usher syndrome. The National Institute of Diabetes, Digestive and Kidney Disease funded one on gene therapy of mucopolysaccharidosis Type 7 and another on therapy of propionic acidemia.

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So those are projects that are underway. That program announcement remains open, and we are continuing to try to stimulate research on treatment approaches that someday we will be able to justify addition of screening for other conditions to the list that we have already. Okay. We have gone through those lists of projects. Let me now just shift to where we are with the National Children's Study. The National Children's Study, you will recall, was mandated by the Congress back in the Children's Health Act of 2000. It is to be a study of about 100,000 children recruited over four to five years of time during pregnancy or before pregnancy and then followed until about age 21. The purpose is to look at environmental influences on health and development. It is the largest study of its kind ever undertaken. You need a study this large and of a perspective nature in order to be able to make cause-and-effect determinations between

environment exposures of various types and various outcomes, either medical or psychosocial and behavioral. We have had extensive planning for this study. At the present time, we are in the field in two of the seven pilot sites. The other five will join in the field in April, and we will have a year of piloting the current protocol for the National Children's Study. There is far more included in that protocol than we can possibly afford with the dollars that are available. This happens. These things expand. Everybody wants to get their idea in, and they are good ideas. We have had to eliminate some already, but the pilot study will be the vehicle that we use for determination of what goes into the final protocol in terms of what is feasible, what is acceptable to the people participating, how much time does it take, because that is a concern as well, and how much does it cost. So we anticipate after the year of

piloting in the field, we will put together that final protocol. That will be reviewed again, and then we will be into the field with the full study. So that is where we are. Some of that will relate to rare diseases. All the kids who are picked up in newborn screening programs will be identified and be part of the National Children's Study. That will not be a large number, even with 100,000 kids, but we will have information more detailed than we have had before on a follow-up of these and whether there is any differences in their responses to some of these environmental exposures from other kids. A couple other things about the study, we will have DNA from all the kids, their sibs and parents for looking at gene environment interaction issues. Plus, we will have the computer capacity to look at the multiple exposures that these kids have to environmental substances or situations. That enables us to look at things in

combination because that is how they occur in the natural world. You don't get exposed to just one thing while you are growing up or even one thing at a time. It is multiple exposures at once. So this study will have the capacity of looking at interactions between different exposures, as well as their interaction with the genetic constitution. That is where we are with that study, and that pretty much gives you a brief overview of what we have been doing in the newborn screening arena, as well as the National Children's Study. I will stop there. I hope we are a little ahead of schedule, and I will take any questions for just a couple minutes. Any questions?

DR. HOWELL: Any questions of Duane?

DR. LLOYD-PURYEAR: I have a question.

DR. HOWELL: Michelle, has a question?

DR. LLOYD-PURYEAR: I have a question, and I know I am not a committee member. If a group comes, is not funded by NIH,

but has a proposal for a project -- and this would be actually if a group wanted to look at SCID, for example, ,and carry out some of the activities we have identified in SCID -- do they get funding from NIH, or do they get funding through the coordinating center?

DR. ALEXANDER: The coordinating center is funded by NIH, and the source of support, it is certainly the NIH-supported activities would come from add-on dollars from the NIH to do the projects within the network. We are still working out the details on how access will be obtained.

DR. LLOYD-PURYEAR: Of the funds, access and decision-making?

DR. ALEXANDER: Yes. And whether people who are not NIH-funded have other sources of funding could apply, be accepted, and then get NIH or different sources of funding to get that work done.

DR. LLOYD-PURYEAR: Okay.

DR. ALEXANDER: Still working it out.

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Yes.

ATTENDEE: Will the meetings, the ones you mentioned in April and the bioethics meetings in June, be open to the public?

DR. ALEXANDER: They are being held by the contractor. Mike, what is your plan?

DR. WATSON: Well, I was not going to comment. I only work on days that ends with six or seven, and so we have actually two meetings. The April 6th and 7th is not the steering committee. That is a meeting of a number of people representing State newborn screening programs and others to talk about the use of residual biospecimens to support investigation research, quality assurance, the full range of things for which they are valuable and for which they are currently at risk by people very much concerned about doing research on babies and privacy and things of that kind that are protected through consent in the programs we are envisioning. That is a closed

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meeting because we did not get a large enough room for that meeting. The steering committee meeting is the 16th and 17th of April, and it is actually a combination of steering committee meeting that meets before and after and a full day and a half of a planning meeting that brings together people from various parts of the world who have addressed particular parts of the broad program that we are developing, people from Denmark who have had a national dried blood spot repository for decades now and have used it for various kinds of research activity. There is going to be some available room. This is not a confidential meeting. I couldn't tell you today how much extra space it is, and I am not going to make it an announcement that anybody can come, but it certainly will not be closed, though there will not be open participation of anybody who chooses to come, much like this.

ATTENDEE: Okay. But it will be on the

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website or something?

DR. WATSON: It will be somewhere when I find out how big the room is.

ATTENDEE: And the meeting in June, the bioethics meeting in June, do you know? I am sorry.

DR. WATSON: Bioethics meeting? That is a work group, a small work group.

ATTENDEE: Okay.

DR. WATSON: That is a small meeting that is a working meeting.

ATTENDEE: Thank you.

DR. ALEXANDER: Any other questions? Yes.

DR. KUS: The children's studies, long-term study, when might we expect to receive some information from it over that period of time?

DR. ALEXANDER: Okay. We are recruiting in waves of four years. So it takes us four years to recruit all the one-year-olds, the newborns.

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We will be releasing data and actually making datasets available to interested investigators periodically through the study. So the first data release will be probably the newborn data, pregnancy and newborn data, and that will probably be released as a preliminary dataset when half the sample has gotten that far in the process, when we have had half the births. Then we plan to release the rest of it. So you are looking at a while yet before those datasets will be available, but throughout the study we envision making the newborn dataset and pregnancy together, the one-year follow-up data, the three-year follow-up data, and then periodically through the study to the scientific community. We also would hope that the community will be applying to the various institutes for additional analyses that they would like to do with the data for support, for financial support for those analyses.

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If people are eager to have additional things collected and placed in the repository, that will probably cost money too, and you will need to get an application in to try and have something like that added to the study which is a possibility. Okay?

DR. HOWELL: Duane, thank you very much.

DR. ALEXANDER: All right. That is it.

DR. HOWELL: An excellent presentation. During the break, placed at your seat was a little printout of an article that was in last week's New York times about newborn screening that was actually issued in response to the March of Dimes report card that got widespread attention and talked about the newborn screening program in the nation. One other issue, I have been told that the $46 for dinner tonight includes both the tax and the tip, so that is a great deal.

[Laughter.]

DR. HOWELL: I said earlier that was extra. So you will not have to go to the ATM

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more than once or twice more. We are going to wrap up this busy day with an update on the HRSA and the CDC long-term follow-up projects and how they intersect with the Translation Research Network, and we have four distinguished presenters, and I am going to introduce them at the outset. We have Anne Marie Comeau, who you have heard from several times already, and Anne Marie is the Deputy Director of the New England Newborn Screening program, and she is on the faculty at University of Massachusetts Medical School. We have, in the same speaking group, Lisa Feuchtbaum who is from the California Department of Health Services, and they have had efforts in long-term follow-up in that State for quite a

long time, and we will hear some material from Lisa. Then we have Nicola Longo who is Professor and Chief of the Division of Medical Genetics at Utah. We will wrap up with Mike Watson who

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will discuss some of the elements of the discussion there and how that might fit in with the program that he is involved with. I guess, Anne Marie, we will lead off with you.

Update on HRSA and CDC Long-Term Follow-Up Projects:

Intersecting the Translational Research Network

DR. COMEAU: Thank you. Thank you for the invitation to talk about long-term follow-up in New England. I am just going to start off saying one of my friends has a saying that life is all about expectations, and to that end, I still like surprises because it helps me to readjust my point of view. Hopefully, there will be some surprises for you in this little presentation about long-term follow-up in New England. The basis of our project is really to build upon the existing databases, the existing infrastructure in newborn screening programs, and to build long-term follow-up into that without

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having to replicate systems. Our goals are to ensure public health quality assurance, not only to quality assurance of the newborn screening program itself, but to ensure that patients are actually in the care that we are hoping to obtain for them by doing the newborn screening public health quality improvements and public health engagement in research, and to remind you that public health people are very interested in continuing with research. The major work group of our budget is a long-term follow-up work group that consists of newborn screening coordinators throughout New England and people from the New England Newborn Screening program. The major update with respect to Massachusetts is that we took our informal state of authority for collecting such data on long-term follow-up, and now Massachusetts has formal regulations. These regulations not only added to SCID newborn screening as a pilot

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research program to the Massachusetts panel, but also ensured that the newborn screening program would be able to collect long-term follow-up data that the health providers will report data back to the newborn screening program as we ask for it on not only the short-term follow-up of diagnosis, but also long-term outcomes. There is notification to the parents that such activities are ongoing with our new booklet. Going forward, we indicate to parents that we will be collecting data on babies who are diagnosed as cases throughout their lives. Our long-term follow-up activities have focused on three areas for data collection and quality improvements, and these activities, these foci focus on hemoglobinopathy, cystic fibrosis, and metabolic conditions. Very briefly, I will go through sickle hemoglobinopathies that is a work group that has come together, gelled mostly within the last couple of years, though we have been working with clinic directors in hemoglobinopathies

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throughout. This little slide shows you the distribution of cases in New England, with the majority of cases in Massachusetts. This slide will show you the members of the hemoglobin work group, the newborn screening hemoglobin work group, which is formulated much like the Massachusetts CF work group, newborn screening personnel together with clinic directors and key personnel in the clinics. The work group members are people who helps us to define or to refine the variables that we are going to be collecting or that we are collecting in long-term follow-up, and so for hemoglobinopathies, again, there is what I call "census data," such as date of last clinic visit, most recent visit, whether or not the baby or the child is alive or dead and cause of death, general demographic information and current practice information. Clinical variables that we are collecting reflect the kinds of variables that

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the hemoglobinopathy work group was most intent on collecting, so that they could use these data to improve their own practices. So they wanted to know whether or not babies and children were having clinical strokes and whether or not everybody was getting transcranial Dopplers and in what frequency and whether or not babies have infection and what the different kinds of treatments were existent in the variety of clinics. There is a data form that goes back and forth between the newborn screening program and the hemoglobin clinics. Most of our data is entered by people within the newborn screening program to ensure a standardization of data entry and standardization of data, basically. These data, the hemoglobin work group was a little bit more careful -- wrong word -- the hemoglobin work group was a little bit more reticent about jumping into giving us data until the regulations were in place, formalizing the collection of data. So we have just begun to

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collect data. This just gives you a sampling, showing that of the cases existent here, 83 percent of them are being seen by a specialist within the last 12 months, that 27 percent of them have had a transcranial Doppler, et cetera, et cetera. I am going to go through all of these different data. Moving quickly onto cystic fibrosis, I am not going to focus on this at all because I have supposed about our CF work group quite frequently. Also, the distribution of CF cases is not unlike that of the hemoglobin cases existent in New England. There is a little bit of a difference in that CF screening is a new screen, and so Massachusetts has had a longer time screening for CF than some of the other States. Some of the long-term and short-term follow-up allowed us to note trends in just diagnoses of CF, and this, again, is shorter-term follow-up in Maine, comparing our projections of

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six babies with CF per year to what we are actually observing is nine babies in seven months. So, despite all sorts of follow-up in Maine, people have been surprised with this. Getting to what my sense has been of what you are probably more interested in is our long-term follow-up of metabolic conditions, and again, this comprises a large group of the metabolic clinic directors. This group is chaired by Neela Sahi [ph] of our newborn screening program. This group has mainly worked by the Massachusetts work group. The Massachusetts clinic directors have come together on a very frequent basis to review the variables that would be collected by long-term follow-up, and we have been extending that to regional groups to ensure that the kinds of data variables that are collected are agreeable to them or that they might actually want other variables collected. I am going to talk to you a little bit -- this is one of the surprises -- on sources of

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the long-term follow-up data that we have been able to collect in Massachusetts, and just looking at this right off the bat, one will see that a large number of the long-term follow-up data is actually collected from primary care providers and not only from the metabolic clinics. These data reflect very active long-term follow-up work done in Massachusetts and Maine. Part of the reason for the data being collected from primary care providers is that many of these babies who are diagnosed with metabolic cases have not been seen in two years in metabolic clinic, despite initial good engagement in metabolic clinic and despite being in Massachusetts where metabolic clinics at most are only two hours away. So, of a total of 299 cases that we know of, a few of them have died. A smaller number have moved, and 40 of the 299 are still being tracked. We have long-term follow-up data on 246 of these cases born since 1999 and 95 of these

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babies have not been seen by a specialist in more than two years. It is just another view of that. One might think that the babies who are not being seen by a specialist might be just the PKU babies and not necessarily babies who have urea cycle defects, but this slide shows you that some of the babies who are not being seen by a specialist are represented across the spectrum of metabolic diseases found by tandem mass spec. This is anecdotal evidence, but some of the reasons that it has been stated for why these older children aren't being followed outside of specialty care is that parents would be going to specialists again and again and just hearing the same thing with nothing new, so limited information and uncertain spectrum of disease, that there was no specific treatment provided, that the child appears well, and unnecessary travel or people who frankly don't like traveling into a big city. I think that is not a trivial issue as far as metabolic clinics go, because most

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metabolic clinics are within academic centers in big cities. One of the other pieces of information that we are able to follow by long-term follow-up is to look at a center-to-center -- I am running out of time already?

ATTENDEE: Yes.

DR. COMEAU: All right.

ATTENDEE: Sorry.

DR. COMEAU: How much time do I have?

ATTENDEE: Zero.

DR. COMEAU: Zero? All right.

[Laughter.]

DR. COMEAU: Okay. Sorry. I was going as fast as I could.

ATTENDEE: You are doing well, but let us just wrap it up, if you can.

DR. COMEAU: Okay. Center-to-center transfer is high.

[Laughter.]

DR. COMEAU: We have follow-up data on a lot of these various metabolic conditions, some

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of which are surprising that some babies, despite good engagement, these are not necessarily the ones followed by primary care, despite good engagement have some outcomes that were not necessarily expected, both for fatty acid, organic acidemias, urea cycle defects, amino acid disorders. These set of slides have been presented before, saying that this is not just data collection for data collection, but that information does go out to the clinics and primary care providers to try to inform people about things that they should be looking for. I clearly don't have the time to talk to you about our databases. I was going to fly through that. Thank you very much.

DR. HOWELL: Thank you.

DR. COMEAU: I am sorry I talked so much.

DR. HOWELL: Thank you very much.

[Applause.]

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DR. HOWELL: We have had a busy day. I think that Tim has a question of you.

DR. GELESKE: I was surprised to see how many patients followed up with their primary care provider and not with to metabolics clinics, because I was thinking at the beginning of your talk, how many kids were being seen in the metabolic clinics and the hemoglobin clinics, but not with their primary care providers and their medical home. I think it opens up the question or the possibility that metabolic clinics should be developing models of co-management, so that they can reach out to the primary care providers, number one, so the PCPs are getting the kids into the clinics, but number two, so they have got tools for management themselves.

DR. COMEAU: Right. I would not say that that is not happening now. I think it probably is in Massachusetts, that there is good co-management, but that is another level of investigation.

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DR. HOWELL: Thank you very much, Anne. Let us see if we can move along with Lisa and hear about all the happenings in California. Most things we hear from California recently has to do with the budget.

DR. LLOYD-PURYEAR: She is here on her day off.

DR. HOWELL: Mr. Schwarzenegger told you to take a day off to save the payroll. Is that right?

DR. FEUCHTBAUM: That is right.

DR. HOWELL: Good.

DR. FEUCHTBAUM: Two days a month.

DR. LLOYD-PURYEAR: Just as word of warning, it is because of the overtime, you have about 10 minutes.

DR. FEUCHTBAUM: Okay. I can do that. I am going to try and do that. Let me just find the presentation if it is in here. Again, I just want to briefly thank the committee. It is an honor to be here today. I

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will try and get through this fairly quickly. I will just describe the long-term follow-up data system for metabolic disorders that is currently operational in California, and basically, it is a public health surveillance system that follows diagnosed cases through age five. We use an annual survey instrument. We have a Web-based, secure, HIPAA-complaint system, and basically, a child is followed up through our short-term follow-up system using the same database, but once a diagnosis is made, it kicks into the long-term follow-up system. Basically, the system allows for the availability to assess whether there is ongoing care in management. We assess clinical outcomes and do a developmental assessment and look at the impact on health care utilization as the kids essentially grow up. We do a yearly assessment or snapshot to capture the status of the child at the end of each completed year. I mentioned it is a

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Web-based system. Each of our metabolic centers is responsible for tracking a kid that had a positive screening test in the program. So we really hold that center responsible for letting us know what is going on with the child. We have a pending case list that any day, anybody at the center could log in and look at the list of outstanding annual patient summaries that are due, and this system is driven by the birth date of the baby. The baby has a birth date. One month later, the child's name appears on a list, and they are due for their annual patient summary. Once they do the annual patient summary, the name falls off the list and appears next year, after the birthday. They really have to account for the status of the child or the whereabouts of the child. I am not going to go through this, but these are the data elements. Briefly, clinical follow-up status. You will see what they are actually in the context of the slides, because I

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have some data to share. I think it would take too long to read that slide. Again, the system has actually only been operational for just about a year and a half. So, at the point that the system went live, as birthdays kind of rolled out, we required the centers to complete the survey. So just a rough overview, these are many of the disorders. Not all the disorders are listed here. The main point being at this point in time, if you look at the totals row, as of February 9th, we had 557 completed annual patient summaries. It doesn't represent all the kids diagnosed, but I will bet it represents about 90 percent of the kids diagnosed through the screening program. So we are always pushing the centers, stay on top of your annual patient summaries, don't fall behind, but overall, they are doing pretty well. I will not be able to get into all the details, but based on this slide, you could see

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that it is cross-sectional data. It is not prospective data, although we can do prospective looks at these cases. So, at year one, we found that among 234 completed surveys, 84 percent of the patients were still active patients. Then you could see at year two, among 175 completed surveys, 80 percent were still active patients in the clinic. You can see the breakdown. About 5 percent seem to be lost at follow-up, reported consistently each year. There are a small number of deaths. A small percent move out of State, and patients do move throughout the State. If they move to another center, we track it, and the kid gets transferred to the new center and then will show up on the pending list at the next center. So we are trying to really track the kid if they move throughout the State. We do a development assessment. It is a subjective assessment. We ask the clinician to give us their opinion. This is an area we want to try and objectify as we move forward with the

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CDC grant, but how many patients at each year are age appropriate as far as speech, physical development, mental, cognitive, base motor and fine motor, and you could see about 80 percent of the kids are doing really well. There is a little drop off in years two and three. By age four or five, you are seeing -- actually, the kids who are age four and five at this point in time are mostly PKU kids, and you can see that they are doing pretty well. I lumped the moderate and severe delay groups together, and overall, I will just say it looks like about 5 percent of the kids are really falling in that category across the years. About, maybe 20 percent -- it varies -- of the children actually have symptoms that are associated with the disorder. So most of the kids are, in fact, symptom-free, or at least the majority of them. Was there a loss of skills in the previous years? Our question. There is little data but we have some. It seems a small

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percentage of kids are actually losing skills, and about 80 percent of the cases in general, we are finding have no hospitalizations at all in the previous year. This slide, I will not go into the details, but we are collecting average days of hospitalization during the previous year, number of hospitalizations, number of emergency room visits, and number of clinic visits to the metabolic center. We do require the centers to see the child at least once a year, and if they have not seen the child, picking up on the point that was made I think by Timothy, we are now asking them to call the pediatrician and find out how that kid is doing, because we are requiring the centers to at least get in touch or see the child and, if not, talk to the pediatrician once a year, because we were finding a lot of the centers were saying "not seen," what do we do if we have not seen them. So, in our latest contracts with

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metabolic centers, we are requiring them to see the child at least once a year or get the information from the primary care provider. This is an interesting slide that I am going to move on quickly. I just will say, the kids that seem to have the highest hospitalizations, emergency rooms, and clinic visits are the citrullinemia Type I kids. As clinicians, you all may know this already. The MMA group, the mute zeros, pretty much the MMA group, they seem to be the highest utilizers of health care services. I mean, you could see it. I think the slides are in your packet. We do an assessment where we ask the provider just to rate the child on a scale of one to six, from critical to excellent. There's issues with the scale, and we are going to be working to refine it and, again, to come up a more objective measurement. So, if it turns out that one provider is very good as another provider is poor, we are

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working towards standardizing people's answers. It is really true. I have seen some interesting assessments, but it has to do with providers are looking and they are seeing the question in a different way. So that, we need for improvement. This is just where I did a little assessment of MCADD, because it is interesting with our database to be able to look at groups of disorders. For example, I wanted to see what are happening with our MCADD kids. It is one of the biggest groups. Basically, most to have kids, 92 percent are in active care at the end of the first year, slightly less in the second. I think that the interesting thing for me was the age-appropriate cognitive function at 97.5 percent in year one, 84.4 percent in year two, but in fact, if you were not considered age-appropriate, there were only 3.1 percent of the kids that were classified as having a mild delay in terms of cognitive function. So, again, I am not presenting all the data. It is hard to

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put it in context. Clinic visits, 45 percent are being seen three to five times a year, and you can decide is that a lot, is that a little, but our data system will provide you with the numbers of who are the utilizers of services. Only 10 percent were hospitalized either two or three times. So most kids are being hospitalized. Well, in fact, I have lumped zero and a one together. So that is really misleading, but the

point being that there is not a lot of hospitalizations. There is a reasonable amount of clinic visits, and you can draw your own conclusions. So, in conclusion, our surveillance approach is able to do what we want it to do which is to assess the availability of ongoing care management, assess clinical outcomes in developmental assessment, developmental status, and look at health care utilization, and as these kids grow up, hopefully grow up -- most of them do seem to do that and have pretty good outcomes,

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as it turns out -- and, again, our system goes through age five. We have not considered taking it beyond then. Thank you.

DR. HOWELL: Thank you, Lisa. Becky?

DR. BUCKLEY: You had a significant attrition. You started out with 234 babies, and then at year five, you only had 35 left. Most of your data are presented in terms of the numbers of patients that you have surveyed, and at year five, you only surveyed 35 children.

DR. FEUCHTBAUM: What is happening is the system went live at a point in time. It is really based on the providers completing cases as the birthdays roll around. So it is not a prospective study. It is not like data collected at year one. It is just not prospective.

DR. BUCKLEY: Different people then?

DR. FEUCHTBAUM: So it is really a cross-sectional type analysis.

DR. BUCKLEY: Okay.

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DR. FEUCHTBAUM: At this point, I am saying, though, we can do prospective. You can take a kid who came in at year one and maybe a group, say 10 MCADD cases, and follow them, but we have only been doing this for 18 months now. So we are not going to have really the opportunity to have a lot of perspective. At this point, the most we would have is pretty much for kids born last summer. We would have two years of consecutive data at any point, either three to four or one to two. Do you see what I am saying?

DR. BUCKLEY: Yes.

DR. FEUCHTBAUM: Every time I go into the system, there is more data. So that is going to really fill out. You could just imagine in five or six years, we are going to have thousands of cases where we will be able to look either as a cross-section or prospectively at what happens to these kids.

DR. HOWELL: Thank you very much, Lisa. Nicola?

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DR. LLOYD-PURYEAR: Oh, Coleen.

DR. HOWELL: Coleen had a quick question, while you are walking back to your seat.

DR. BOYLE: Yes. Can you give us some sense of -- Anne showed that about 90 out of, whatever it was, 240 children had not been seen by a metabolic clinic in the last two years. Can you give us some sense of what is going on with California relative to that?

DR. FEUCHTBAUM: Well, we do ask them to account for the children, and only about 5 percent were what we called "lost to follow-up." So I would say 5 percent. It is not all kids screened. It is reports filed, if you will. So, among the reports filed, only 5 percent were lost to follow-up, where we are really asking the centers to account for where the child goes.

DR. BOYLE: That is different than they have actually been seen at a metabolic clinic. I mean, they can contact a primary care physician.

DR. FEUCHTBAUM: So the percent seen at

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least one time is the question? I would have to get you that data, but it is a high number. I mean, they are pretty good, and again, we just require that they have to see the child once a year at the center, as a condition of getting -- we do provide some reimbursement, not a lot of money, but we provide reimbursement for the centers to give us this data.

DR. HOWELL: I think that reimbursement is probably a big carrot, Lisa.

DR. FEUCHTBAUM: No, it is not a lot of money.

DR. HOWELL: Although it is not a lot. Nicola is going to tell us what is happening in Utah, and then we are going to have Mike wrap this up and we will have a discussion.

DR. LONGO: Thank you very much for inviting me here and giving me the opportunity to listen to what has gone on so far because it was a very interesting experience. What I want to tell you in the next few minutes is what we are doing in Utah. In Utah,

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we do not have the long-standing experience of either of the previous two presenters, because what we have done, we just started doing the data collection as part of a CDC-sponsored project. The difference between what we do and what the other people do is that instead of having a program which is self-standing and centered on the follow-up of patients identified by newborn screening, we have integrated the long-term follow-up of children identified with metabolic disorder in the Birth Defect Registry. Why? Because the birth defect programs usually have a long-standing history of data collection, and they have been sustainable in the sense they are being funded for several years. In addition, they know how to collect high-quality data and continue in collecting data. So they have a system in which the data are corrected effectively. They have alignment of target resources, and what it means is that to collect the data for birth defect, they have to visit a different

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hospital, and at the same time that they collect data for children who have birth defect, they can collect it on children who have metabolic condition. Finally, it is an effective use of funds because the same people that have to go in one place to collect one type of data. We collected that type of data. So there is no need to reinventing the structure to obtain data. They are able, again, to collect high-quality data on the population that we want to follow. They are interested in outcome data just beyond the initial period because they have done that in the past. They track utilization of services, as you have seen previously.

We have seen people are seen by metabolic physician. They go to the emergency room, and all of these other problems, they have been doing that type of work for many years. They are able to disseminate the result of things, and they are able to share data with other center in a way to get a large number of

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patients.

Let me go back a moment to the history of what has been done in Utah in term of follow-up. So the first thing is that we had pilot study with Mountain State Genetic Network which was sponsored by HRSA to define the parameters to be collected in the long-term follow-up. That has resulted, together with Dr. Janet Thomas, in the design of templates that we use in the metabolic clinic to collect data when children come to see us. In other words, what happened, that we have a certain measurement that we do on the patient that we record every time that we come to clinic. The advantage of that is that it reminds us that we have to obtain those labs or we have to do some type of study to determine how the child is doing. Finally, there was the incorporation of the long-term follow-up in the Birth Defect Registry, just this last December, by the action of Dr. Lorenzo Botto who is my colleague in the

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metabolic clinic and another metabolic disease center. Finally, they have collected data so far on paper on all patients identified since the newborn screening test was expanded in Utah that was on January 1, 2006, and up to date. The way it is done, there is nurse director, which is a person that goes to different places to the metabolic clinic, where the staff from the health department where the patients patient had been identified, the data from the newborn screening lab, it had performed the screening, and then it goes to the metabolic clinic to see what it is available there. It explores all of the electronic medical record and then goes to visit the different hospital where the children can be. Then all of the data are checked against the vital records. In other words, we make sure that the child is alive at least or at least still in the State. Subsequently, all of these data are

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reviewed by the physician to make sure that the diagnosis is correct and that everything seems to match. They use the standard demographic information in all of these types of screen, the same use for the Birth Defect Registry, except that they were modified to accommodate longitudinal data and specifically modified to accommodate biochemical data in different patient. So, in addition to the demographics, they collect data about the pregnancy and possible complication. One thing that we have inserted is how the diagnosis was confirmed, specifically what the metabolic lab used or if there was an enzyme assay or molecular studies, and the reason is that that tells us the degree of certainty of the diagnosis. Unfortunately, for some diseases, there is still not a complete agreement on the best way of confirming the diagnosis. Finally, they collect all of the time

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that they have a clinical encounter, either with the metabolic clinic or with a primary care physician and specifically finding a morbidity and use of different services such as dietitian, such as early intervention and other type of services. They collect both common and disease-specific elements. What this means is that there are common elements that are equal for all of the patients, such as the functional outcome, how children are growing, how they are developing, what is their IQ, if they have an occupation, and then there are specific data for each of these, such as a medical treatment and whether patients are compliant with the treatment. That, many times, is deduced from the result of metabolics testing. What we have done is that we have started a pilot study just to enter all of the patients, in addition to the patients that have been identified by newborn screening. We wanted to see a moment what happened to patients, all of

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the patient with a specific metabolic condition which is called glutaric acidemia Type I. We still do not have the complete data, but I can show you in a moment what we have in Utah. Why do we want to study glutaric acidemia type I? Because it is a disease that it is identified by extended newborn screening, and patients with this condition, like many patient without a metabolic disorder, they can appear completely normal at birth. Many of these patients have or develop macrocephaly. They can be mildly hypotonic, even if they are doing very well. What happened many times at the time that they have their first episode of high fever, fasting, vomiting, many of these children develop acute dystonia that results in a permanent damage of their brain. As a result, without treatment, about 90 percent of the patient would become dystonic and they would become wheelchair-bound for the rest of their life. By contrast, most patients identified by

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newborn screening, they do relatively well, although some of them will develop dystonia even without acute decompensation. On the MRI that you can see there, they show a lot of different fluid around the brain which is a collection of -- in this case, I think it is mostly blood because there is brain atrophy. What we had in Utah, we have about 12 patients with glutaric acidemia type I. Utah is a small State, and in all of our patients, the diagnosis has been confirmed either by DNA testing or enzyme assay, and the first thing that we have found is that if there is extreme genetic heterogeneity in Utah, since all of the patients have different mutations, and of the patients identified by newborn screening, most of them were doing very well except one that had some mild delays. But the data that we realize that it is important to enter in our database are the data on brain imagining. Why? Because, for example, in all of our patients, we have detected that

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there is brain atrophy which is present at birth, and brain atrophy, despite the name, does not cause many symptoms. The biggest problem in these patients is the generation of the caudatum and the putamen. So what we want to do, really, is to follow the MRI after birth when the children are either older or when the child has a significant clinical event to determine when the change becomes active. So, as a result of our preliminary review of the data, we think that many of the patients that develop dystonia without an acute deterioration in this disease have damage of the caudatum and the putamen at birth or shortly after. So this, I think it is a valuable piece of information to collect, and this piece of information can change the way that we manage these patients because some of these patients might need early intervention and other services starting from birth, in addition to the standard metabolic treatment.

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So, in conclusion, we think that long-term follow-up is essential for understanding the natural cause of rare diseases and the effect of screening and treatment. Different model can be used for this activity. So we have seen previously self-standing registry for metabolic disorder. What we are trying to do in Utah is incorporation into birth defects from various programs where present can be on an ongoing infrastructure with public health resource capabilities. However, as you can see, a small center like ours cannot obtain a significant result because the number of patients is too small. So data from multiple centers need to be combined to obtain statistically significant results. Finally, most importantly, longitudinal data, multiple years are needed to define outcomes. I am saying this one because many time people have receive funding for a year, two years, and it is not enough. We need to find a system to receive consistent and prolonged

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funding to enable the collection of longitudinal data. I want to thank all of the people who have been part of the study, and especially Dr. Lorenzo Botto whose picture is shown there and who is the principal investigator of the Birth Defect Registry and of the long-term follow-up of patients with metabolic disorder.

DR. HOWELL: Nicola, thank you very much. Are there any urgent questions before we ask Mike to discuss his program and how it might tie into all these other programs we have heard about?

[No response.]

DR. HOWELL: I think not. Mike, you are on. Dr. Watson obviously serves as a liaison member of this committee and, as you know, is Executive Director of the American College of Medical Genetics.

DR. WATSON: All right. So rewind yourselves back to the end of Dr. Alexander's

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presentation and remember Nicola Longo's wish for a larger system, and that is pretty much what we are charged with developing, if we can find our slides. All right. So, as Dr. Alexander already has told you, the NICHD-funded Newborn Screening Translational Research Network is a project designed to develop an infrastructure to facilitate research and clinical investigation that will improve newborn screening. These are the slides that did not one on that laptop that did not have enough capacity earlier today. We are going to talk about three different domains, because Dr. Alexander already implied the desire to build a system that actually accommodates a number of agency interests and areas of focus. The first area for me is the patient care domain. That is where the providers and the patients are seen. The clinical provider network that we will form under the Newborn Screening Translational Research Network will tie together

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the people involved in different types of newborn screening conditions, the metabolic disease physicians who see those patients. We are also talking to people involved in the care of hemoglobinopathy patients, those involved in endocrine patients, be they the primary care provider who might be on the front lines for things like congenital hypothyroidism or the pediatric endocrinologist that could be on the front line for things like congenital adrenal hyperplasia. There is a number of patients from hearing loss and CF that come through genetics clinics. Fortunately, those do overlap significantly with the metabolic disease centers in the United States. What we could get out of those particular provider groups and the patients they see are the patient demographics that could be linked out of registration systems within institutions into databases. I think that is the place where consent

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to participate in long-term follow-up will take place. We draw about 12,000 people a year out of the newborn screening programs who turn out to be true positives. A consenting 12,000 will be much easier than 4.2 million, and we don't want to do anything that would limit the number of people willing to participate in university screening by some perception that research might take place. I think it is likely that many of these responsibilities will lie within that diagnostic community setting. Patient diagnosis and management takes place there and is documented into their medical record systems as they become available, certainly within the academic medical centers. That is where most of the metabolic disease physicians are and the genetics community sits. It gets more difficult as we move more out in the primary care, having those electronic capabilities available to us. We have a public health domain that we have thought about a lot. We have already heard

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presentations about long-term follow-up data. That really is an important component of an evaluation of a public health program is knowing something about the outcomes of the kids. It is only with that, that you know whether or not they have actually moved through a newborn screening program efficiently to get to diagnosis and confirmation and into intervention at an appropriate time to realize the outcomes that are expected. One of the things that develops in these programs by capturing long-term follow-up information is the clinical history of the diseases. By doing it within the States in those conditions that are already in newborn screening, we capture the clinical history of the treated disease. That will be the basis for the next-generation therapeutics on which clinical trials will have to be run, and we will finally have a decent clinical history that will not be based upon what exists in case studies and the literature and the occasional observational

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studies. However, a database of this kind based on follow-up is also useful in epidemiology, surveillance, health services research. Population-based biospecimen repositories can also be developed out of these public health programs because it is really the only place where we have a general population set of materials that could answer the questions at that level of clinical investigation, many of which we have talked about today in the context of SCID where many of our gaps existed in figuring out whether or not that was a screenable condition. My third domain is that of research and clinical investigation. In this domain, we again have the clinical provider networks, however not just dealing with the conditions in newborn screening where information is provided for a public health evaluation component based on outcome, but also are able to address the candidate conditions for newborn screening. One of the recent nightmares of my life

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was doing the work towards the uniform panel for newborn screening in which we readily acknowledged that the evidence bases for the rare diseases that we were considering was miserable, and we had to rely heavily upon expert opinion, small observational studies. One of the much missed recommendations in our report, in addition to a panel of conditions, was that there should be a system in the United States for the development of evidence bases around the conditions, both in newborn screening and candidates for newborn screening, that would empower a better public health decision-making process as to what should be in newborn screening in the future. These folks are also able to develop the patient registries within their studies and in their institutions, as well as patient biospecimen repositories. It is a place where clinical trials can take place because these evidence bases become the bases upon which any clinical trial of a new therapeutic or a

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therapeutic for a condition that by virtue of a therapeutic might be able to be considered for newborn screening. It is also where clinical investigation takes place, and many of the programs Dr. Alexander described earlier are in the development of new treatments and new technologies. Many of those occur within academic centers. Many occur within private industry, but utilizing perhaps the bio specimen repositories we develop, depending upon the type of research that is being considered. When I put the Vin diagram together, I end up with one group of people from an investigative and research perspective who end up at the center of this activity, and that is the people who are seeing the patients and the patients themselves. I think if we look at how do we develop an informatic structure that accommodates all the people, it ends up residing centrally in one particular place in my model, and I am happy to

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discuss whether I am wrong or not, but I got a funny feeling that if we want to get at the candidate diseases and the conditions already in newborn screening, that there is a central group of providers and

patients who are at the core of that activity. Dr. Alexander alluded to the fact that we are looking at informatic systems and are talking to the NCI about modifying their cancer biomedical informatics grid to accommodate this project. It has already been modified to support the cardiovascular research network of the NHLBI, and I have had a year and a half of conversations with them about doing this. I am waiting until the steering committee meets, because this is not a dictatorship, but it is something that this group will decide as to whether that is the appropriate IT infrastructure to support the project. It actually can umbrella many of the databases that have already led to the long-term

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follow-up programs and the regional collaboratives that you have already heard about. They are systems in which if we can accommodate the local provider and their interaction with their patient as the database that ultimately is transferrable up into a central data warehouse area where they can access their own patient in an identifiable way, any of their patients with a particular condition; however, they also have to de-identified data of the others that are participating within that expert group dealing with a particular condition. That allows us to at least have everything central, protect patient privacy through security mechanisms that separate the de-identified and the identifiable data. It will allow the provider to access their own data as needed. So the infrastructure that will meet this project's needs -- Am I still within our time limit?

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DR. HOWELL: Oh, sure.

DR. WATSON: A patient registry development is central to our activities. That is a resource, obviously, that NICHD is interested in. If they want to be able to put out RFAs to investigators to address issues that can improve newborn screening, they will need a wide range of resources, be they biospecimens, be they an improved evidence base about the conditions that are in newborn screening or the candidate conditions for newborn screening. We are going to operate in a highly protocol-driven activity, much like the National Cancer Cooperative Study Groups. The care plans that he alluded to earlier have actually been developed through the HRSA-funded regional collaboratives. Three of those regional collaboratives have been working very closely together along with another one of the regional collaboratives within which one of the States was supported by CDC in the development of their databases.

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Those are very tightly aligned right now and are approaching a consensus just by virtue of the various groups that have been working together in their development. The reason the Translational Research Network supported the meeting in Denver this past weekend was that our intent was to come to the next generation of those regional collaborative-developed care plans to now move into the National Library of Medicine. We have already moved the newborn screening results into the National Library of Medicine for language standardization and an electronic health system environment. All that is done for the results coming out of newborn screening. However, we want to next do the information that tells the newborn screening program what the diagnosis is, and that is a mix of laboratory and clinical information. We will be working with the NLM next on taking the care plans and getting those languages developed to operate appropriately in an

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electronic health system environment. We want to minimize duplication, and I think when you just realize the fact that the NCI, the caBIG infrastructure that was built, is approaching $150 million over the past four years in developing this infrastructure. You begin to appreciate the problem we will have if we duplicate these databases independently all over the country. So figuring out how we could collaborate together to utilize an infrastructure that supports everyone's needs in both research investigation,

surveillance, and other activities is going to be critical. Patient data. I have already talked about the identifiable data aspects, de-identified. Within the programs in the regional collaboratives, that data warehouse is now being accessed in some States where they have a code that identifies the patients identified in their newborn screening program, so they can draw out the outcome data on their own patients from

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that State.

The only others that access identifiable data are the providers and the patients. The patients have actually used access to their own

identifiable data when needed in an emergency situation, as has been developed in Region 4 through the Midwest Emergency Medical System.

That was from the earlier talk. So I can say thank you, and are there any questions?

DR. HOWELL: Thank you very much, Mike. Ned, you have some questions?

DR. CALONGE: Just one. So putting this talk together with the early one -- well, actually two now from both --

DR. HOWELL: Three.

DR. CALONGE: Do you think we are getting close to the tipping point for this all coming together and making an integrated system? I ask that because we are obviously involved in electronic medical record and are we getting to the tipping point where that actually becomes reality. This actually looks like it may be

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closer to happening than the EMR that we would all like to get to.

DR. WATSON: Yes. We are four months into this. So what we have right now is a virtual Translational Research Network that has to be turned into a real one, and I am going slow on a few pieces where I want the steering committee to weigh in, but there are pieces of this that are critical to be able to function in an electronic health system world. Things like the care plans where we can begin the standardized languages and move through the standardization committees are pretty obvious, and I don't feel uncomfortable moving forward with that independently and will continue to do that. We are in the process of talking about what kind of a national NIRB do we need to support this project, because I think building a national IRB that actually understands the issues of newborn screening and follow-up and the things that are involved here will have a lot of value

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beyond just its support of this particular project. I think we will move quickly around the genetic and metabolic disease side of this, because they tend to be in academic medical centers, and caBIG has already networked out into the 50 or more major cancer centers in academic medical centers in the United States. So I think we will be well ahead of the curve because much of what caBIG is, is middleware. They could not get any institution to say I am going to all use the same lab information system or same clinical laboratory or clinical information system. It is a middleware project that links their

LIM system into a translation step, back to the national databases. I think we could get their fairly clearly in the genetics world because we are academically based, and those tend to be further along the electronic health system development pathway. Primary care, as we already know, is

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further behind, but the incentives apparently are coming to try to drive that side of the health care system into a much more electronically compatible mode.

DR. HOWELL: Certainly, we hope that this is going to be an enormous asset to the newborn screening community and will fit in with the recommendations of this committee. As Duane already pointed out today, this is a natural place where some of the things that we would like to do with SCID could be done and so forth. Natasha, did you have a comment or a question? DR. TERRY: No. My comment really was -- I think Ned really wrapped it up well -- that this really looks like the foundation of something that could either just link to electronic medical records or actually be a database of electronic medical records and that those conversations have to happen together and that you don't want to duplicate things or write things that actually end up not matching up, but

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this is just very similar to a lot of other conversations that are happening outside of newborn screening and outside of genetics as well.

DR. HOWELL: I think many people in this room are very familiar with the caBIG program, and it has the advantage of accessing data from many, many sites through a confidential way and so forth. So, hopefully, that will really mature. Are there further discussions and comments about the presentations this afternoon? I think they were extremely informative. They identified several sites where things are going on, and I think that hopefully those can all work together and in a larger network as we move ahead. Any further discussions?

[No response.]

DR. HOWELL: Well, let me thank everybody. It is been an extremely productive day.

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I might point out that with regard to those things that need to be looked at to move SCID up the scale, up to number one, I think they have considerably been identified, and we will hear about those in the morning, but let me thank everybody for your hard work today. It is been a very productive day.

We start off tomorrow with one of the really, really critical things about a national program, and that is the institutional review board.

Dr. Alexander commented that one of the major projects funded by NICHD really had an extraordinary delay because of deciding and accomplishing informed consent. So trying to decide how that happens will be a key thing tomorrow morning. I think that will be very, very helpful. So let me wish you all a good evening, and we will see you all back at the crack of dawn. In the morning, we will start again.

[Whereupon, at 5:10 p.m., the meeting

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ADVISORY COMMITTEE ON

HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

Transcript of Day Two

Friday, February 27, 2009

February 26-27, 2009

Bethesda Marriott-Pooks Hill

5151 Pooks Hill Road

Bethesda, Maryland 20814

C O N T E N T S

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P R O C E E D I N G S

DR. HOWELL: Ladies and gentlemen, I think that

the Committee had a most productive day yesterday. We got

a lot of things done, we have got a lot more to do in the

shortened day today, but we are going to begin today with

a discussion of the Translational Research Policies:
Introduction to Institutional Review Boards, Informed
Decision-Making and Consent.
Translational, Research Policies:
Introduction to Institutional Review Boards,
Informed Decision-Making and Consent
DR. HOWELL: As Dr. Alexander mentioned briefly
yesterday, and I agree, I think that the issue as clinical
studies start to be done in research and the networks, the
institutional review board and informed consent, and so
forth, is going to be one of the more important areas that
we need to tackle.
We have a very distinguished panel here today to
lead us through this and help solve this problem
completely and solidly this morning, and we are going to
lead off with Dr. Jeff Botkin, who is known to this
committee, and Jeff is Professor of Pediatrics, University

of Utah, an Adjunct Professor of Internal medicine in the
Division of Medical Ethics, and an Adjunct Professor of
Human Genetics.
Jeff is also a member of the Secretary's Advisory
Committee on Human Research Protections at the Department
of Health and Human Services, and also a member of the
Working Group of EGAPP.

Joining him is Edward Bartlett from the Division of International Activities, the Office of Human Research Protection. He has more recently worked as an IRB member and administrator to a major teaching hospital in Washington, D.C., and he is responsible for the development of human research protection in the international setting. We will look forward very much to hearing from Mr. Bartlett.

We will end up the group with Alan Fleischman who sits on this committee as a representative from the March of Dimes. Alan is the Senior Vice President and Medical Director of the March of Dimes.

He also is a key person in the Ethics Section of the Advisory Committee of the National Children's Study, which we heard yesterday. Alan is currently the Clinical Professor of Pediatrics and Epidemiology and Population Health at Einstein College of Medicine in New York.

We will look forward to Dr. Botkin's leadership in taking us through this issue.

Jeff.

DR. BOTKIN: My thanks again to the committee for the opportunity to talk about this issue.

Our plan with this panel is for me to give some of the regulatory background concerning research with

children, highlighting points that are relevant to translational network.

Dr. Bartlett then from the Office of OHRP is going to pick up, talk about again regulatory background for IRBs and what is feasible with respect to creating relationships between IRBs for efficient review of national or multi-center protocols.

Dr. Fleischman will be talking about additional experiences in this field, main successes and areas where work is in progress to make sure that IRBs are developed in ways with multi-center research that can facilitate the conduct of research.

So, we are going to try to be as efficient as we can with our presentations, so that we have ample time for discussion about this issue.

I won't go into any great detail with the history of research ethics. The point of this slide is to talk about how, in this country, there are a couple of seminal events that occurred not that many years ago that highlighted the need for a more robust system of research oversight.

Henry Beecher, who is a well respected physician from Harvard, published this study in the mid-1960s, Ethics in Clinical Research, and what he did was go

through the literature, pick out studies which he thought illustrated ethical problems in the conduct of research. His point with this was not to highlight a few cases, but rather to highlight the anonymous cases that he presented, that he said indicated serious issues with the ethical conduct of research.

Part of the point was to say this was not a few bad apples or a few questionable cases out there, but he was making the claim that it was relatively common to see serious breaches of ethical standards of the time, so he pulled out 22 examples.

I have Example 3 here, chloramphenicol for typhoid fever, 23 additional subjects died in the placebo-controlled group.

My claim also would be nothing like this would happen in this day and age within our system, and I also would make the claim, while they certainly haven't solved all the problems, if one compares the conduct of research in this day and age to the conduct of research in the mid-1960s, I think we have made enormous progress. It's burdensome, it's complicated, but in terms of actually protecting subjects from this type of research, I think the system has been remarkably effective.

Tuskegee, of course, another seminal event, came to light in 1972 at what was the height of the civil rights movement, so confluence of social movements at the time to say it's time for a new approach to the conduct of research, that simply trusting investigators to make appropriate decisions on their own was not an adequate approach to the conduct of research.

The National Commission was convened and they came forward with what remains a classic paper that still provides a guidance in this area, the Belmont Report highlighting three principles: respect a persons, beneficence, and justice is the guiding principles for the conduct of research.

You can see the shortened definitions of those concepts, and these again remain guiding principles for the oversight of research.

So, its effort subsequently is the development of so-called common rule, which is Subpart A of the Federal regulations, 45 CFR 46, that governs the conduct of research in this area. It has been signed off by 17 Federal agencies that conduct human subjects research.

Part of the point here is this is, in part, why these rules and regs have not really been a living document. It is very difficult to make changes, we have

been told, that if you want to make some changes in the regs, anticipate five, seven years' worth of work, because it is not just one regulatory agency, but you have got to get approval through the entire series of 17 agencies that govern this work.

So, it is daunting process and in part why the regs per se have not undergone significant change since they were first adopted.

The FDA regulations, 21 CFR 50, governs the conduct of research for research is governed by the FDA, so that would be basically drugs and devices, for the most part identical to 45 CFR 46 with a few exceptions, and I will highlight one of those exceptions here in a little bit.

Here is the basic structure for the oversight of research, sort of a three-legged stool peer review. That is the institutional review boards. These, of course, are multi-disciplinary panels with the lay participation, and I highlight the peer review aspect.

Sometimes the fact that it is peer review may not be as transparent as it should be at the institutional level. That certainly has been TRUE of the past at our institution, and it has the strengths of a peer review system, as well as the warts and weaknesses, not

necessarily efficient. Mistakes could be made.
Informed consent, of course, at bedrock, talk
however about opportunities or instances in which consent
is not required, because it is not a blanket requirement,
and then finally, professional integrity. That remains a

significant element.
The regs are only as good as an investigator's
willingness to follow. If they don't follow what they
said they were going to do, then, the system is less
effective. Fortunately, that is not a consistent problem,
but it is a recurring issue.
One more detail, then, about IRBs. This will be
a significant focus of the discussion this morning, review
boards can be organized, of course, at several levels,
academic institution, public health institution, research
organization that would be multi-site, a number of
commercial IRBs that are out there in this day and age,
and some of those are excellent. Western IRB, an
outstanding IRB, there is a variety of different ways in
which these organizations can be organized.
The institution sign off Federalwide Assurance,
FWA, that commits the institution to following the Federal
regulations governing human subjects research, and
research institutions can defer oversight responsibilities

to an external IRB. Again, that is a significant focus of the discussion today and of great interest when trying to develop a Translational Research Network.

A couple of caveats here. Federal regulations provide a floor for policies. If you, as an institution, think you want to go above that floor, then, that is your prerogative as an institution, so they can be more stringent than required, and they create policies and procedures for domains that are not thoroughly covered within the regs itself.

I think a particular area of interest in this domain has been tissue banking. There are not careful guidelines developed yet at the Federal level or in tissue banking, and so you will see a variety of institutional policies about the return of results aspects of the banking enterprise that provide for a significant element of variation between institutions, and that is perfectly acceptable, of course, from the regulatory standpoint, because the regs don't thoroughly cover this domain.

Further, local interpretation of regulations is appropriate as they apply to individual studies. Oftentimes, as you call OHRP with a question about how are you thinking about this issue, oftentimes they return to say that is a matter of local interpretation, it is up to

you to decide how you think this issue should be dealt

with.

For example, level of risk associated with

different types of interventions, that is almost entirely

a matter of local institutional or IRB interpretation, is

a genetic test minimal risk in that particular protocol,

for example.

So, there is considerable variation between IRB

systems, documented, this is a matter of much frustration,

understandably so for investigators, but again is a

hallmark of peer review process, and difficult from my

perspective at least to significantly reduce some elements

of variation there given the nature of the peer review

process.

So, a few definitions here. What is research?

Again, this is directly relevant to a variety of protocols

that might be conducted in the assessment of different

aspects of newborn screening interventions.

Research means systematic investigation including

research, development, testing, and evaluation, designed

to develop or contribute to generalizable knowledge.

Well, is that helpful?

It is in a couple of ways. Here is how

institutions I think generally interpret this terminology. Systematic investigation generally means you are collecting data in a formal fashion, and is generalizable knowledge, and that oftentimes means you are intending to publish it. publish it for a broader application thinking that your experience is going to be relevant to somebody else.

Now, a couple of gray areas here. Innovative therapy, a novel therapy by a physician in the attempt to benefit individual patients. Physicians have wide license to do as they see fit to help individual patients and can use quite creative interventions that do not constitute research.

Now, it becomes potentially problematic from the IRB standpoint if the physician is having a series of patients that are undergoing the innovative therapy with the attempt down the road potentially to publish depending on how the experience pans out.

Certainly, IRBs struggle with some investigators who take this approach and then claim that it wasn't research, but it's retrospective chart review with innovative therapy, et cetera. So, you can see that that

can be a potentially problematic area, but with respect to this particular domain, clearly, clinicians can take innovative approaches to kids with, say, a metabolic condition and treat those kids in ways that they think is appropriate for that child, and that in and of itself does not constitute research.

Quality assurance, quality improvement. Again, a significant gray area for which there has been lots of discussion and some problematic cases, and probably the hallmark here, the easy way to think about these issues in stark terms is to say if the institution is doing a QA/QI project to try to improve some aspect of care within that institution, they will be collecting data prospectively, and there may be an intervention, but the intent is simply to improve the quality of that process within that institutional environment.

As soon as the investigators begin to say, well, you know, this looks pretty promising, I think we need to publish this data, then, the IRB may well want to talk about that and ask the question, you know, is this research for which individuals should be providing it, sent as a review process to make sure that the individual

welfare is adequately protected.

So, again, a gray area in individual cases.

What is a human subject? Living individual about whom an investigator conducting research obtains, one, data through intervention or interaction with the individual. That is pretty straightforward, or, two, identifiable private information.

So, if you are collecting information on somebody that is identifiable, then, you are engaged in human subjects' research even though you may never have any physical contact with the individual whatsoever.

That is obviously TRUE for medical record exams, research on tissues, sore tissues, for example, is human subjects' research as long as those tissues are identifiable, and databases containing individual identifiable data.

I am not going to read this. I tried to highlight the last two, it doesn't come through so well here, but these are exempt research. These are types of research that do not require active IRB oversight.

The last two here, the ones that are supposedly highlighted, are ones that may be more relevant to this domain of newborn screening.

Research involving the collection or study of existing data, documents, records, et cetera, in such a

manner that subjects cannot be identified directly or through identifiers, and then the last one, research and demonstration projects which are conducted by or subject to the approval of a department or agency heads which are designed to study public benefit or service programs.

Generally, what happens in this context is that it's a big circular, but who is it that makes a determination about whether something is exempt. The IRB makes that determination.

What we have found as an institution, as many have, is you leave it up to the investigator, then, a lot of studies fit these criteria that others with a more objective view may not agree, so you actually have to apply to the IRB in order to be told that the IRB does not have governance over your particular project.

So, here are vulnerable populations, and these are additional subparts to the regs that cover different types of vulnerable populations. Subpart D is the one that we are most concerned about in this context, which is children, may or may not be a new subpart coming down the pike about individual impaired decision-making capacity.

Let's talk about Subpart D. Four categories of approvable research with children. In order to get a project with kids approved, you have got to fit into one

of these four boxes or it's not approvable.
Research not involving greater than minimal risk.
This child doesn't really know what that means, but
minimal risk is defined as the risks of everyday life or
routine physical or psychological exams, enormous volumes
of ink have been spilled on trying to interpret that, but
again this is an area where an IRB needs to make its own
determination about what constitutes minimal risk, and
that may be relevant to a particular environment in which
the research is conducted.
If it's being conducted by a grad student or a
fellow, it may make a different assessment than if it's by
an experienced investigator who has been doing some
intervention for a career.
405 These are not the FDA numbers, but 45 CFR
46 numbers. Research involving greater than minimal risk,
but offering prospects of direct benefit to the individual

subjects.
It is pretty clear here that enormous risk can be
applied to children in the conduct of research as long as
there are reasonable prospects of proportional benefit,
giving therapy protocols for an obvious example here, and
you can provide life-threatening interventions to kids,
and that is acceptable as long as there is a prospect of

proportional benefit.

So, justified by the anticipated benefit,

risk-benefit ratio at least as good as available

alternatives and adequate provision for assent and

parental permission.

406 is the more complicated and more

controversial one. This is greater than minimal risk with

no prospect of direct benefit to the child, but likely to

yield generalizable knowledge about the subject's disorder

or condition.

Significant caveats here, must be only a minor

increase over minimal risk. This is not defined in the

regs. The consistent interpretation is that this should

only be a little bit more than minimal risk, so switches

words if that is a helpful way to think about it, and

again why you see variation from one IRB to another.

Knowledge of vital importance not defined,

procedures are reasonably commensurate with the subject's

actual or expected treatment, and then adequate reason for

assent and permission, so this is a category that can

justify or has justified in many IRBs a fairly wide range

of risk in interventions.

IRB, for example, an example of a type study here

was a protocol that was looking at bronchoscopy in kids

with CF to follow colonization with pseudomonas. It's not a therapeutic intervention. The assays were not being used to make treatment decisions. They wanted to see what the clinical progress of the infection was in this population of kids.

So, is bronchoscopy with kids with CF on a serial basis over time, does that sound like a minor increase over minimal risk or not? Our IRB eventually thought that it was, but this is the type of research that would be approved under this type of protocol.

If it doesn't fit those other categories, you can go to a 407 process, not otherwise approvable, but Federal panel, expert panel reviews the protocol and makes a recommendation to the Secretary of HHS for approval.

The process for this has been significantly streamlined in recent years. In the past, it has taken many months, if not more than a year, to get something through a 407 process. There have not been very many of them, but the process now is it has been regularized and streamlined to a greater extent, nevertheless remains a significant task.

Parental permission, consent required for 404 and 405, but two parents for 406 and 407, child assention only required IRB to determine the age of consent.

Many institutions will dictate when that ought to be on a regular basis to say at our institution age 7 or older, or 9 and older, that is the general age range that assent is required, but assent can be waived for certain kinds of research, say, oncology research where it may be the last chance for a child. In that circumstance, the IRB may say you don't need to ask the child for assent if the parents think it is a good idea, then, the child can be enrolled.

So, waiver of consent is a significant issue and will pick up this with the next panel a little bit later this morning, as well.

Making the point that while consent is a critical bedrock to this whole area, the regs anticipate that there are types of research in which consent should not be required.

This does not have an FDA counterpart, so if you are intervening with a drug or device that is regulated by the FDA, the FDA appropriately wants to say you can't waive consent. If you are doing that kind of intervention, then, for the most part, you will get the permission of the parents to do so.

So, outside FDA-governed protocols, four criterias for a waiver. Research involves no more than

minimal risk. Waiver alteration will not adversely affect the rights and welfare of the subjects. That is a little ambiguous. Research could not be practicably carried out without the waiver or alteration. Again, that is a matter of judgment on the IRB. Generally, this doesn't mean it is going to be more expensive to get consent or a little more problematic, but you really couldn't do the research in any feasible way if consent is required.

Lastly, whenever appropriate, subjects will be provided additional pertinent information after participation. This was designed primarily thinking about, say, psychological research protocols in which there may be some element of deception or failure to provide complete disclosure about what the research is really about. Once you collect your data, then, then you go back to the subject and say, well, here is actually what we were doing in the conduct of this research.

So, here is a case just for your consideration.

We won't go through any detailed discussion of this, but one that is relevant here. Investigator wishes to use 200,000 residual newborn screening samples to assess the population prevalence of a condition that is under consideration for a panel.

The investigator also wishes to identify

screen-positive children and assess their health status with interviews and review of medical records.

So, is this research? Probably no question about it, right? Formal collection of data using identifiable individuals and that is relevant to the second question, does the research involve human subjects.

Probably the first part doesn't. If you have anonymized those specimens, you don't know who they come from, and it would not be human subjects research.

The second part, trying to track these kids down, interview them, and assess their health status, no question that is human subjects research. The prospect of direct benefit to the participants. Don't know. Well, that's in part that's right. Now, I think this is one you might get a lively discussion about. The first part, probably not, you are just doing epidemiology perhaps on an anonymized sample, there is no prospect of benefit there, but now you are tracking down kids with some preliminary information about health status. Might it benefit them if they had not been previously aware of the child's condition, but now have been alerted to something for which there may be a beneficial intervention.

You might make that claim. That has assumed you tell them that's right, although if you are -- are refer

them for intervention, that's right, not simply the investigator who is a genetic epidemiologist, who wouldn't have the ability to intervene perhaps.

How about minimal risk? Again, not an easy answer here, and that is, of course, part of the point of presenting it, and one of the things that we try to encourage our investigators is to have them know what these regs say, so that they can make the pitch to the IRB to say here is the way we think this thing ought to be approved, because it has implications for how the study is conducted. That doesn't happen very often. They put together the idea and then it's up to the IRB to sort of sort through and try to figure out which box to put it in for approval.

Then, can parental permission be waived in this context? Obviously, it is relevant to the last question, which is minimal risk, but also the question of whether it can be practicably carried out.

You might think about two different levels with this particular hypothetical case. One is do you need to get consent from all 200,000 parents for the initial screening of those samples, or would it be sufficient to get consent for prospective data collection on the kids who screen positive, who you are trying to assess their

health status.

So, this I think would be a very interesting

close call for an IRB to evaluate and to make a call

about, first of all, of course, broadly whether it's

approvable and under what sort of context and what sorts

of interaction with parents might be most appropriate from

a human subject protection standpoint.

I think what we are going to do is I will just

take probably one or two questions to make sure we move

forward, and then we do have a larger block of time after

the three panelists speak to address these issues, so any

particular questions for me at this point?

DR. DOUGHERTY: I have a question I have been

meaning to ask someone. Well, you are it.

[Laughter.]

DR. DOUGHERTY: Well, here is the situation. You

know, at my age I tend to go to the doctor and my husband

does, too, or for treatment, and sometimes, often more

often that frequently, there is a little box when you are

filling out your history, and all that kind of stuff, that

says your samples or whatever may be used for research, do

you give permission for that.

That's it. I mean they don't say what kind of

research. I mean that could happen as parents give birth.

DR. BOTKIN: Yes.

DR. DOUGHERTY: But what is the ethics of that kind of checkoff?

DR. BOTKIN: Great question. Increasingly utilized approach. Institutions around the country are aggressively pursuing tissue banking, for example, what we are seeing nationally and internationally is increasing interest in using databases associated with individual care, electronic medical records combining those with public health databases, et cetera, in order to conduct research, and oftentimes that research does not involve the full panoply of elements of informed consent that are required by the regs.

Let me just speak just a second to that.

Basically, the regs say if you are going to get a consent, you have to have eight elements and then there is a couple others that the IRB ought to think about.

So, in that kind of context, that would not be considered adequate consent for the conduct of research.

What oftentimes happens in this context is that the IRB will say this is a circumstance in which consent can be waived or altered, so that is the altered piece, so generally considered to be minimal risk, that you can give

just a disclosure with an opt out sort of approach with some basic elements of information there that the IRB then may think is significant.

Now, a lot of times that doesn't happen at all.

Lots of research is conducted with samples that nobody ever gave you any sort of notification or opportunity to opt out, but your samples are sitting in a Pathology Department or where it came for one research project and somebody else wants to use them for a second research project, and the IRB would need to determine, well, generally, on a case by case research project by research project basis whether that constitutes minimal risk or not.

If they want to take that sample and test that sample for a BRCA1 mutation, on an identifiable sample, the chances are pretty good the IRB is going to say no, you can't do that, you have got to go back to her and talk to her and get a full consent.

If you are doing it on an anonymized basis, then, it may well be acceptable as a minimal risk protocol.

The question was?

DR. DOUGHERTY: Creation of registries by

individual clinicians or clinical practices. I think that is what some of this is about.

DR. BOTKIN: But OHRP requires to know what institution the IRB is generally then required is that things that are established as a research resource requires separate IRB review from research projects that access those resources, so if you are setting up a tissue bank or registry for the purposes of conducting research, then, that is an IRB approvable enterprise even though it's not a hypothesis driven activity.

But the once you set up your tissue bank, then generally, you need to apply to the IRB to access that tissue bank and use those resources for research purposes, so it is oftentimes a two-stage process.

Mike.

DR. WATSON: On that point, they are sort of minimal. You have to have some minimal level of information in a registry. When does it cross over?

DR. BOTKIN: In terms of being identifiable?

DR. WATSON: Well, I mean you know what disease they have, but if you want to have some information about whether there is parts of a phenotype of a disease, I mean

there seems to be a transition point in there somewhere.

DR. DOUGHERTY: Or a publication of a case series, you know, these are all the prostate cancers I treated by my electronic robot, and, you know, they all did well.

DR. BOTKIN: IRBs approve sort of retrospective chart review stuff all the time without individual consent. That is less an issue. The data elements in repository, I don't know whether I can answer that. I think that it seems to me the threshold is the question of identifiability.

We will talk about this a little bit more with the next panel, but the common rule basically says if it is readily identifiable to the investigator, then, that is the threshold of identifiability. HIPAA, different. You have got to have 18 identifiers removed in order for it not to be identifiable, so the different standards between HIPAA and common rule in terms of that particular element.

I would be interested, perhaps Dr. Bartlett might want to speak to that issue, as well.

Let me finish up with Celia.

DR. KAYE: This is an identifiability question.

Is there a standard or an evolving thought about identifiability of populations? You are aware in our region, about populations, for example, Native Americans

who view themselves as injured by anonymized individual samples being used to make a statement about the population.

Is there any evolving thought about that?

DR. BOTKIN: A lot of ethical debate about it in the research community about that problem. The regulations themselves do not speak to that, and so it's a potential loophole. You can strip sufficient individual identifiers to make a sample anonymous, but if it retains ethnic or tribal group identification with it, then, it is still considered unidentifiable. It does not require consent, but may well pose a risk of stigmatization or wrong to those who contributed the samples.

So, it is a loophole and I would say that IRBs are probably not particularly sensitive to that issue as yet, but could be, but this would be an area in which the IRB could set a higher standard than what the regulations require and say in order to conduct this research, you also need to strip it of specific identifiers for ethnic or tribal group, or whatever it might be.

DR. KAYE: Thanks.

DR. BOTKIN: Dr. Bartlett.

DR. BARTLETT: Good morning. That was an excellent presentation by Jeff. Thanks for setting the

stage. I assume the PowerPoints are self-activating. Is that a fair assumption?

Great. Thank you.

Previous to my current employment I was the IRB administrator at a major tertiary medical care center in the D.C. area, and I was also an IRB member, so I saw some of the issues in terms of how protocols come through the pipeline, how IRBs sometimes interact with other IRBs or don't interact with other IRBs, so that experience will illuminate some of the comments to share with you.

What we will talk about are a little bit more of the process of how do you deal with research in the multi-center context, what are some models about what are sometimes called alternative IRB review, and a recent or an upcoming proposal to hold IRBs directly accountable which springs from the alternative IRB review concept.

So, let's talk about IRB review in a multi-center world when the regulations were first conceptualized and written in the 1980s and 1991 Multicenter research was more the exception than the rule. Certainly in this area, multi-center research is the rule, and so we are talking about how do we do multi-center research when IRBs, at least the original paradigm was research being done at one institution.

So, this is kind of how things work and I have seen this firsthand, so let's say that there is a study being done in five different sites, five different states, and so sort of the common way that has been done in the past is each IRB in each of those locations did a full-scale review of the entire protocol, and so almost inevitably there were differences in the recommendations or stipulations by the IRBs, and so the investigator was kind of left to their own devices to sort of sort out these different recommendations, reconcile them, go back to the different IRBs and try to get them all straightened out.

Obviously, that may be a frustrating experience for the investigator. It may be in some cases, depending on the number of sites, a one- to two-year process. Are there other ways that this can be done?

Well, the answer is yes, most definitively. This is Section 114 in 45 CFR 46, and it's on Cooperative or we could call it Multi-Center Research. We will cut right to that last phrase there, With the approval of the department or agency head and institution participating in a cooperative project may enter into: one, joint review arrangement; two, rely on the review of another qualified IRB, or, three, make other similar arrangements for

avoiding duplication of effort."

Well, what do those words mean? Well, let's parse the words, let's figure out what is going on here.

Here is the idea of a joint review arrangement.

So, we are talking about the same scenario we have got five different performance sites. One is the IRB at the direct awardee's location, and then four other performance sites. That could be four public health departments around the country.

Here, rather than each of the five IRBs reviewing the entire protocol independently, instead of that, we will figure out some kind of division of labor among those IRBs.

So, for example, the direct awardee's IRB may be responsible primarily for the scientific design, inclusion criteria, statistical methods, more that aspect of it, whereas, the local performance site IRBs could be -- and these are examples -- could be responsible for assuring the knowledge of local research context, making sure the incentives are appropriate to that subject population, making sure local laws, regulations are being met, making sure the consent form is understandable for that population, et cetera, et cetera, et cetera.

So, that is just one way that the division of

labor can be structured. There is obviously infinite possibilities of how to do that.

Here is the second option out of the regulations.

Rely upon the review of another qualified IRB. What does that mean?

Well, so here I have squares for the institution and a circle to designate the IRB. So, here rather than having five different IRBs, now we have a single IRB, and we can call it a central IRB.

Now, that could be the one IRB -- let's say that it is a direct award to Georgetown University and then

Georgetown subcontracts to five other sites, public health departments around the country.

The Georgetown IRB could be that one central IRB, or conversely, one of the public health departments could serve, and I am looking at this from what the regulations allow. One of the public health departments IRB could be that central IRB for all of the sites, or there could be a commercial independent IRB that serves as that central IRB.

So, again, there is a lot of possibilities, there is a lot of flexibility in how this can play out.

This slide explains some of the paperwork aspects of how do you accommodate these arrangements on the

Federalwide Assurance. I am not going to spend a lot of time on this.

Now, let's go to that third option spelled out in the regulations, which says make similar arrangements for avoiding duplication of effort, and if you are wondering, well, did the person who write this know exactly what they had in mind, I think not, but there were basically saying, well, there may be other ways to skin the cat, and so here is one possibility.

So, here we have got now a study being conducted in three different states, and each state has four performance sites. Here is one possible way to do it.

You could have, instead of having 12 plus 1 -- instead of having 13 IRBs, you could have 4 IRBs, 1 at the direct awardees IRB, and then you could have, in each state, an IRB for each of the 4 performance sites.

Again, there is many options, many ways to do this.

So, which is the best model? Well, I don't think there is any one best model. All of them are potentially workable depending on the many ramifications and nuances of the research, the level of risk, the diversity of populations. You know, have the institutions worked before previously. There are so many considerations here.

So, any of those 4 models, any of those 3 models are potentially workable.

Let's now build on that. That is what the regulations say. Basically, the regulations are fairly permissive. There is a lot of ways to do this. In 2005, with a follow-up in 2006, there was two conferences to explore what this particular provision in the regulations meant.

They were held here in the D.C. area. The 2006 meeting I think was perhaps 200 people, fairly well attended, sponsored not just by our office, but also NIH, AMC, and ESCO.

One of the key conclusions of this conference was that even though there is significant flexibility in the regulations, some institutions in fact are quite reluctant to designate an IRB outside of their own institution. I saw this with my own eyes in my prior employment.

There is a number of reasons for this, and one of them is the legal concerns that, hey, if our institution designates an external IRB, and if that external IRB somehow messes up, who is going to be responsible, who is going to be held responsible in a regulatory sense, who has the regulatory liability for that. That is a reasonable concern.

Because the way the regulations are structured now, the jurisdiction goes from our office to the institution, and then through the IRB, so the institution is conceptually viewed as an intermediate between our office and the IRB, which obviously does, in fact, place that institution, does seem to place greater responsibility on that institution.

So, that was one of the common concerns recognized at this conference. So, this is what we are doing to address this. We are contemplating a modification to the common rule. As Jeff pointed out, this is not an easy task, but this is important enough that we believe we should look at this very carefully.

Right now almost as we speak, what is called a Request for Information is under development to publish in the Federal Register to elucidate and try to understand and try to get a handle on what this concept means, that the external IRB could be held directly responsible, not simply the institution that designated that external IRB.

So, in order to conceptualize how to do this, how to make this a workable concept, we are thinking in terms of whether some responsibilities that seem to be unique to the IRB, some responsibilities appear to be unique to the research institution, some responsibilities could be

fulfilled by either the IRB or the institution.

The responsibilities that seem to be specific to the IRB would be, for example, and there is no big surprises here, the IRB would review the proposed research, review it and approve it.

The third bullet as far as alteration or waiver of informed consent, or of the documentation thereof, those seem to be very clearly the responsibility of the IRB.

In contrast, what is the institution supposed to do apart from the IRB's role? Well, the institution certainly it would appear would have the responsibility to communicate the expectation to investigators that they get IRB approval before they start the research. That seems pretty reasonable, and likewise, that no investigator do research without informed consent unless that waiver has been, in fact, approved by the IRB. Again, it seems to be pretty straightforward.

Some institutions that maybe could fall either way, depending on the number of considerations. The first bullet, who decides on exemptions? That could be an institutional responsibility, it could be an IRB responsibility. It could be a departmental responsibility.

Who is responsible for developing the IRB

procedures? It could be either way. What about documentation and recordkeeping requirements, is that an institutional or IRB requirement? Again, you could argue that either way.

Then, some people are asking, but are there responsibilities in fact are shared by both the IRB and the institution? We are not sure what the answer is to that yet. That is part of the reason to do the Request for Information.

I think I have time for one of two questions.

Yes.

DR. TERRY: So, there are some who say that IRBs are already more interested in preventing any kind of heavy liability for them or their institution that they might be attached to.

Are you concerned at all that this might make them even more risk averse, so, for example, the kinds of issues that are on those kind of dicey lines that Jeff talked about are difficult ones to sort out, and if they are even more concerned about their own risk, will they be able to be open enough to allow risky protocols that perhaps would have benefit to proceed, or are you

concerned that, in fact, the IRBs already absorb that and this won't change that for them?

DR. BARTLETT: I want to make sure I understand your question. You correctly state that that many IRBs are worried about regulatory and legal liability of protocols. You are asking whether this would actually increase the IRB's own concerns about their liability? Do you want to elaborate on that? I mean what do you have in mind?

DR. TERRY: I actually run an IRB that wasn't on Jeff's list, but it is a consumer IRB, it's not an institution or a Federal one, et cetera.

My sense from them, and also my sense from all the various IRB meetings, is that IRBs already are perceived as an obstacle to some kinds of research and the complaint is that, in fact, they are more interested in the risk of the institution than they are in the risk of the research or the subject or the participant.

So, just this kind of -- you know, I am sitting here thinking of the IRB, you know, when I go to primer meetings, for example, and talk to the people who sit on IRBs, they are already very worried, and the idea that

this may be coming down the pike, I think, I don't know, but I think they might consider this even more worrisome if they are held more accountable and that the liability falls to them rather than the institution that they are working with.

I just wonder your perception on that.

DR. BARTLETT: So, you are asking whether an external IRB would be more reluctant to be designated because of the fact it would be held to have greater responsibility?

DR. TERRY: I am asking that and an internal IRB, you know, a university IRB, would they also feel that more burden has shifted to them, and not the university.

DR. BARTLETT: Okay. I don't think internal IRBs, I don't think that is an issue with the internal IRBs. I think those dynamics are reasonably well settled, but I think your point is well taken as far as external IRBs and you are right, that is exactly the point is the organization that makes the mistake, would, in fact, be held accountable if a mistake occurred, yes, that is the point of it.

DR. BERRY: Hi. I am Sue Berry from Minneapolis.

The question I have for you was that many institutions,

including mine, have gone to a lot of effort to strengthen our IRB procedures by going through AHARP accreditation. One of the issues in terms of deferral to another IRB is that you typically want it to be an AHARP approved IRB. Is there some way to facilitate some of this by making sure we can create central IRBs that meet that expectation, because that simplifies the process of sharing that responsibility, and is there a role for AHARP in some of this facilitation? Thanks.

DR. BARTLETT: Certainly. In fact, a number of commercial IRBs in fact, already are AHARP accredited. AHARP is the organization that does -- it's a nongovernmental organization based here in Washington, D.C., that does accreditation of not just IRBs, but of human subject protection systems.

So, yes, in fact, some of the commercial IRBs have been AHARP accredited, so that seems to be one reasonable approach.

Yes. Do we have time for one last question?

Okay.

DR. LONGO: Nicola Longo from the University of Utah. First of all, I want to say that I think that the problem of having different IRB approving different protocol, this is a big problem in the field of rare

disorders, because there is nothing that can collect enough patients to conduct any type of clinical research. Maybe this question is about establishing registries. There are several rare disease networks that just collect and follow patients with rare disorders just to follow the natural history without any intervention, and what I have been amazed that even of things, IRB approval for that type of registry has been a serious impediment in conducting these registries.

My question is, is it possible to have a central IRB which is further out. At least for this type of research that I think involve not much more than minimal IRBs could provide a blanket IRB to be usable by all centers, in this way all centers can enroll subjects at the same time and conduct research without the impediment of having, you know, one side forget to submit their peer renewal and they are stuck.

DR. BARTLETT: Right. Thank you. And you are with the University of Yucatan? Oh, Utah, okay.

DR. LONGO: Utah, Utah, yes, yes, but my role obviously an oversight has been part of a committee that was overseeing some performed by the Rare Disease Network.

DR. BARTLETT: Thank you. I think I am going to answer your question by saying that that question has, in

fact, been addressed by the National Cancer Institute.
The NCI has established its own IRB, which in fact reviews
I believe all the cooperative research is reviewed by the
NCI IRB.
So, that is one model that could be -- there is
no reason it couldn't be done by, for example, NICHD, to
facilitate that sort of thing.
Thank you very much.
DR. FLEISCHMAN: What I would like to do is take
us from the theoretical into the real piece in an attempt
to discuss how we might make this work. The last question
was a very good one and the last answer was a very good
one. The only problem -- and I will get to this toward
the end of this talk -- is that every local institution
has the right to accept or reject that central review
based on the present regulatory structure, so the devil is
in both the details and in us, us as representatives of

individual institutions, academic institutions, hospitals,
research centers of various kinds. We will determine our
own destiny, and we will have to do the work in order to
make this possible.
So, I would like to say that my opinions are my
own, they don't reflect the views of anybody I have worked
with or for, and I start here with the complexity of this

system, which is not just the IRB, but this comes from the Institute of Medicine or is adapted from the Institute of Medicine Report on Human Subjects Protection Programs remembering that the IRB is only one part of what is a much broader commitment to protecting the child inside his or her family.

I just want to talk about four things before I get started. One is we have heard this is a local process, and it is. It was created that way when those regulations were written in the '70s, passed in the '80s and '90s, and research was a local enterprise, so the regulations put all the power and authority into the local IRBs and institutions on purpose.

That is both good and bad. It is supposed to help us to have a local flavor and a local understanding, a local help to those who are around us. At the same time, since most research is no longer local, it creates great impediments.

The other issue was that there was no grievance process, so if you are an investigator at St. Elsewhere's University, and that university says no, when that university says no, this isn't exempt, or this needs written informed consent, well, you must go back and talk to all those 200,000 families before you can look at a

sample.

If they say that, there is no grievance process.

If you send a letter, an irate letter to the OHRP saying St. Elsewhere's IRB is not interpreting the regulations correctly, I will bet a nickel the response would be -- and that a lot of money -- the response would be they have the authority, as Jeff pointed out, to set a higher standard than the regulatory floor.

This is indeed a problem for us. So, some of my best lawyers are friends and they tell me don't go to the IRB until you are prepared to be there. We will talk about that.

What is at stake? Scientists and clinicians want to do good. I believe that. They want to do good.

Parents want what is best for their child. They are often altruistic and care about other children, but particularly -- I am a neonatalogist by background -- particularly at that time in life, parents are quite invested in thinking about their child's interests and future, more so perhaps than their altruistic beliefs about other children, and we need to remember when we begin to think about research, that research is for future children, but present children and present families are the ones who are asking to take whatever levels of risk even if that risk is only the risk

of lack of confidentiality or loss of some kind of personal integrity.

So, the scientists want to generate new knowledge, but there are different ways we want to do this in the newborn screening world. We want to develop new screening methods, we want to assess populations for prevalence, we want to assess populations in various ways, and then as Jeff's good example showed us, then, we want to identify specific children who might be affected, and we have two approaches there in terms of research. Sometimes we just want to learn about who they are, what their health status is, or we might want to actually do something for them, with them, to them, that is to say enroll them in a clinical study of some kind.

These are all different levels and we need to understand why level we are seeking our approval for when we want to generate new knowledge as scientists and clinicians, and Jeff's interesting example, if I were the consultant to the researcher, not the IRB, I would have suggested to the researcher split the study.

Let's talk about the easy part and then let's talk about the more complex part. Now, is that disingenuous if I am thinking about the second study? I don't think so. I think one can do that and still have a

full and complete analysis of the ethical obligations of the investigator and the IRBs as we do staged thinking about much of the work we do.

So, what is the role of government and public health departments? It isn't really to do research. You know, there are creative people like Anne Comeau that are embedded into health departments and government who are quite interested in moving the field of research in our field.

There are people in many of our states who want to do that, but in general, our government and our public health departments are in the business of protecting the interests of populations and forcing laws and regulations, monitoring health status, investigating health hazards and epidemics, and assuring clinical services for underserved populations, and are very concerned about confidentiality, because that has been embedded in the public health context.

But they are rare interested in research, and, in fact, there has been a lot of argument between the public health enterprise and the research enterprise as to what constitutes research in public health.

It is a big issue, and the CDC has opined -- and if you read that very carefully, you find not a lot of

enlightenment -- because the public health operation basically argues we are not doing research. The research people reading their arguments would say you are doing research. So, we don't get clarity, we merely get more definition of the problem.

But we need to understand when we go to our public health department or government IRBs, they are quite protectionist in their thinking as we would want them to be, because that is what our governments and our public health departments need to do.

So, we need to prepare understanding that. Well, how about our universities and institutional review boards? Their job is supposed to be to protect human subjects. I wish that is all they thought about, but they actually rarely facilitate research although I believe that is their second most important job, and they actually behave as if their first job is to ensure compliance and protect institutional interests.

Now, I were the president or dean of an institution, I would worry a lot about my institutional interests. When you pull the plug on Johns Hopkins Hospital and University, and a million dollars a day are not coming into that institution because they have had some problems in reviewing research, that is a lot of

money, and I get a really bad, bad publicity if I am the president of that institution, and I have got it all over the newspapers, I have got it all over the United States, and I hurt my research enterprise in real ways, so I want to know who is responsible in my shop for making sure we comply.

It's Jeff Botkin in Utah. And you know Jeff is the most flexible nice guy in America when he's outside of Salt Lake.

[Laughter.]

So, let me give you two examples of two states and how they dealt with this. First, was the Massachusetts approach, and Anne is here, and she can correct anything that I have not said exactly right. This will be a forthcoming article in a book, so it is a pre-print, but I had the pleasure of reading it, it's a very well written article.

She talks about two population-based studies, one done in '99, one done in '87. These are old now, really, but the expansion of newborn screening is directly relevant to things that Anne is continuing to do in Massachusetts.

These authors argue that screening for conditions to obtain new and generalizable scientific knowledge

without evidence-based proof of benefit to the child constitutes research. They staked out that as their definition from the public health perspective of what constitutes research.

So, screening for new conditions without evidence-based proof of benefit is research in these investigator's assessment. So, they stake that out and they decided in '99 they would mandate in Massachusetts 10 disorders be screened for in a mandatory universal method and they would create two, what they called pilot programs, i.e., research programs, one having to do with cystic fibrosis screening and the other having to do with 19 additional disorders, and they went to two IRBs to get permission to do this research.

One was their Department of Public Health and the other was the University of Massachusetts where the newborn screening program is sited. They went to both of those IRBs and they asked that parental permission be required but written consent be waived.

They asked that parental permission be required, but written consent be waived, and the IRBs approved that approach, developing an oral authorization approach, and that a brochure would be distributed to every family upon admission to the hospital for labor and delivery, and that

verbal consent would be documented on a form, and this is

from the old brochure.

In '99, when they did that, they said there would be routine newborn screening and there would be optimal newborn screening. There would be no cost, there would be no extra blood for this optional newborn screening, and if you didn't want the optional newborn screening you still get the, quote benefits of the routine newborn screening.

The brochure was clearly given to every family and then at the time of the obtaining of the actual blood spot, of the actual sample, the nurse would then go ahead and put an X in the Declined CF or the Declined metabolic area" if one of those two pilot studies was being declined by the families, and it was very clear here that you could decline, and you would get this to take home as part of the newborn screening process. It has worked extremely well and, in fact, the numbers of families who declined were quite, quite small, 1 percent of less.

So, this was an approach used in Massachusetts for the so-called pilot or research expansion of newborn screening, and it is the same approach that is being used

now, I believe, for the SCID testing program.
So, they also decided that they would do a
prevalence testing of HIV in childbearing women, a very
important public health question in 1987, and many states
embarked on such a procedure. They would measure maternal
antibodies in de-identified residual newborn blood spots.
This was done in New York and in other states, and the
results were reported as a rate of HIV positivity per
1,000 births, a very important question in 1987
Their justification was this was exempt from IRB
review, this was not human subject research because this
was de-identified, anonymous prevalence surveys.
Now, there were people at least in New York, I
don't know if they were this silly in Massachusetts, but
in New York, there were people who believed that we really
could re-identify if we really wanted to, after we found
out who the positives were, even though we couldn't, but
that was a whole issue, but the IRB was correct, this was
exempt, this wasn't human subjects research, it was a
prevalence survey.
They also justified this work by saying the
knowledge of HIV status was not beneficial for the newborn

in 1987, and it wasn't. It did become such later, but it wasn't in '87, and the retrospective scope is a very bad instrument.

The knowledge of confidential HIV testing was universally available to these women, and was recommended, so they could justify exempt review. That's the Massachusetts work.

In California, in 2002, the state legislature mandated pilot testing in tandem mass spec and they decided parental consent, a written parental consent was required. So, they became upon a similar problem, and were handling it in a different way.

So, the hospitals now in California, in their great wisdom, decided that they might need local review at each of those hospitals. That's a lot of hospitals, and the hospital staff had to distribute the booklet and obtain the signature of each family, each mother primarily, and place a yes or no sticker on the blood collection card saying whether or not this card could go for this research.

This work again our California colleagues are here, and they can help me with this. But their decision

was they needed written consent, and lo and behold, only

47 percent of the eligible births were enrolled, but 90 percent of parents offered participation consent.

So, here again we have the problem of the logistics, of the complexity of this problem created for us in inability to perform a population-based research study.

Now, our California colleagues concluded -- and I am quoting -- The legitimate needs of society and the interests of newborns should not be sacrificed to respond to the autonomy interests of a few parents who do not wish their infant to participate in the study and the future parental consents should be waived."

These were angry people who wanted to do good work, and I am not sure I would have voted the way that IRB voted, but that's the problem, it's not the parents that was the problem, it was our approach toward review of this issue.

So, how can we make it work before -- before we get to the IRB? We need to become experts, researchers, programs, translational networks need to become expert at the regulations and understand everything that Dr. Botkin and Dr. Bartlett tried to help us understand, and we need to ask these questions.

First, is the study research? Does the study

involve human subjects, is the study exempt? Does the study require consent or may it be waived? Is oral consent justifiable and possible if consent can't be waived?

How many institutions will be involved and what of the three methodologies should we use? The multiple individual reviews, the joint review arrangements, whether cooperative agreement approach?

So, is the study research if it's generalizable knowledge, if it's about methods, population prevalence or individuals, we need to distinguish research from surveillance quality improvement, and clinical care.

And the devil is in the details. Does the study involve human subjects? Well, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals.

Now, I would say cannot is a little overstatement. Cannot, if you don't work very hard at it.

Since if I have your blood, I know a lot about you, but if I promise not to try to find out by arrangements with those who have given me these anonymized samples, and if I am held accountable by my institution for that promised, then, it's highly unlikely that I am going to identify you

even if I could theoretically in the genomic era.

I think everyone in this room understands what I am saying. So, if we have a process where the investigator who is getting de-identified samples promises not to seek reidentification in any way, and is separated by a brick wall from the identifiers, because identifiers may well exist somewhere.

Then, that is the identified and it is not human subjects research, and we justified that research.

Is the study exempt? Well, public data sets are, existing de-identified data specimens are, studies of public benefit and service programs are, and we need to think about that sometimes in the public health perspective.

Again, I just quote that regulation which you have already seen. Does it require consent? Jeff raised these four issues about when may you waive or alter consent. You need to understand that before you go to the IRB to justify requests for waiver or alteration in consent if you believe that that is the appropriate way to do it, and as Jeff pointed out, it is not just because it would be hard to get consent, you have to justify it could not practicably be carried out.

I think most population-based studies could not

practicably be carried out with written consent in the hospital context, but that then means it must be no more than minimal risk, and not affect adversely the rights and welfare of subjects. You must justify that in your application. Use the language and justify the actions before you get there.

How many institutions will be involved? Let me talk about two very briefly, two approaches. The Children's Oncology Group, even more successfully than then National Cancer Institute adult oncology group, has engaged every children's hospital, every major oncology program in the United States, because all children's oncology research is centralized, over 85 percent of the children with cancer in the United States are on clinical trials, and this has been a very important strategy that

the children's oncologists have used, which has been incredibly helpful to the children of America, however -- however, you don't have to real all of this, and it's in the Journal of Clinical Oncology -- even when people cede to the central IRB the review of the research, they still remain locally responsible for the so-called local context and many very fine children's hospitals have not ceded to this central IRB, and it has to do with the kinds of things people have said, that is, I have got a great IRB,

I am the president or the dean, I am responsible for this institution. Why would I cede to somebody else when I have got Jeff Botkin responsible? I want his IRB to do the work, and I am paying him.

Then, at those two big programs, Ed pointed out some of the real issues, but also the IRB administrator said we are going to lose some of our resource. If we are reviewing 150 protocols a month, now we are supposed to review 75 protocols a month, they are going to take away four of my people, but I don't have a lot less work, because I still have to review.

You know, I have got to know what is going on here. We are ceding to that other IRB, but the dean says you don't need as many people. This is real, this is real in institutions, so it is not only the dean worried, it's the IRB administrator that is worried.

I think we have not yet figured out how to make those worries go away. So, the Children's Oncology Group has a terrific program. It has really been very successful, but it doesn't change the problem that our colleague from Utah raised. Even if we have central review, we need local acceptance of the central review.

Then, there is the National Children's Study, which I have had the pleasure of working with Dr.

Alexander on now for a very long time, and we have, we are now in the field, we are not in the field. We have given birth to two sites, one in Queens and one in North Carolina, and the other red sites will be in the field very soon.

So, we have learned a lot. The first thing we did was we brought in all the chairs of all the IRBs three years ago to talk about the study. We didn't ask them to approve the study, we wanted them to begin to think about their problems with the study.

Where would we have problems in getting approval in their IRBs, in a sense wanting to buy them into the process before anybody walked into their room with a proposal? This was very helpful. It identified some things we would never have dreampt of because 3,000 flowers bloom out there, and some are blooming more than others.

So, we got some real understanding of where the problems would be. We created a Human Subject Work Group with a senior person from each institution on it, to think about the problems prospectively before we got to the table.

Now, something interesting is going on. In Queens, one of the vanguard sites, there are tons of

hospitals, lots of people, they all have good memoranda of understanding and they have all ceded to the Mount Sinai medical Center IRB in cooperative agreements, and it seems to be working.

In North Carolina, for some reason the institution decided they didn't want to be the place that all those other places ceded to. We don't know why that is yet, but we are going to find out, but it may well be that they didn't trust those other institutions, and until

Dr. Bartlett and OHRP sorts out what are the legal responsibilities between the places, they may not want the smaller institution to be implementing something that they are responsible for through their IRB.

So, these things go in both directions is the problem we are learning at the National Children's Study, and we are trying to be helpful and help people get the appropriate paperwork and everything else done.

So, in conclusion, this is hard work to do multi-center trials in the United States in 2009 or 2010 Central IRBs may be helpful, but they are not the answer. The answer really is a lot of work of collaboration, a lot of work of preloading the thinking, and thinking like IRBs do and helping IRBs to think through their analysis.

Thank you.

[Applause.]

DR. HOWELL: Thank you very much, Alan.

These have been three very thoughtful

presentations. Let's have some questions of the group.

Dr. Chen, we will lead off with you.

Committee Discussion

DR. CHEN: Dr. Fleischman, thank you very much

for the excellent presentation. I am curious for your

thoughts on OHRP's, this effort around defining

responsibilities. I also used to sit on an IRB, on an

independent IRB, and the responsibilities are there

whether you like it or not.

I think all IRBs have struggled with these lines

of responsibility from the researcher, and while they are

appropriately delineated in this draft RFI, I am not sure

how that changes things, and I wonder if you see more

potential in that effort than I do.

DR. FLEISCHMAN: I think the response of the

research community and the IRB community will be very

helpful in this regard. This is a well intentioned effort

to try to help this alternative approach toward IRB review

for multi-center trials. It is a well intentioned effort.

I think we need to try to help as best we can

within the present Federal regulations. So, I am

sympathetic to what OHRP may be able to do in this regard, and I am not sure we are going to change the hard line administrator or the hard line dean who is worried about a lot of this, not the legal liability, I think, as much as the regulatory liability. The legal liabilities I think

there is very little evidence of concern there. It's the regulatory liability I think that people are worried about.

DR. HOWELL: Mike.

DR. WATSON: One of the problems I am obviously pondering and trying to put this Translational Research Network together is very much related to the Rare Disease part of this.

We have, on the one hand, widely distributed patients seen in centers, maybe 100 centers in the United States for metabolic disease, and they are going to be much more comfortable entering into a large data collection activity if it's done through their provider than if they are sent off to something like the Rare Disease Clinical Consortia where there may be 12 centers where they have to go to get their care with somebody they don't know to be participating in some of these activities and trying to figure out what is the balance between making the patients comfortable because they are working

with their own provider and increasing the IRB difficulties in the process because the Rare Disease Clinical Consortia have been getting maybe 20 percent of patients with some of these diseases, which has been inadequate to learn what they want to learn and do what they want to do. So, where is the balance?

DR. BOTKIN: Increasingly, pharmaceutical research is being conducted in the private clinician community. Pharma has figured out that consistently going through institutions is both cumbersome and doesn't always get to the kinds of patients that they are interested in. That's people with hypertension and diabetes, et cetera, who don't necessarily come to a tertiary center.

It is relatively easy to sign up individual practitioners and involves a site review and FWA signature, but I think that process works relatively efficiently. I think the less efficient part of the process is when you are trying to sign up an institution that has a pre-existing IRB and wants to have some oversight responsibility for seeing what happens in that respect .

DR. WATSON: And you know where we are, the people who see most of these patients, many of these patients.

DR. BOTKIN: Yes.

DR. HOWELL: Coleen.

DR. BOYLE: I would like for you to address the issue specifically of studies that are exempt under the category I think of public health practice. Alan, you have actually indicated here study of public benefit or service programs.

One of the issues, I don't know, Harry Hannon sitting in the back there somewhere, at least the study that this committee has been trying to move forward was the issue of looking at the States that actually deal with second screen and whether or not that is of value, and really try to develop an evidence base around that, and there has been a real challenge in trying to move that study forward.

I don't know how many states are actually involved, 12 states or I don't know how many states actually do that, but clearly from state to state, they view that very differently whether it's public health practice or program evaluation versus research, and, you know, trying to address that, trying to do those studies well from this committee's perspective. I think that was the impetus behind this panel here.

I see that as public health practice, that's our coinage in the CDC perspective, but there are what I would consider public health emergencies that occur, public health challenges that occur that we need to address in a rapid fashion, because again we may be doing a specific practice that isn't evidence based, that would err on the side of children sort of being harmed and we need to do that rapidly.

It is not generalizable knowledge, it's really trying to change how we are to evaluate how we are doing things. From what I have heard you say, and both of you say, we need to better equip our states' programs when they go forward with their project to the IRB, to really make a better case that this, in fact, is exempt, i guess exempt research. I don't know if I am making myself clear there.

There is a question there and then just a comment. That was really the impetus behind this panel.

DR. FLEISCHMAN: I think, Coleen, if I were sitting in Atlanta, I would invite all the commissioners of health and the chairs of their IRBs to a meeting to discuss this very important problem.

I would then have a better understanding of what their concerns were after you had presented an approach toward an anonymized population-based, public health practice surveillance program. It is not anonymized, then it's research.

If it's research, then, you need the engagement of the IRBs and you need them to be helpful, you need to hear what their problems are, so then you can figure out how best to do this. But I don't think you have any other solution to that.

But the problem is that we allow individuals out there in those states just like the National Children's Study, we are trying to bolster them before they get to the important place where they are asking the question, so they are better question askers.

DR. BARTLETT: I want to echo some of the things that Alan is saying. When I was the IRB administrator, I saw my role as trying to work with and to assist investigators in order they could do a better job.

For example, I spent a lot of time simply working on consent forms, so they could be simply understood by the typical patient coming in.

But to highlight some of the points that Alan has

made, establishing lines of communication in advance and some of these studies that are more public health types of protocols, they are different than many of the typical protocols seen by IRBs. They don't fall strictly in the medical model, they don't fall strictly in the social behavioral world, so that there are certain wrinkles to them that need thought.

The example of in some cases of dividing a broader study into two pieces in some cases is a very good strategy. It helps the IRB to better understand the different aspects of that, and also just understanding the lingo, the thought process, those are also very helpful ways to better work the system.

DR. HOWELL: Can I ask the panelists a question, it has been commented that many state health departments have not perceived their role to be one in the research arena, and do the panelists have any information about the number of well functioning IRBs that are in the public health sector?

I mean is this an area of -- one of the problems may well be that since it has not been perceived to be a role of public health, that the IRBs are not well established and experienced in dealing with this, I don't know the answer to that question. Ned, you probably know

the answer.

DR. CALONGE: Well, I know the answer in Colorado, so I think that we are involved in research, because it's one of the 10 essential services of public health research to forward the practice of public health, so we have a number of protocols going on at any one time, and we have a very active IRB.

I would like to think that it is acting well since I am ultimately responsible for its actions.

DR. HOWELL: I am sure it is well then.

DR. CALONGE: I think that there probably is variation from state to state. Someone, I think it was Jeff, said the general assembly, the legislature doesn't see our job as research, and that has been pretty clear to me.

They see research as what someone else does, not what their state public health agency does, but we have been able to define it as part of our essential services and continue to do so.

One of the issues that is interesting, though, is that our local health departments -- and I would be interested in this -- would like to use the state IRB, and it is under-resourced to do so.

So, one of the biggest problems I have is I

cannot get general fund support for our IRB, so we have to do it within direct cost recovery and it is a severely under-resourced strategy, so I can't help my local health departments.

DR. HOWELL: Excuse me, Jeff.

DR. BOTKIN: Quick comment about that, too.

There is a lot of resources that are out there, and I think that advanced planning, advanced discussion has been discussed as critical. You want folks putting together the protocol who understand the basic of the regs and are willing to make a pitch for how they think this thing ought to be approved.

I would very much encourage folks to talk to OHRP, and I very much agree with Alan, IRBs are not so concerned about legal liability here. They are concerned about OHRP coming in and shutting down the research at your institution. It hasn't happened much recently, but it has happened a number of times in the past.

So, talk to the OHRP. You may not always get a clear answer if they don't think there is a clear answer to be given, but if they think there is a clear guidance to be provided, that's what IRBs want to hear.

If OHRP says it sounds appropriate to us, then, you have got some substantial power in working with the

IRB about that interpretation. Ed may want to comment on that.

DR. FLEISCHMAN: The other thing is, Coleen, I don't know your research project, the devil is always in the details, but my argument would be how much do you need non-anonymized data, can you create the answer to the question or part of the question without having to do what you think you have to do.

So, is the perfect the enemy of the good or at least the adequate, and if you have some information, is it better than none.

So, I mean I think, you know, you really have to decide at what level you are going to -- what your needs are and what your research question is, and what does it require.

DR. HOWELL: We have Chris and then Sharon.

DR. KUS: Alan, you presented the cases, the California and the Massachusetts written consent and oral consent. Can you, given that there is going to be a lot of use for pilot studies in newborn screening, expand more on oral consent and the viability and what constitutes it, is there a definition of it, all that kind of stuff?

DR. BARTLETT: I am going to answer it in a regulatory way. So, when we say oral consent, we are

saying one of two things. We are saying either we are going to waive the whole consent, the regulatory requirement for informed consent, which has the criteria that we are presented, or we are saying we are going to waive the requirement for documentation of the informed consent, which is actually different criteria than are here. They are in Section 117, if you want to look at it.

So, you can reach that objective in two regulatory ways, waiver of informed consent overall or waiver of simply the documentation. They are different criteria to achieve that.

That said, you can waive the regulatory requirement for informed consent, but that does not preclude you, however, of providing an information sheet, of doing an oral explanation. You can still do those things even as of the regulatory requirement for the full informed consent.

The question is, isn't this a local IRB interpretation, well, I guess it is always a local IRB interpretation if I get the gist of your question.

DR. BOTKIN: I would be clear. I think whenever you are dealing with these sorts of notification, opt in, opt out, you are working within that domain of waiver or alteration, so you have to fulfill those criteria.

The IRB may say you don't need to do anything at all, zero, or they may say we want you to bend over backwards and make sure folks are educated and have a brochure, et cetera, but that is working in that gray zone between nothing and the requirement for consent.

DR. HOWELL: Sharon.

DR. TERRY: So, it is clear identifiability is one of the crux issues, and I wonder -- and this is a question for any of the three of you who have thought about this -- with regard to population-based newborn screening kinds of research, the paper last fall from

Craig, that talked about identifiability even in small amounts of DNA in pools, caused NIH to move its GAIN data, the Genetic Association Information Network data, behind a firewall, which they had previously put in front of the firewall and thought that it was de-identified.

What does that do to this kind of research, as well as the considerations that IRBs will make given that paper and the reaction of NIH?

DR. BARTLETT: We are really aware that NIH, in fact, NIH came to our office to discuss that. The regulations say readily identifiable, so in our view, even with knowledge of that particular study, that doesn't meet the threshold of the information being readily

identifiable.

DR. HOWELL: Thank you very much.

We have some patient folks at the microphone.

Anne.

DR. COMEAU: Thank you. I have one comment and a question. Alan, thank you again. I want to echo your idea of bringing IRB people together. I have never really understood why the Massachusetts model hasn't been replicated more successfully. One of the things that we don't necessarily talk about a lot is the work that we did ahead of time in pulling together meetings of the 55 hospital CEOs and IRB chairs to educate them about what it was we were going to do.

After having reviewed cost volarity protocols with the two IRBs that you had talked about, after that meeting the IRBs, they were told that, of course, you know, per regulation, they had to follow our IRB protocol and they could make it more stringent.

We made it very clear later on when the couple of hospitals who made things more stringent tripped and got sued because they had made the protocol so complex. In population-based settings, you have to have protocols that will work.

So, we had an oral consent protocol that

everybody needed to follow and a couple of hospitals decided that they wanted to go the extra line and have those written consent protocols da-da-da-da, and then when the parents call up and say I didn't want this, and I have all these papers that I signed and signed and signed, but somehow what the signed in the hospital's protocol didn't get transcribed onto our protocol, and their child was screened.

A couple of those hospitals were actually sued.

So, that was something that we also went back to the IRBs and educated them that the protocol that everyone had kind of agreed to was pretty good. It wasn't perfect, it was a compromise, but that they could actually get in trouble by making it more problematic for their staffs.

The last thing is although it is not regulation,

I think we also need to keep in mind the idea of consent for consent's sake, and consent for education, so, Jeff,

when you talk about the 200,000 screens and do you need to have consent, I think you are suggesting a model where you don't necessarily have to have consent for the screen, but you would consent at the time where you want to go into medical review.

As a parent and consumer, I have to say I don't think I would like that surprise. I mean if I am told

ahead of time that by participating in this low risk research, I might get a call, and then I get a call, it's like, well, you know, of course, I am going to be nervous about the call, but I have been warned ahead of time, and I think that there is a public trust here that we need to keep in mind that it is not necessarily the burden of IRB regulations, but is something that will help the public to allow us to do the kinds of research that we need to continue doing. Thank you.

DR. HOWELL: We need some brisk comments from Nancy and Joanne, and so forth, because we go to our break soon.

DR. GREEN: I won't keep us. I want to address Alan's message about plan ahead, that if the IRB bounces it back, in some ways you are too late or you are where you don't want to be.

To identify another resource for the Translational Research Network, just to remind people that the clinical translational research centers funded by NCRR, at this point are involved at 30-odd institutions and are quickly expanding and many of those awards to major medical centers where much of the metabolic centers exist, also have structured research contracts or agreements with community hospitals and other

institutions, so I think that spread of this CTSA network is large, so at least within the pediatric part of the CTSA, and I suggest you may be part of this now, there is an IRB consultation service.

It doesn't have jurisdiction over the IRBs, but it does provide consultation for specific or generic questions for investigators or groups of investigators where they can pose a question and get some professional help ahead of time before submission to the IRB, so that is a resource for that translational network.

I would like to identify that committee is chaired by Alex Kahn at the University of California.

DR. HOWELL: Thank you very much, Nancy.

Joanne?

DR. BAKER: It's Mei Baker from Wisconsin.

I just wanted to introduce anther model -- I don't know, it's not a model -- U.W. Madison, we have what is called institution research. Their funding is like $40 million to do a lot of different things. One thing they did is in Wisconsin, major university and a hospital, the IRB get together and they come to some -- I don't know the details -- the idea is in Wisconsin, any research, multi-factor research, their IRB office is accepting any offer, they already work out beforehand. I have

collaborated, I submit to IRB, and they don't need to do

anything, because they are already -- so I don't know if this model will work here if we do newborn screening research, all the different states, you know, can do a similar thing.

DR. HOWELL: Thank you very much, Mei, and thank the panelists for a great thing. Before we go for a break, the Committee has received the modified letter on medical foods you have at your desk, that Coleen worked on very hard. There are a few very small additions that have to do with the exact definitions, the State health department thing.

DR. LLOYD-PURYEAR: On the last recommendation, we need to, after for Medicaid coverage, include the words in the State Children's Health Insurance Program, so that that is part of the coverage.

DR. HOWELL: The CHIP just got signed.

DR. DOUGHERTY: For clarification, the law actually changed the name of the program to CHIP.

DR. LLOYD-PURYEAR: State is not there anymore?

DR. DOUGHERTY: State is not there anymore.

DR. LLOYD-PURYEAR: Also, just to note that we will need to include in other enclosures the recommended

screening panel from this committee, the medical foods that are required for those conditions, and references to justify the medical foods.

DR. HOWELL: Read this carefully and we will vote on this, because we will send this forward to the Secretary at the conclusion of this meeting.

We will now break and return shortly.

[Break.]

DR. HOWELL: Ladies and gentlemen, we are going to resume. We have a busy residual part of the morning and we now are going to hear a presentation on the Residual Blood Spots: Policies and Uses.

We have presentations from Harry Hannon, who as you know has retired once again from the CDC, and is spending time at the current time at the University of Texas Health Science Center at the Newborn Screening and Resource Center with Brad Therrell, and he is going to discuss his work on storage, retention, and use of the blood spots, and we are going to have some comments from Jeff Botkin as he proceeds.

Harry.

Residual Blood Spots, Policies and Uses

DR. HANNON: Thank you.

Actually, I retired on January 2nd, went back to work at CDC on January the 5th. It is supposed to be a short duration. Actually, as someone told me one time, I am a three-time loser. I left CDC three times, but I am still there.

I would like to give you an overview. This is a very complex and sensitive topic to be discussing. It is also a very hot and timely topic. We have about 15 minutes or so to capture the essence of the snapshot that I am going to present.

I put a little overview here, and as I go through the presentation, I hope that you can capture the root messages that I am trying to put forth on the table. If you don't, you can ask questions at the end.

We plan to cover the storage issues, retention times, uses of residual blood spots, restrictions, policies, and then a very hot topic, controversy media and parent involvement.

Then, the issue that Mike Watson put on the table the other day, of biospecimen repositories at a national level, which has already been addressed at least once at

Reading this paper again after it was written by
the Committee for the old CORN group, this was a very good
paper. I didn't realize at the time we were putting it
together how good and timely it was, but if you will take
this paper and read back through it, you will find out
that at that time, this is about 12 years ago, we captured
all the essence of the issues around stored specimens, and
made some recommendations.
As you will see through the course of the talk,
there is a lot of recommendations been made across time.
Somehow we just don't know if anyone is listening.
We made recommendations about the fact it could
be a DNA bank and for use for investigations of
epidemiological new disorders, a lot of different things
were addressed in the paper.
We made recommendations on how best to store
them, we talked about stability issues and how you should
retain them, and the issue was that if they are valuable
specimens that everyone claims they are, then, they must
be treated a valuable specimens in terms of the storage.
A lot of the analytes are not stable, so you have

to be very careful about what you are planning to look for
in the spots you have saved, but DNA is very recoverable
and it could be robustly amplified from the dried blood

spots, even 10 or older, year older spots work quite well.
This is a snapshot of how long specimens are
retained by the different State screening programs, and
you can see by looking at the migration of the green,
purple to the red, there is a transition toward longer
retention of specimens across the nation.
You can also see by looking at it, there are some
odd times people keep specimens for no rational,
understandable reason. You see there is a 4 month, there
is a 2 month, and a 1 1/2, and then there is an 8 month
instead of going to 1 year, so I mean it is really weird
on how some of these time intervals are selected.
I am sure that the program is out there on
justification for those times that were selected, but
there has been a large movement toward indefinite storage
and some of those are migrating through the 5 to 23-year
period.
Informed consent or just consent issues or
transparency or educating the parents about what is going

to be done with the specimens, I made this slide, and this
actually comes from the California brochure where they
have in multiple languages, but as you read the little
statement that happens to be on the front cover of the
pamphlet, which is about 15-pages long, just by accident I

put the Chinese below, not realizing after I looked at the slide that when you read the last -- it says request in writing, may not be used by contacting person written below.

That was in Chinese I guess you could figure that out. It is below that, but really in terms of the information you provide to the parents, that is essentially what you are giving to English-speaking parents, something they really can't comprehend or know what you are going to do with it or what is going to happen to it. It is just by accident it occurred that way. I didn't plan it.

There is lots of reasons for retaining residual dried blood spots, one that we talk about for long periods of time. One big issue has always been legal accountability, and early in the game we were told by I think her name was Lori Andrews from the American Bar it is just best that get rid of the samples, they cannot help you, they can only harm you if you get into a legal battle about a delayed diagnosis.

Future DNA testing is where we have arrived now, but the first one is part of the reason about some of these one-month, six-week storage issues.

Reconfirmation of newborn screening analyte

results if you do them in a timely process. New method evaluations, comparison, epidemiology, Alan Fleischman talked about the HIV and the pilot studies that were done, for about 10 years we did the HIV seroprevalence survey, special health register, these are patients and families, birth defects, other issues, murder, chicken baby syndrome, all those kind of issues.

This is all in that original guidelines paper in '96. These are some other reasons from the Journal of Law, medical ethics in 2004 These are some of the same issues that we discussed in '96. Confirmatory diagnosis, quality assurance, research use, clinical testing, postmortem, disease causes, non-medical use, kidnappings, deceased persons, paternity, criminal ID investigations, lost child.

These are some examples of previous uses of spots. One, the diabetes type 1 risk, autoimmune, disease onset, assay consented to ask whether they screen the baby. This is the first flip-flop of genetic testing followed up by phenotype testing, which they screen the babies for genetic risk by consent, and then they follow up for the disorder diabetes.

Searching for early markers of disease. They are doing some of that with fragile X, trying to find a better

marker, surveillance for a lot of different issues,
autism. Allele frequencies for public health assessment,
understanding hearing loss, COD connection, searching for
frequency of deaths caused by SCID. That is a CDC study
where we have 2,000 samples and matching controls for all
the children who died under 18 months of age to look and
see if any of those happen to be were caused by SCIDs with
the tracks assay.
Environment exposures, the existence of these
banks have also sort of driven or a repository system is
driven the other way, that they have widely known they
exist now, so everybody is figuring out what they can
measure out of blood spots, and then how they might take

the samples away from the program and do their research
investigations for these markers that might contribute.
I don't say that that is not valuable, but I
think sometimes the State programs and their retention of
these samples and work and effort and resources that go
into them are somewhat lost in the old process, that the
secondary applications which are part of the screening
process that come to exist, I don't just think the State's
investment into those repositories is taken into
consideration.
Then, of course, quality assurance that we have

the case specimen exchange, which is a very important companion to all the proficiency testing, and there is a rotation of positive case samples from lab to lab, which helps overall quality assurance efforts.

This is what I was talking about just a few minutes ago, and the fact that these repositories are known to exist, people begin to think about how can we use them in the benefit of public health, and here is a list of genomic needs that have been identified for using these repositories, evaluation of genetic tests, gene environment, gene-gene interactions, those are all

important questions we would like to know and understand, the prevalence of gene variation in disease. They are all important, I am not trying to underestimate the importance of what the spots are used for.

We saw the 1996 paper about the idea that there needs to be consent, we need to store them a certain way, we need to be open and transparent about the fact we are saving them. We need to educate folks and we identified all the reasons. We talked about legal aspects about ethical issues associated with retaining the samples.

Blueprint for the future. You can see there that we needed to develop policies for late and unlate residual samples and research, dried blood spots.

We needed to organize collaborative efforts to develop minimum standards for storage of residual samples at State levels. We needed to consider creating a national or multi-state population-based specimen resource of research, back on Mike's biospecimen repository that doesn't come with a whole big set of problems.

Then, we have the APHL position statement 2005, which talks about the need for standards in national consensus policies that State Departments follow in carrying out the authorize programs.

In the beginning paragraph there it says APHL supports the development of national consensus policies, procedures, and standards for retaining residual dried blood spots following newborn screening analysis. This is about the third time we have talked about guidelines and policies.

Here is a controversy. Media, parents, all creating noise because we don't have transparency, we don't have openness. We have no effort of assurance of privacy protection, protection for discrimination, and informing them, educating them on what these samples could be used for, how potentially they might harm, or any of those issues that are not addressed in our efforts to inform the parents that these samples are being retained.

This is a nice, interesting article that came out. It was a photo cover of Discovery in July 2003, which says now the genetic testing really begins, a source with a single drop of blood taken from each newborn, and ends when scientists predict everyone's physical and mental future.

Then, you get over and they talk about finding terrorists and other folks, you know, but they are not screening for blood spots. You know, it gets really stretched out in terms of urban legends, and so forth, that can happen. So, you have got the parents reading these somewhat semi-scientific articles and issues you been hearing about blood spots.

The next one is the newborn screening storage law -- this is Dr. Rinaldo created this one I guess with his colleagues in Minnesota, but this article is talking about the new Act, Newborn Screenings Saves Lives Act.

I got a call from the staff, I read this thing numerous times. I never found anything in it about the fact that we were going to retain these samples, not even any mention about storage or residual specimens after screening.

They take this committee to task, it says that this committee is self-serving, they are all researchers,

they are all interested in assuring that these samples are stored forever, so they can feed their samples to their research friends. Those kind of things are really derogatory to all our activities especially when they come out in a late article like that. This is 2008

Jump back just a minute to 2004 This is an article in JAW, Journal of Law, medical ethics, winter of 2004 They talk about some issues around the modern controversy which is now even more modern.

It says that there need to be rules for properly regulating biobank, should be transparent, open, should have supervision, should have supervision, someone a gatekeeper, should have strict rules for scientific studies and adherence to them.

Should have informed consent requirements. We need to gain the public confidence and participation in what we do with these samples. It is critical to our efforts, that we need to develop model -- participation of the public is critical in what we are doing.

We need to have a model consensus forms, we need guidelines for appropriate research use of these samples. We need education material for parents, safeguards and ethical reviews in place. So, it is not something we haven't talked about since '96 and in 2000 blueprint.

This is very recent. This happened Sunday, February the 22nd, 2009 So, it is not an old topic, it is not going away in the media, and they talk about the same issues and things without parents' consent or possible use of medical research.

Keeping them indefinitely, they have 4.2 million samples, de-identified in a storage facility at Texas A & M. I am not sure about what conditions they are stored under. I do know that there is DNA transfer from specimen to specimen by contact. I know that the CLSS standard LE4E5 says that you should store those at 180 degrees to each other, however, looking at the process in a paper that is coming out shortly from our lab, if you rub spots together, you can get DNA transfer, and it can be detected by using forensic [ph] methods.

We even looked at transfer of male chromosomes to female spots and male having CF transfer. We looked at the transfer, Delta 508 from spot to spot. There was some transfer, but it did not interfere with the CF method, so you need to be cognizant of this potential possibility in terms of the way the samples are stored. These are some 10-year-old spots. Take that into consideration when you look at our methods, however, we have not found any interference although we can demonstrate by using

ultrasensitive methods that there is some DNA

contamination.

In 2002, after a short survey that we estimated, this was sort of created by the newborn screening blueprint for the future that we had this meeting, and address strategic plans to look at the multi-state banking of residual newborn training blood spots.

Objectives of the meeting. We will bring all the partners together to talk about the potential use of banks that are of value, how long they were stored, how they were stored, database issues, and multi-state models for the future, feasibility issues, barriers, status of State storage, uses, policies, and design strategic plans for banking implementation.

The last bullet never got achieved. I am not sure exactly why. Part of it might have been I played Dodge Car with a vehicle in D.C. and lost.

There is wide summary of the State policy data. This was a survey done by Richard Olney and myself and others. It was an electronic survey design about 17 questions. It was implemented by APHL to all the lab directors, and this is just a brief summary, 45 of the States had written guidelines concerning the use of the

residual samples.

In the '96 paper, we didn't even talk about storage conditions, use of. We talked about disposal and how you appropriately dispose of them. We have in existence rules and regulations and policies which say we will store them 6 months and dispose of them.

If you look on some of our slide reviews, I ask questions about when you dispose of them, and so forth, it is not very well adhered to. They keep them and then it takes resources and staff to follow up the other end, so they have a policy, and disposing of them is not as strictly enforced as the indications are made.

Nearly 80 percent of the States favor future storage of identified samples at the State level, 16 percent informed parents. You saw the example of an informed parent. Small sentence in the middle of a lot of other information, and they can contact somebody in writing.

This is actually from the first survey, not the second one. After we had the meeting we did a second survey to update the data, and the previous slide was based on the second survey.

This is asking the States what they thought about assuming someone would pay for it, could we build a national repository, and you can see overwhelmingly there was little desire to move them from a State level.

Our challenge is, of course, in terms of pursuing this national repository or any other virtual repository, which I think Anne generated that word at the meeting in Atlanta was a virtual repository, and we discussed the data based around that, but I think that was her contribution to the theory.

Noisy meeting, because it got real touchy and there were a lot of vocal representatives there who easily shared their feelings.

We need resources, data sharing issues, IRB ethics reviews, legal-ethical social issues, informed consent issues whether we educate them or we get signed consent. Educational efforts of parents and others, but we must always remember in this process that we are talking about secondary applications, not primary applications, what do we do secondarily must not impede upon the primary purpose.

That was a big issue with the HIV seroprevalence survey. We had to convince everyone when that survey was

done that these samples, they cleared all the primary responsibilities for that specimen, and then we applied the secondary applications. That was very critical to get in the buy-in for that national seroprevalence survey.

Outcomes. Was develop a strategic plan for a virtual database of available specimens for research use. There was a large agreement to the fact that we could create a virtual bank and the states were the stewards of these specimens, were willing to participate when the idea and project and public health issues were put on the table to justify there was such a study.

Here is the issue going back to the Journal of Medical Law established a central gatekeeper. There has to be some supervision. We have to convince the general public that we have safeguards in place to warrant their trust as recipients and storage of their specimens. We have to convince them that they can trust us, and that is hard to do coming from the government.

Develop consensus standards to storage, QA, cataloging, retrieval. Some of these you would invest hundreds of thousands of dollars to find two specimens based on the way they are stored. You would have somebody spend days in some hot or cold place, trying to go through bags of specimens to find these. There is no systematic

way. They are thrown in a bag. They might know the day, they might know what specimens are in there, but then there are a lot of specimens, once they find a bag, to go through. There are some days they do a much better job at this, but it is not a nationwide investment.

Plan pilot studies. This is to demonstrate usefulness. I think we have done enough pilot studies to understand they are very useful. Address the gaps in feasibility issues. We need larger stakeholder meetings for buy-in, we need to get them all together. Ideally, we need dollars to buy them. That is what it should say, buy-in, we need to buy them.

Core thinking. Still need for development of State policies on retention, storage, and use. We started out in '96, 2000, I don't know how many times we said storage and policies. APHL 2005 We do have them. There is a difference between having and adhering. There is a difference between having consensus opinion on them and using them. Anybody can develop them, but they become personal. They don't become consensus agreed upon by all the stakeholders.

So, if we are going to develop policies, we need stakeholder buy-in and agreement, and the NIH funding, as Duane talked about that yesterday, that's Mike Watson's,

the database, biospecimen repository. We can build virtual specimen databases for use in conjunction with long-term outcome databases. It is possible.

I think using the database with specimens makes this a small valuable. States are interested in collaboration. They just want real partnerships, they want to be at the table, they want to be heard. They want their time and resources, they invest it, understood and felt. They are not against valuable public health studies that benefit all of us.

There is a tendency about in the States and a lot of places that refer to these original specimens as records for policy implementation. These are actually patient records, and that is what the article from Texas states, that these are patient records because they have all the demographic spots that are attached to them, and so forth, that they could be considered as patient records, which come with restrictions about disruption.

Thank you and as you see the root message is we talk about standards and stuff about policy, we talk about informed consent, we talk about consent, we talk about education. We talk about the value of this committee and the contributions. All we got is talk. Thank you.

DR. HOWELL: Thank you very much, Harry.

Dr. Buckley has a question of you.

DR. BUCKLEY: Could I ask how many States consent for the parents when they obtain the dried blood spots?

DR. HANNON: Consent?

DR. BUCKLEY: Uh-huh.

DR. HANNON: What is your definition of consent?

DR. BUCKLEY: Well, they check something on the card.

DR. HANNON: Well, I think South Carolina has a check box that you can opt out.

DR. BUCKLEY: Doesn't Maryland also have a --

DR. HANNON: Maryland removed theirs. I talked to Maryland. Maryland had a statement -- Maryland actually asked for consent on newborn screen, and had her statement below the signature that we would retain the sample, had the parents sign that.

DR. HOWELL: Harry, the mike.

DR. HANNON: They just recently removed that statement from that consent point about retaining the specimens. They planned to go to descent screening that you have to opt out in the near future. That was according to information provided Friday.

DR. THERRELL: Wyoming does and D.C. does, and Maryland is just changing theirs, so there were three, and

then there are these pilots that have started up with something.

DR. HANNON: The pilots will come under a different IRB restriction, but, in general, it's a very weak consent process.

DR. BUCKLEY: Well, the reason I asked the question is wouldn't that be something that this committee could recommend if we are talking about transparency and the future use of these, that maybe we recommend to all States that they inform the family and that they had to have a choice of opting out if they want to, to have either newborn screening and/or retaining these for future study.

DR. HANNON: The Journal of Law, Medicine, and Ethics said that we should not only inform them, we should give them an educational brochure which alerted to them of all the potential and possible use of ways that harm might come to them by agreeing to or consenting to having these samples retained.

The second reason is that we should get consent.

Go ahead, Brad.

DR. THERRELL: I think Jeff is going to cover this, but there are I think four States that you can't opt out for any reason.

DR. HANNON: Can't opt out of screening we are talking about. We are saving, secondary applications, you can't opt out of primary applications, but there is very weak or issues and things going on in terms of opting out or opting in even for secondary applications.

I don't know what is in Jeff's talk, so I should wait to hear it. I saw his slides, but I was afraid to read it, because I might talk too much about what he is talking about.

DR. HOWELL: Why don't we move ahead and hear from Dr. Botkin who is going to address some of the issues on the same subject, and then maybe we can have some additional questions.

DR. HANNON: Sorry about not talking into the mike. I am old, stubborn, and difficult.

[Laughter.]

DR. HOWELL: Well, at least you are truthful.

DR. BOTKIN: Thanks again.

My comments are going to mostly reinforce a number of issues that Dr. Hannon raised, and then I am going to tell you a little bit about a project that we have discussed starting to address at least one aspect of this very complicated domain.

So, talked about this already, reasons for

newborn screening, specimen storage, and I won't go through these, so I think the research arena is the one that I am primarily interested in talking about. I think these other ones are not research, and I think generally are fairly straightforward from an ethical and legal perspective with respect to the department's ability to conduct these sorts of things. Obviously, forensic use is usually required, legal collaboration around issues that they may be applied for.

So, I am primarily interested in the research domain and making the obvious point that the research may be related to newborn screening or it may be related unentirely.

We had a local genetics company 10 years ago that was looking at our residual newborn screening samples for the prevalence of BRCA1 and BRCA2 mutations for example, and obviously, the type of research is becoming increasingly common, and our department is certainly getting an increasing number of requests to access the samples that we have stored.

Our department is also actively engaged now in evaluating heavy metal exposure of women prenatally, and one of the beauties about the use of the specimens anonymized is that you can retain geographic locations on

those and see what communities may be exposed to environmental agents or even viral agents as was the case with HIV, and that was one of the key outcomes I think of the HIV prevalence studies years ago was not only the general prevalence within the State, but where the infection was more prevalent or less prevalent within the State populations.

The terminology here, and I think this is a big problem in the field in general, identifiable specimens or what I am calling the identity of the tissue source can be determined by somebody. I will talk a little bit more about this. Linked or coded specimens I will refer to as identifiable specimens, so the key here is that somebody has got the key and somebody can figure out who the specimen came from.

Deidentified specimens or anonymized specimens, no one can identify the tissue source, and I think that you will see sloppy use of this language commonly, and this is my at least going definition for the context of this particular talk.

As we talked a little bit earlier, 45 CFR 46 states not readily identifiable as investigator, which is a pretty low threshold for deidentification. HIPAA is more stringent, but given the fact that HIPAA often

doesn't apply to public health enterprise, it may not be relevant to some of the work that we are discussing today. So, what are the advantages and disadvantage of so-called anonymized specimens? I would say this is the most straightforward and most common form of research that we are aware of with the use of residual specimens. A number of pros to anonymizing or deidentifying the specimens are obviously the valuable research. Research does not involve human subjects under the U.S. regulations, and therefore requires minimal IRB review, not absent IRB review because generally IRB is the one that makes the determination about whether it's exempt or not, and IRB likes to review the deidentification process. So, if you have got samples that are currently identified, and you want to put them through a deidentification process, the IRB actually wants to know about that process to make sure that it is robust. So, obviously, no consent usually necessary for anonymous use once they have been anonymized, because who are you going to talk to, but consent may be appropriate for the collection and storage to begin with. Well, what are the cons? Unable to link with health outcome of the child, and I think this is a big deal. It cannot discriminate FALSE positives, FALSE

negatives, so you can't discriminate the spectrum of clinical manifestations of the disease, and you are unable to contact families with potentially beneficial health information when you have got it.

How about linked or identifiable samples, pros and cons, there? Pros, they are really the flip side, health tracking possibly, you can figure out how your specimen result correlates with the clinical outcome of the child.

Return to health information then becomes possible, and that is an active debate with research enterprise in general now, when it is that you should be returning results to individuals, but obviously, in certain circumstances it can be critical for the health of the child.

What are the cons? IRB review and oversight necessary, informed permission may be necessary, which to some extent undermines the value of having the specimen already, because it may require an enormous amount of effort to go out and contact the family, and in that sort of circumstance, it may be possible to get a new blood specimen if you are already working with individual families. You understand the distinction between having a blood spot, though, and perhaps a later specimen.

Return of information may pose a risk to the

child or the family. It may not always be beneficial to return information if, in fact, the information is not accurate or people make decisions that are a misinterpretation of the results, et cetera.

Now, here is the OHRP guidance from 2004, and I think Alan had gone through this in a little bit of detail this morning, so this is my iteration of that same set of guidelines, which I think is a big deal in this arena, and I am not sure IRBs are consistently aware of this particular set of guidance.

So, here is the setup. Investigator A obtains tissues conduct of research, banked with identifiers. Investigator B obtains specimens from A, but without individual identifiers. So, the specimens remain linked, but the key is held by Investigator A. So, Investigator B can't figure out who these folks are.

Now, if Investigator B signs an agreement that she will not seek the identities of the tissue sources, then, Investigator B is not conducting human subjects research. So, that is a big deal.

I have some disagreement with this. I don't think it's an inaccurate interpretation of what the rules say,

and I do think that that probably adequately protects subjects in many circumstances, but note that this does not prevent information from getting back to research participants.

It may well be that Investigator B says, well, look at Specimen 487 as a mutation that this person ought to be informed about. Tells Investigator A I don't know who this is, but you had better think about talking to No. 487 here, and then the subject says well, who gave permission for them to be doing that kind of work.

Now, it's all hypothetical, I don't know that any instances of that occurred, but it prevents certain types of arms to subjects, but does not prevent potential difficulty of returning information to folks about research for which they did not provide consent.

I think the NIH has been a little reluctant to use this guidance in some of their guidance of research nationally.

DR. CALONGE: So, I assume that this went through public comment period and before it was accepted as guidance, and it would be very interesting to see whether or not that was a good rigorous system, because I could

see a lot of people looking at this thing, that's not what we thought you meant.

DR. BOTKIN: I can't speak to that. I don't know whether Ed knows about how that process worked, but generally, OHRP is pretty careful about the whole process of issuing guidance.

DR. BARTLETT: So if it's guidance that represents a significant departure for a significantly new interpretation of something old, that would go through a formal notice in the Federal Register and review and comment. In contrast, for example, a frequently asked question type of thing where there is no new ground being plowed, that would not typically go through a review and comment process.

DR. BOTKIN: This guidance also doesn't state who oversees these agreements, make sure that they are properly drafted, stored, reviewed, et cetera. Our IRB has taken that on, but that's not required by the guidance itself. So, this I think is a very interesting set of guidance that could be enormously useful to research in this area.

So, they were in screening, as we have stated,

two States and D.C. have permission process, so there is

no infrastructure in place for obtaining permission for research. Opposition to permission by public health and nursing personnel I think for the most part the general attitude out there is we really don't want to move to a newborn screening consent process in general for the reasons that were articulated and illustrated by the California study, talking about, well, we will get to that.

So, acquired permission for retention of sample for research purposes. There is a question mark there. We have been discussing that, acquired permission for research use. So, I think there is two levels of potential permission that we are talking about here, and with the permission address research specific to newborn screening conditions alone or would it be a broad authorization for other research uses.

What I am setting up here is the complexity of the conversation that if you are going to have a meaningful dialogue with people about these choices, and I think as Dr. Hannon said, you are already getting well beyond what might be easy to convey in any sort of concise

conversation with parents and really have a meaningful dialogue about the pros and cons and the risk and benefits that would be associated.

So, here is what the task force said for use of these specimens. For use of unlinked specimens, can retain demographic information, IRB review ought to be conducted for epidemiologic research, but no consent would be required.

If identifiable samples are going to be used, IRB approval should be obtained, general permission should be obtained, questions should be asked by the IRB and others about whether this is the optimal source of tissue for the research, whether there is unidentified samples that would not suffice for the conduct of the work, and whether acceptable samples might not be obtained from consenting adults for the research.

So, here is one of the central points I wanted to draw out. This issue of community consent, and I have consent in scare quotes here, because I don't really mean consent. There are some communities that have formal procedures whereby there is authority, travel IRB, for example, and out-go IRB can give formal permission for research to be conducted within that community. Many communities don't have such a structure, so I am using the consent term here loosely and what I really mean is community engagement dialogue, some sort of deliberative democracy process that will engage the public in a

meaningful way.

What I see is a conflict between the individual consent model and the public health model. I think we have been talking about that issue quite a bit today.

The individual consent requirement in the process undermine the public health approach, and I think increasingly with research, what people are tapping into are large databases, large sets of tissue repositories, to look at population level issues, large numbers of individuals, and I think there is a serious challenge in trying to shoehorn research at that level into the individual consent model, and in part because the individual consent process itself undermines the object of study.

What you are trying to study in the newborn screening environment is the system, the entire set of procedures from sample acquisition to diagnosis and treatment, et cetera. All of those links in the chain are essential parts of that research assessment, if you are going to really assess the program per se, and because individual consent is not a part of newborn screening programs, clinical programs, then, if you insert that requirement in the research context, then, you have biased or altered the object under study.

So, the question, can we remove the burden on the individual consent model, which it is not designed to sustain, and I would say the California model and the Massachusetts model were excellent in terms of illustrating some of the pros and cons here, but none of those processes I would describe as a robust dialogue with people where they had a thorough understanding of the choices they were making.

Perhaps many parents did, but I would guess that many parents didn't, very different from the kind of research consent that we normally talk about where you really want to have a robust dialogue with folks, so that they are making an informed choice about whether they want to participate and what is going to happen with themselves and their sample over time.

I don't think that is feasible in this context.

Now, we note that there is a parallel in the regs, and I am going to rely on this, the emergency interventions permit a waiver of consent.

It has some similarities here. When you have got an emergency circumstance, you can't have a meaningful dialogue with folks about their participation, so you simply drop the consent requirement. The answer has been no when you don't have an individual consent, but you have

to have a level of community disclosure and consultation before you can conduct that kind of work.

That didn't work very well in my experience, but that doesn't mean that it can't work there. It just means that there is a model out there that says if you are going to do this, it ought to be in the light of day. The folks ought to have an opportunity to think about this and make informed decisions at least at the community level if not at the individual level.

So, here is some policy considerations in this domain. Public dialogue and the value of retention and research use. There is no question this is a sensitive issue and I will highlight this again a little bit later.

Substantial funding needs obviously public dollars going into this enterprise and a question about whether to restrict use to research purposes related to children. These are being acquired under mandated testing by the State, and therefore, the logical question might be does that imply that research uses ought to be directed towards the welfare of children as opposed to other members of society.

I personally think that that is a requirement, but I think it's a question to be addressed.

Notification not the option for research use at

the time of education for newborn screening. Again, it's a policy consideration here. I think these are essential elements, but I wouldn't call them informed consent. Affiliation with the IRB protocol reviews obviously, and then this last one, which I don't think we touched on quite yet, which is the process for prioritizing access to limited sample source, and this is not something that IRBs typically care about, but you can only get so many punches out of a spot. Maybe you want to do a snip chip analysis and save the data, but for the most part you have got to figure out what is the priority that you are going to use for these samples and understand that choices have to be made at that level as well.

So no question need for a newborn screening research. The availability of effective treatments does not mean an early detection will be beneficial. I at least find that too often the conversation is focused on whether or not there is an effective treatment and what we really are talking about here is that is really detection work compared to later detection, clinical detection I think is really the key question here, and at the point being made newborn screening is a system with many links in the chain from screening to the beneficial outcomes and

the assessment ought to not just look at the test and not just look at the treatment, but look at the system, how it deals with these results.

So, here is a proposal for one type of testing that may be familiar to folks here, but let's see what you think.

Use of residual specimens in program assessment.

An approach is potentially applicable when a new newborn screening test is being introduced, so you think it has got enough data behind it to initiate a broad scale program, but you want to assess that prospectively.

So the idea would be to retain residual specimens if you haven't already for a several year period of time prior to the implementation of the new test population wide, analyze and retain specimens retrospectively.

This is the unscreened group, what you are trying to identify is which kids would have screened positive with your test in the specimens that have been stored, identify and track those children to the extent possible who screened positive and compare the health outcomes of those kids with the children who are prospectively identified through the implementation of the new screening intervention. I hope that makes sense.

So, this approach avoids detection by preparing

screened population with an unscreened population. An unscreened population typically is enriched with kids who are more severely affected. Screen population has the full spectrum of kids who are going to show up on your tests, so if you prepare the outcomes of those two groups straight away, screening is going to look pretty good because that population has been diluted with less

severely affected children, when, in fact, screening may not have had any effect at all. It's an ascertainment bias issue.

Secondly, the consent process undermines the validity of the study. The system is the test article and newborn screening programs do not include consent. If you are only getting 40 percent of folks and there is a bias with the communities and socioeconomic groups and ethnic groups in terms of who permits or who consents to the research, and you have got a significant bias in your assessment of the program because it is not a population wide program any longer.

So, this isn't a feasibility question. I think the feasibility problem is substantial, but this is a problem about the validity of the study outcome and the consent process can undermine the validity of the program assessment, and, of course, it avoids the large challenge

of the permission process for potentially thousands of parents which again I think you can get a signature on a piece of paper.

You can't have meaningful dialogue with that many people and really have robust decisionmaking, so move from a camp over the years, one that thought that consent was a good idea for newborn screening to the camp that says if we really think meaningfully about what this entails, we are kidding ourselves if we think a signature on a piece of paper is doing anything other a legal liability check.

So, here is the wave of criteria. I went through these before, minimal risk, rights, practicability, and then information later, and I want to pick up on this here.

My contention -- I am hoping not to lose my ethics decoder ring on this -- but here is my contention. Retrospective screening for genetic metabolic condition confers minimal risk if several stipulations are met. Preliminary data suggest screening is likely to be beneficial. I think we will skip the example yesterday. It would probably be an excellent example of this. Disclosure of abnormal results occurs through a carefully designed protocol like a lot of the negative impacts of FALSE positives can be ameliorated if you have

careful disclosure of results by knowledgeable individuals, so I think the research protocol can help with that disclosure process. I don't know that there is data to sustain that, but that's my guess.

Consent obtained at the time of the results for subsequent data collection, so the waiver would be for the screening act itself and for the identification and contact of those folks. Any subsequent data collection prospectively would be under a consent model.

Public discussion and consultation over the protocol and public notification of the research, and again I think the critical thing here that Dr. Hannon emphasized, this is sensitive stuff, and it cannot be seen to be conducted under the cloak of darkness.

So, here is a project that we got funded last year by NHGRI that is going to touch on some of these issues. That is sort of the theoretical foundation for this project more broadly, methods for promoting public dialogue and the use of residual newborn screening samples for research through your project, three specific aims.

The first one is to conduct a comprehensive assessment of health department policies and procedures relevant to the retention of the samples and the role of public input on policy development. So, we are interested

in this question of what do the State regs, State

legislation say, but also at a more trench level what do they actually do, because we know there is not always 100 percent correlation between how these things actually happen and what the guidance says at the State level.

So, how are states actually dealing with this particular issue, and has there been any substantive role of the public in that process. I am really thinking primarily about newborn screening advisory committees as potentially a voice that might speak to this issue.

Secondly, prepare responses -- and this is the meat of it -- there are three methods for obtaining public input on the retention and use of the residual samples. The idea here is that this is a very complicated area and if you simply give folks five or six sentences about what the issue is and ask them their opinion, you are not getting very informed opinion. Folks will give you their thoughts, but it's off the cuff, sort of response, and this is a big area with lots of areas, domains of public policy.

So, what we are trying to do is establish methods to give folks a more robust understanding of what the issues are with the retention and use of these samples.

So, we have got three different methods that we are going to use, surveys that will have that relatively brief description and see what their answers are to key questions, focus groups that is a much more robust way of getting dialogue going about the issues and we think sort of gold standard of getting public input although everybody knows how tough it is to set up a focus group, so we don't see this as the answer to public input.

Thirdly, we are going to use this technical approach with the knowledge networks. This is a very interesting research support organization. It has been around for a number of years now that has a statistically representative sample of the U.S. population, and folks either have or have been given a computer, and they will get from us a 12-minute video that will describe issues around retention and use of newborn screening samples, and then answer questions that address that, and we think that this type of approach may be a more feasible way of garnering an informed public opinion about these kinds of issues.

Lastly, going to conduct a regional work group that will include national experts in a variety of domains

here to once again tackle these issues with a more thorough understanding of public attitudes on this issue than I think have been formed prior attempts at policy recommendations in this domain.

So, our initial impressions. This comment has been made a number of times already today, research residual specimens not necessarily a high priority for State health departments. This is actually proving to be a significant issue for our little project here, but it is going to be a hugh issue I think for the translational network for the reasons that are described.

This is not their job, but it has helped some departments, and I think that Massachusetts, New York, and Wisconsin, and California have been leaders in this area, but I think a lot of other health departments don't see this as a priority and will be a challenge to engage them in research use of these resources, and I think as we have seen already with our discussions, people see this as a threat to the conduct of their program.

There is an attitude out there I think specifically with respect to residual samples to say, you know, we are just keeping our head down on this, and we have been specifically told by some folks that we don't

you talking to people about this issue, because they think that it's sensitive, as it is, and they think it is going to provide negative consequences for the efficacy of their screening programs in general.

So, this is a big deal. Members of the public are not aware of retention and use, fairly straightforward. High levels of public and professional concern over the use of residual specimens, and not to presage our results, because we are just getting started here, but we have had a number of focus groups and preliminary conversations, and a fairly consistent reaction is a dropping of the jaw, it's like what, the State is saving what? How is it they are doing that?

So, I think that this is a potential disaster if the public is not more effectively and thoroughly engaged from the beginning of this, and that there is a high level of transparency about this, and ultimately some public sanction that this is an okay thing to do.

DR. HOWELL: Thank you very much, Jeff, and Harry.

I think that we will take just a few questions before we break for lunch. Are there some key questions?

That's a very informative discussion obviously, and certainly amplifies the press that we have seen about the

concern of certain people about these spots.

Sharon.

DR. TERRY: I would very much agree that the public needs consultation and not so much from the side that informed consent needs to be given for these samples, but having seen what a woman named Deborah Peale has done in the health electronic medical record arena for about eight years, so totally confused this issue that the Congress each year doesn't give enough funding to HIT, and now Twila Brase doing the same sort of thing, the effect of these people is quite astounding, and there is no voice on the other side of the picture.

So, that would be one comment I would make, and one thing Jetta Klines [ph] is very concerned about is that there is no voice and we are very much looking to make that kind of consultation broadly.

Then, Jeff, as far as your work, I think it would be really good, and you probably have already done this, but to talk to Genetics [ph] Public Policy Center about their work on biobanking in general, which I know is different than this.

But the issue that arose in their results are essentially that the nation really does want big biobanks and that they are very much interested in participating

across socioeconomic divides, across levels of education, and all sort of things, and they use knowledge networks for their work, so there may be some kind of crossover or marriage between their two studies that would be very informative, because I think it is probably more awareness about the fact that those banks exists, and not so much that they do exist.

DR. BOTKIN: On your first point, I would just say I am guessing that health departments would very much appreciate some set of consistent guidelines, so that they can speak about this, again, limited impressions so far, is that they are just nervous about even talking about it, because they have not had a chance to carefully think it through and develop a policy that they know has the backing of the larger communities, so I think getting a robust statement out there about what is justified will give some reinforcement to folks.

DR. HOWELL: Alan.

DR. FLEISCHMAN: I think it is really marvelous, Jeff, what you have embarked on, and I think it is the right part of the country to do it in, in the sense that it will have most credibility coming from your region. I would predict, as I think you do, that informed public opinion will be quite negative toward the goals of

this issue, and so my question to you is assuming that you learn that the jaw drop is also consistent with concerns that I don't share about the consequences of the potential risks of such work, I mean we have no evidence of real risk, we have theoretic concern about risk, that is to say, confidential issues, stigmatization issues, most of it is theoretical in my opinion, but is of concern to Americans in general.

Where do you think this might go, to a recommendation toward informed consent as part of newborn screening? I mean that has other real risks that we could measure. That is one question.

The second thought. Jeff brings up the OHRP point about deidentified data and whether it is human subjects research, and the Investigator A, Investigator B

issue, which I think is a very powerful way for us to do work with the identified samples.

Jeff brings up one major lacunae in the regulations, and that is, the accountability of Investigator B to keep his promise. He said her, I will say he, because I am suggesting some might not keep their promises.

But I think if Investigator B is obligated to go through the IRB of his institution, and have the

institutional imprimatur, if Investigator B does not fulfill his promise to not seek reidentification, then, the institution can be held accountable, whereas, if we don't go through that process, Investigator B is just sitting out there being held accountable, and when I asked Dr. Collins what he would do with such an investigator, he said I would never give him another grant.

Well, yeah, maybe, but there is no legal authority to behave in that way unless there is some kind of accountability, but institutions can hold investigators accountable in ways that are quite serious to their futures, that perhaps the Federal Government can't because of the lacunae in the regulations.

So, I think as we go through this, that would be an important part that we could recommend about clarifying the Investigator A, Investigator B relationship.

DR. BOTKIN: Well, I think that is well within the prerogative of institutions to establish that expectation of their investigator, so it is not require by the regs, but can be required by institutions to govern that process, so I think that is an important suggestion.

With respect to the first question, I am nervous about the results that might emerge from our project, and I think that on a preliminary basis, what folks want is

they just want some role, they want people to talk to them. This whole idea that all this is happening behind a curtain is primarily what seems to be irritating folks, and not acceptable for folks, and I think again very preliminary stuff that is coming back at this point is folks want to say I just want you to ask me and we think these things ought to be focused on newborns, and for the most part, seems like folks are being okay about research with deidentified specimens, so we may end up with something very much like what the AAB 2000 comment said, which is if they are going to use identifiable samples,

then, you need to have some robust dialogue with folks about that, and that may end up precluding the kinds of valuable research that I think need to be done, if done, also stating that public opinion doesn't dictate what the public policy is, but, you know, you are trying to pull this in with the right of other considerations.

DR. HOWELL: I think this discussion will probably continue for a very long time, but in view of that, we are going to stop for lunch, and we will return quite promptly at 12:30 Thank you very much, Jeff and Harry.

[Luncheon break.]

DR. HOWELL: The Committee seems to be largely

here. Obviously, the poor souls that had to go find lunch that didn't have enough time to do that, but that is another issue, and so forth.

But we are going to now go with the Subcommittee Reports and Discussions, and we will start.

The subcommittees, I think each of the subcommittees had an extremely profitable meeting yesterday from what I understand, so we are first going to hear from the Subcommittee on Laboratory Standards and Procedures with Dr. Vockley.

Subcommittee Reports and Discussion

Subcommittee on Laboratory Standards & Procedures

DR. VOCKLEY: This will be a fairly quick report because while we had some really interesting discussions, I don't think a lot of detail is necessary.

We did have a report from Harry Hannon about this routine second screen follow-up, the project that has been mentioned several times already this meeting, and while it is still in the final stages of sorting out, Harry had reported to us that they are at last getting the IRB issues resolved, that their enrollment is nearing the needed level to actually accomplish something.

Have IRB in places for about 15 percent of newborn screened, covering about 15 percent of newborns

screened in the U.S. and actually about 65 percent of all newborns who are in States that are receiving routine second screens, so they should be able to actually start getting some answers around this issue.

Remember this is for the thyroid and congenital thyroid hyperplasia screening. It does not cover tandem MS, and so there seem to be a pretty good consensus that the second screen doesn't do too much in that context.

We also heard a little bit about the protocols for CF screening, which involve a second screen, but really a reflex, so IRT going to DNA, and that seems to be the direction that most of the programs are now following for that.

We had a very interesting report on the Region 4 collaborative project that we have also talked about in the past, led by Piero Rinaldo, to essentially collect the data on newborn screening responses or results, so that it would allow States to compare themselves with what other States are doing and essentially use this in feedback to hopefully improve their programs.

This is really becoming quite a robust database now and I think it is safe to summarize the future plans for data collection as to continue to expand, however, what is equally important I think is a little bit of the

evolution of the database.

One way is that they are now really trying to engage the clinicians who are dealing with newborn screening results, newborn babies who have been screened, to make use of the same tools.

They have already got their laboratorians on board in every State that participates has got these tools in place, but now they would like to try to engage the clinicians to do it, so he convinced me. He is going to send me a password and I am going to start taking a look at it. It seems like it actually has some very interesting possibilities to help us out when we have got these babies in front of us.

Then, there was a little discussion both at this time and at the end of the meeting during open comments about the need to standardize that language of newborn screening and the words screening results.

We heard a talk yesterday about that, so I am not going to say anything more. Those issues all were nicely captured in the discussion yesterday.

We tried to focus a little bit on some technologies that we might be seeing as a committee in the coming meetings, and since many of the proposals that we have had, and that are potentially in the offing are for

storage diseases. We heard from Bob Vogt about the CDC efforts to push that screening forward.

Genzyme has been engaged or agreed to synthesize all of these substrates and provide them to the CDC for standardization of the assay and then distribution to screening centers. The ones that they have in hand right now are for Pompei, Fabray, Gauche, Karbay, and Neiman Pick, and MPS-1, 2, and MLD are all relatively close on the horizon with still just some issues in the standardization of the substrate synthesis.

So these are being used for -- the screen technology that the CDC is looking at is a MS-MS to look at the products from these substrates. They are putting together their own package right now that includes the internal standards, and just to remind you that while the analysis steps of this procedure or these procedures can be multiplexed.

Each assay is an individual assay, so you do each individual assay separately and then you can combine the final products, your final mixture and analyze that together.

So, there will be potentially variability in what States elect to do here, and we certainly will not as a committee be obligated to say all or nothing. So, this

isn't tandem mass spec with azocarnitines and amino acids,

you get everything whether or not you want it. This is a little bit of a different paradigm.

One of the other questions that came up in the meeting was what other technologies are out there, and, of course, there is a fairly robust antigen detection technology based on bead methods, and that CDC at this point is not doing anything with that.

Dr. Rinaldo informed the committee that Mayo is going to put together a head to head comparison of these two tests with a reflex follow-up of a specific enzyme assay afterwards, so that will be something for the committee to look forward to.

Finally, we had a report from Mike Watson on the Newborn Screening Translational Research Network that overlapped what he talked about to the full committee. We were interested in how the technologies for screening might impact that, and I think that the consensus is that it is just too early where we have got it on the radar screen and we will have to watch it, but there is not a whole lot more to report to you than what Mike already did, so that is all I am going to say about it, and I am done.

DR. HOWELL: Thank you very much.

I have a question. As the Mayo is going to do an antigen base, immunoreactive test and compare it on all of these - Gauche, Pompei, Fabray, Krabay, MPS, the whole panel?

DR. RINALDO: Actually, the immunoassay, sorry, the method we are developing in combination with Johns Hopkins include 14 targets.

DR. HOWELL: Including all of these?

DR. RINALDO: Plus others.

DR. HOWELL: So, you are going to compare those data with the mass spec data?

DR. RINALDO: Yes.

DR. HOWELL: And then you are going to do an enzyme assay at the end of all of that?

DR. RINALDO: If either one, of course, or both, test abnormal, we will do a second tier test using the Chermoles [ph] method. That's the one that is being used in Taiwan, for example.

DR. HOWELL: Are you into that? Are you just beginning?

DR. RINALDO: It will start between late spring

and early summer.

DR. HOWELL: So, we should have some information on that fairly soon.

DR. RINALDO: I think by September or October, there should be some data.

DR. VOCKLEY: I was going to say just to remind you that the Hopwood [ph] method is one that is truly multiplexible, so that is one of the major differences in the two. You can have as many antigens found in beads and reading out a different color as you have potential dyes.

DR. HOWELL: And this is a Luminex based assay?

DR. VOCKLEY: It's Luminex.

DR. HOWELL: Very interesting. The other question, when can we expect data from Harry about the second sample, which I think he started working on before his first retirement? Where is Harry?

DR. VOCKLEY: He's in the back. You want to give us a date, Harry?

DR. HOWELL: When will we have some info from the second sample, Harry?

DR. HANNON: Well, APHL has electronic database for entering the data, and those are starting to enter

that data, so by the time, I think you all have another

face to face in September?

DR. HOWELL: That is correct.

DR. HANNON: I think we are going to have something by then.

DR. HOWELL: Terrific. Thanks very much.

Now, we go to the second Subcommittee on Education and Testing, and that's co-chaired with Jana Monaco and Tracy, and Tracy is going to speak about that committee.

Subcommittee on Education and Training

DR. TROTTER: Thank you, all, and Jana and I would like to thank the large turnout we had for our meeting yesterday, which was the most people I have seen in the Education and Training Subcommittee meeting, and it was a fruitful meeting, as well. We appreciate that.

We had some updates from our usual strong partners who have been involved with us for years from the NNSGRC. The GEMS database is back up, whether that is good or bad, we are not sure, but it is what it is, and links are being established or reestablished, so this is a new ongoing process at this point.

Joyce Hooker brought us up to date on some of the projects the regional collaboratives are doing. We had asked for sort of a listing of what was going on in the

different regions from an educational perspective.
She came up with 50 different programs, 50 plus
actually different educational programs that had either
been done or in the process of being done at this point,
which we will be looking at each of those a little more
carefully and see where we can use those in other areas,
and hope to again avoid overlap and just create more
opportunities for other people to utilize something that
has already been done.
The Genetics Alliance reported their education
mini-survey that they had done of 12 voting members of the
committee, and just to give you a flavor, one of the
questions was: Do you see genomic education as a high
priority for you as a member?
It is interesting that five agreed that was true.
Four didn't agree or disagree, and three disagreed with
that. So, I assume they were at other meetings yesterday.
I think we heard in the last two days that if we
aren't going to educate everyone, we are probably not

going to get done what we need to do. So, just a little
talk to the other five people later.
Make case for what was the end result of our
meeting, which is a proposal to formally pursue education
of primary care physicians. We talked about this I think

the last time we had a face-to-face meeting of why we thought it was important. This article from -- there is a number of the authors at our table today, talks about the new challenges, education management, obviously, increased screening gets increased positives, whether they be FALSE positives or real positives it doesn't matter, you have to deal with them pretty much the same as a primary care person in the first days.

Interesting in a survey done in 1998 by the MA, our patients, 78 percent of patients think we know what we are doing. So, they claimed we, as primary care physicians, are their first choice according to information on genetic disorders.

They are confident that we would choose the correct genetic test and interpret the results correctly, and that we would be knowledgeable to answer their questions about the test results. I really appreciate

that thought.

In a similar survey about two years later, however, PCPs in general, and these were family practitioners and pediatricians actually in this case, 60 percent felt that they were not qualified to recommend or order a triple medical test.

So, this is a dilemma, is that we are going to

have more of them, they are going to be more readily available, they are going to be even available to the consumer over the Internet, as you know, and they are going to come to us needing more information.

The Newborn Screening System is actually sort of the perfect test of this in that the system is in place, and there is back-up in place, and there are things that aren't quite in place for some of these other things yet.

So, we are partnering with the usual suspects in trying to create some focus on this, and using some scenarios that I think would resonate with almost everybody in practice, and that you are going to get an out-or-range result, you are going to need to find out about AC sheets and what your State program does, who do you call, and how that works, and assuming you actually

have a child who is affected with whatever disease it is, you will coordinate their evaluation, and you ultimately become their primary medical home.

The trickle down effect of that is if we could spread this out so every primary care physician got one positive that was real -- I don't know how you do that one -- but they would all be very well educated at the end of the year, because under the crucible of this, they would not only learn about it, but they would educate their

local hospital, the people in the labor and delivery areas, and their pediatric units, families, and everyone else.

So, we hope that our educational efforts sort of work in that direction.

I won't try to sell any more about why it is important except that we are all going to be dealing with it more and more and more, and we seem to know less and less about it.

Which brings us -- we had a great presentation, Greg Farrow came from NHGRI and presented to us, and discussed with us, a meeting that they have scheduled for June of this year, which they have entitled, Developing a Blueprint for Primary Care Physician Education and Genomic Education," which we thought was a catchy title, and interestingly, we have been over the last six months trying to put together a meeting of the minds of people at the AAP, ACOG, AFP, to how do we get -- what are the barriers to getting information to these folks and how do we get around those barriers.

So, this is going to really jump start this, this is a very good meeting, as a subcommittee we applaud what they have gone forward with, and hope to be able to work with them. After much discussion, we have come to the

committee, today, to ask for your approval that we add a sort of maternal and child health focus round table to this meeting, and Greg was willing to do that.

This is a day and half meeting and we felt that maybe a two-hour session at the end of the meeting with people who are -- because the bigger meeting is going to include allied health folks, internists, and people who may not be very specific to this -- we thought everybody is going to have to take their piece and do what they can do with what they know, and this is what I know.

So, we thought if we took at the people who are preconceptual perinatal, neonatal, pediatric groups, who are present at that meeting, to come together at a round table and create more specific strategies, programs, and I would hope from that that we would have possible future meetings to pursue the blueprint that they are going to come up with.

This focus will build on two -- there are five goals of the meeting and two I felt were specific to what we would like to do, and I think what the committee probably thinks we should be doing -- which I have listed here, identifying core educational needs in genetics and genomics as defined by the primary care communities. I think we, who are sort of genetic-centric have a pretty

good idea of what we want to do, but I am not sure we are always in tune with what they want to hear.

Then, to propose some actual strategies that are doable, take advantage of what is out there, all the way from graduate education through CME.

We hope that you feel that is a reasonable project to start with. I would hope it would be a launching pad for us to focus more discreetly onto a strategy that will work over the next few years in

educating the work force in primary care.

Questions?

DR. HOWELL: Questions or comments of Tracy?

DR. TERRY: As a board member of NCHPEG, I would be remiss to ask, should they be on your list of organizations that will partner with you?

DR. TROTTER: Yes, they always are actually.

DR. HOWELL: They are very much involved in this meeting. I think Greg has been actively planning this meeting, and he plans on approaching the other important institutes of the NIH which he has not yet done, but he had several institutes that are represented around the table on his tentative hit list to be involved, and so forth.

It seems like that would be a very good

environment to be able to do some educational things at a meeting that is already moving along and is very appropriate, but further comments?

DR. VOCKLEY: Not on that, I agree completely. I just wanted to be sure that as you start thinking about getting educational programs together out in the field for primary care physicians, there are a number of efforts already underway, so I am not sure how you are going to identify them all.

I mean I can tell you about one that I know, for example, with newborn errors of metabolism where Mark Corson [ph] in Boston has a grant to put together a program. He goes out on an almost every week basis, a couple of days is out in the field talking to primary care practices and pediatricians and family practitioners, and has developed educational materials for that, so I know there are lots of those kinds of efforts ongoing, so we should tap into those.

DR. TROTTER: Actually, it is amazing how much material is out there and that are very good things. What we are having trouble is getting at the institutional level, maybe to begin with, is getting the primary care folks to tell us who do we best get that to them, what is the best way for that to happen. That is what I hope we

are going to clarify.

DR. VOCKLEY: And I think Mark's approach was t take them himself, so delivering them and giving them a CME type talk and then handing them the materials is a very effective way if you have the person power to do it.

DR. TROTTER: Send him my way. I have a great agenda for him.

DR. HOWELL: Denise.

DR. DOUGHERTY: At the AAP, which is a big organization, they now have a quality cabinet and various activities going on. One is called QUIN, Quality Improvement Network. So, they are working with either individual providers or chapters to try -- this is in the context of maintenance of certification -- and this might be a good topic, so, your practice has a child identified through newborn screening, what do you do now.

DR. TROTTER: We approached them, Tim approached the Academy a couple of years ago, maybe a year and a half ago, with a recommendation. We put a module together with exactly that sort of title, okay, now we need him, and that we would have people -- we sort of had some success in getting that involved in some of the CME things, but again we are hoping to get decisionmakers involved in this kind of meeting and this kind of process, and sort of jump

start getting it into, you know, things that are going on like that, which are very helpful.

DR. DOUGHERTY: Well, they now have a senior medical officer for the quality cabinet, and it is getting a lot more organized with the AAP, so it might be time to remind them.

DR. HOWELL: Mike, did you want to say something?

DR. LLOYD-PURYEAR: How about the thing we have at the Academy --

DR. WATSON: The QUIN Network? We did the AC sheets for Newborn Screening, but we have extended them to Genetic Testing, to transition of newborn screening patients where we write an adult PKU AC sheet for instance.

We have them around family history, that gets dropped on the desk to help figure out how to sort that out all in the same format.

We are working at the QUIN Network around a validation of the formats of each of these kinds of AC sheets. The genetic testing focuses, for instance, on t things commonly referred by a primary care provider, Fragile X carrier screening, those kinds of things.

They are ones we have, the formats for each of those different types agreed upon as being a futility,

then, we fill them out for a wide range of things in each

of those areas I described.

DR. LLOYD-PURYEAR: We have also been working with chapters in each of the regions. They pair geneticists with a chapter champion to give a joint presentation at local universities, so that it is not just a geneticist, it's with a primary care provider.

DR. HOWELL: Fred, you have a comment?

DR. CHEN: I just wanted to add, Tracy, that the Subcommittee was really pleased with how open Greg was to letting us add this focus on maternal child health, which certainly is paramount for this committee's work, and I really think it was useful, if you looked at their original agenda, it is very easy for those discussions to sort of turn into discussions about adult genetic testing, about over-the-counter or Internet-based genetic testing, pharmacogenomic stuff into really be able to bring some of the newborn and screening focus at both the main meeting as well as at the sort of proposed additional meeting was really good, and I think we really appreciate Greg's openness to that.

DR. TROTTER: It was a very good meeting.

DR. HOWELL: I sense a feeling of support of

that, that we need a recommendation and a second from the voting members of the committee about whether or not to have this at the upcoming meeting.

Can we have such a recommendation?

MEMBER: Recommended.

DR. BUCKLEY: Formal support?

DR. HOWELL: Formal support. Becky, are you seconding that? So, we have a recommendation and a second.

Those favoring that, let us hear, aye.

[Chorus of ayes.]

DR. HOWELL: It's unanimously accepted and I assume that you will be the ringleader of making this happen, is that correct?

DR. TROTTER: Okay.

DR. HOWELL: Sounds good to me.

Any further questions for Tracy or Jana? Jana, did you have anything to add?

MS. MONACO: Vote for both of us.

DR. HOWELL: Coleen, we are now going to go to the Subcommittee on Follow-up and Treatment, which had an army of people present.

Subcommittee on Follow-up and Treatment

DR. BOYLE: I wanted to start with informing you all that we have reconstituted our subcommittee. Off to the left are our actual subcommittee members, to the right is the full committee members or the liaison members who help us or sit on the subcommittee.

You can see the ones that are in italics are new members. Those are Cilia Kaye, Sue Berry, Jim Siggie [ph], Carl Kooley [ph], who was unable to attend this time, and Fred Lorian [ph], and Fred I think was on the phone from California. Alan Hinnman continues to serve with us on the subcommittee, as well as Jill Fish. So, we are delighted that all of these new members will be working with us as we taken on some new challenges in the subcommittee.

I am going to give you a little update from our last meeting together, which was in September. As you know, we have been working for probably almost two years now, April of '07, I think, that we initially took on the task of looking at the issue of long-term follow-up and trying to define that in terms of the major components of long-term follow-up sort of at a visionary or high level

view.

That resulted in a manuscript that Alex Kemper, he has been very engaged and he is the back of the room somewhere. Alex, raise your hand. There you are. He has been very helpful in helping us move that process forward, and there was a second component of that, and that was trying to flesh out the roles and responsibilities of major participants of long-term follow-up.

We have spent a lot of time on that and we are still in the process of developing a position paper on that, so we hope to have at least by June or July, whenever it is that we are going to be getting together for our virtual meeting, have a draft of that. I was hoping to have one this time and it didn't work out, so we will make sure that moves along.

The other main activity that we have been working on is the medical foods issue, and you know June 2008, Sue Berry actually at a September meeting, Sue Berry presented both about our June meeting as well as a survey that we are doing in three States, the 2008 meeting of experts around the issue, concentrated really around the issue of medical coverage, insurance coverage for medical foods,

and had brought in a number of experts both from the private insurance world and the public insurance world to provide us guidance.

You all have a copy of the committee letter that we have developed as part of that work group. I did -- I don't know if we are going to do this now or later --

DR. HOWELL: We will do that later.

DR. BOYLE: We did make some changes to the letter based on comments. I received a lot of comments yesterday afternoon, not substantial, but I think I will tell you a little bit more about them when we do the voting part of it, but I think that is a much stronger letter based on those comments.

The survey that we are doing in three States, New York, Minnesota -- what is the third State? Whatever they are, they vary by State -- in the southeast, sorry. Thank you. So in the southeast, whatever the region, Minnesota included --

DR. HOWELL: Four.

DR. BOYLE: Region 4, okay, and the New York region. The survey has been under development for quite a while now, but we are pushing towards full implementation

of that survey and actually in March of this year. Yesterday, as Rod mentioned, we had a very active meeting. We actually were looking at the issue of thinking through the data needs for a long-term follow-up and the impetus behind this was really the recognition by

many of the grantees to CDC HRSA as well as NIH, that we seem to be funding somewhat complementary activities in terms of developing beta systems and follow-up for Newborn Screening, so Michele and I thought it would be a very good idea to use the opportunity presented by our subcommittee to bring our grantees together, to really look at and reflect as to what it is that our grantees are doing and could we develop sort of a common approach to long-term follow-up given that there is so much different perspective in terms of the funding opportunities that CDC is providing, the funding opportunities that HRSA is providing, and obviously, the Research Network that NIH is supporting.

So, Alex Hinnman, very nicely helped -- Alan, sorry -- Alan Hinnman helped work through this issue in terms of the objective, but we were I think quite ambitious in starting out. We thought we would actually try to develop a common data set of variables, but this was a discussion to begin to think through how we would develop a common set of variables that would address the difference information needs that would really assure optimal long-term follow-up.

We were really using the framework that the subcommittee had developed for long-term follow-up, that

is, the major components of long-term follow-up, the care and assurance and care coordination, the quality improvement aspects, the Evans based treatment and management, and then the research opportunities that are needed.

We were thinking from the various perspectives, that is, the health care perspective, the consumer perspective, as well as the public health perspective.

In terms of the meeting summary, this really did take most of the meeting time, but I think it was very useful. We did hear a summary of the long-term follow-up activities both blood spot as well as at the early hearing in detection/intervention programs. That as done by HRSA grantees, PC, as well as Mike Watson provided us a nonvisual overview of what was being done by the

Translational Research Network.

Then, we also heard from Greg Downing about the Health Information Technology Infrastructure, so again, not much higher level view of this and what perhaps our vision on the ground, how that might relate to the infrastructure and architecture and other sort of behind the scenes activities that are going on and how we might be able to interface and maybe even use that as an opportunity to springboard what it is that we are doing

for long-term follow-up activities.

There wasn't a whole heck of a lot time for discussion, but some of the discussion issues that we did talk about were the need for harmonizing peace definitions across these multitude of States, really trying to focus on what it is, what are the pertinent questions within those four components of long-term follow-up.

Obviously, the desire to standardize data elements and the level of resolution that is needed by the different parties or users of the data in terms of answering or addressing of questions, and then it was also brought up there is a lot of other activities that perhaps weren't represented yesterday that might be helpful in terms of trying to get a better sense of what our next steps are in this issue.

I am not clear what our next steps are, so I am getting to my last bullet before I get through the other ones. I think what we had talked about was really trying to define what the critical questions are under each of the major components of long-term follow-up.

The goal is really try to get towards a minimum data set for a long-term follow-up. That would be useful for answering each of those critical questions. We need to address or try to identify areas that lack standards

from an ITN Information perspective. That could really cause a problem in the one that I just brought up of the issue on the variability of case definitions.

There was a suggestion perhaps we could do, you know, there has been a use case for newborn screening that really stops at short-term follow-up. We heard about that yesterday, and that perhaps we could move forward on actually developing a use case in some of the qualities case issues we heard about in terms of defining outcomes for children, so that might be a possibility, at least engaging others in that activity.

Then, it was also brought up what is the role of the subcommittee in this work, which obviously, this is a big undertaking versus the work of the agencies and sort of addressing this.

We haven't come to resolution on that, our parting words is that we would take this up on our monthly phone calls and think through what it is that this subcommittee as well as this committee could do to help move this issue along.

DR. HOWELL: Are there questions of Coleen?

Thank you very much. I think we are going to get back to one of the products of committee but I think that the product that you developed, for instance, on medical

foods is certainly an extremely valuable work, and so forth.

I think that really concludes our subcommittees, and so forth, which takes us on the agenda to the area of Public Comment.

I was going to say we have no Public Comment, but we have a last minute thing here of a Public Comment sign-in.

Melissa, did you want to sign in, Melissa Freezy [ph], or did you sign up on the wrong sheet?

Okay. Melissa does not want to make a public comment, but next time if you sign up on the public comment sheet, we are going to make you make a presentation with PowerPoint.

Dr. Freezy is a new project officer, NICHD, and we would like to welcome her, et cetera.

In your Public Comment section of your book, there are some letters that I would like to call your attention to, and they are for information.

I will go in reverse order. The first one is from Jackie Wagner, who is the Executive Director of the Hunters Hope Foundation. It is simply outlining the activities of that foundation and pointing to the fact that they have a video on their web site that she commends

you to look at. I have seen the video, it's a very moving video about an infant with Krabbe disease, and I think that will be informative to this group that will be soon considering that condition. I think that will be very informative.

There are two other letters in the file that I will simply point out for your information. We have a letter from Dawn Lobell who is a parent, a woman living in Maryland, who is the parent of a child with a condition that has been detected by Newborn Screening, and she is very concerned about some of the discussions in the State Senate of Maryland, Senate Bill No. 160 that has to do with Newborn Screening.

Elsewhere in your book is a letter from Dr. Kelley, who is a leader in the metabolic group at Johns Hopkins, and his comments are about the same legislation, and I commend you to read those letters. I don't think there is anything, we are not a legislative body, but the concerns that they have about some of the discussions in Maryland are certainly issues that we will want to consider at some point.

I have been told -- and it is kind of like anytime you have a public comment about something -- I have been told that the background behind this legislation

is much more complex than meets the eye, so at least I commend you to read these letters and be aware of the discussions that are going on there.

DR. LLOYD-PURYEAR: Dr. Kelley's letter is under Committee Correspondence.

DR. HOWELL: Richard's letter refers to the exact same situation, so I commend you to put those together when you review those.

Committee Business

DR. HOWELL: We now come to Committee Business. We have got a lot of business to do.

The first thing I would like to bring up is that you have seen the letter on medical foods that Coleen alluded to, and she has sent out an copy that made a few important changes in the letter and the letter I think is very good, and then earlier Michele commented about two very small comments about the labeling, et cetera, and I would like to hear a recommendation that this committee accept this recommendation and that we send the letter forward to Secretary.

Can we have such a recommendation?

DR. TROTTER: So recommend.

DR. HOWELL: Is there a second?

MS. MONACO: Second.

DR. HOWELL: Those favoring the recommendation?

[Chorus of ayes.]

DR. HOWELL: Unanimous. We will get that letter on to the Secretary.

Now, Ned wanted to make a few comments about his excellent document that he has been working on, on evidence review that is really becoming a classic document, but he has a few additions that will make it even classier, and I agree with his comments.

DR. CALONGE: This is on the heels of the discussion we had yesterday about direct evidence, and comments from colleagues whose comments I value greatly during that discussion. The Services Task Force approach to direct evidence has actually evolved over time, such that we wouldn't consider making recommendation on direct evidence that wasn't from a randomized controlled trial, however, when we had the discussion yesterday, I went back to the original definition of direct evidence, which is a little different than where I think we have evolved to, which is that all of the evidence comes from a single body of evidence, or, in this case, the single study.

What that gets to the point is you can have direct evidence of varying quality, so at RCT would be high quality direct evidence, but an observational study,

case series or other approaches population-based screening

could also provide evidence of the intervention that could be associated with an outcome within the same body of evidence, and therefore meet the criteria of direct evidence.

It may be of a lesser quality, the issues about biases and observational studies or other things are things we need to keep in mind, but it doesn't change the fact that it is direct evidence.

So, what I wanted to do with the document is just point that while, yes, a well designed large, randomized-controlled trial represents the best approach to direct evidence, there are other areas of direct evidence that could be considered rated for quality by the Advisory Committee and used to guide our decisions.

I think as I talk to individual committee members, that most people feel that this would be a useful addition and a good recognition that there are other kinds of direct evidence than the RCT which I would only hesitate to say if we say we will never have an RCT, then, we will never have an RCT, but it's not that it's not possible to do.

So, that was an addition, an acknowledgment I

would like to make to the Committee and will add a sentence I think is all it is going to take, Michele, to the paper.

DR. HOWELL: Ned, I think it would be helpful for the Committee for you to explain to the Committee the kind of evidence you are talking about, which I thought was very informative.

DR. CALONGE: The example that I brought forward actually came from a description that Dr. Rinaldo put forward almost a year ago where he pointed out that in a State, you know, before the testing there were X number of deaths a year from a disease, and then after implementation of testing there were no deaths.

Well, that would be direct testing, so the intervention and the outcome were measured in the same body of evidence, and it's undeniable that that is kind of direct evidence. Whether or not there are biases that interfere with the directness are other issues that we can bring up and discuss, but I think that is an example.

So, if I go back to cervical cancer screening, which I mentioned before, one of the ways it got to an A was in the Netherlands. There was X number of deaths from

cervical cancer every year, and the Netherlands instituted a national every 3 year pap smear program, and within 10 years the mortality rate from cervical cancer went to zero, which by the way, you can't get less than zero.

So, I think that again would represent a body of evidence where the intervention of the outcomes were in the same body of evidence and would represent direct evidence.

DR. HOWELL: I would sense that the Committee would support that, but in view of the fact this is an important document of the committee, I would suggest that we vote on that.

Can we have a recommendation?

DR. CALONGE: I would move that we expand -- Nancy said lower the bar -- I would say expand the definition of direct evidence to include -- to go back to the original definition, which is a single body of evidence represents direct evidence.

DR. RINALDO: Second.

DR. HOWELL: There is a second to that.

Any discussion?

DR. KUS: Just one question. So, that would mean

that you could have a yes answer without a random trial,

right? Is that what your --

DR. CALONGE: It means that you could have a yes answer to the question, overarching question No. 1 without RCT. Now, it doesn't mean that you would then say that's high quality and convincing, but it says it's direct evidence.

DR. HOWELL: Further discussion?

Those favoring that recommendation, say aye.

[Chorus of ayes.]

DR. HOWELL: Any opposition?

[No response.]

DR. HOWELL: No. abstentions.

So, it was unanimous. I think that is a very good thing, and I think that is fairly compelling evidence if you have that kind of data available.

Yesterday, we voted to recommend a Class C recommendation for SCID. There was great enthusiasm for the test, the treatment, et cetera, and there were a few bits of information that were felt to be necessary before we were willing to come back and say it should be moved upstream.

I asked Jerry to convene a small group of experts which he did to come up so that we not only will have that recommendation, but we will have a specific list of things

that we would like to see soon.

DR. VOCKLEY: Thanks, Rod. As Rod said, I think the discussion made it clear that there was an extraordinary amount of sentiment that this is going to be a disorder that ought to be on the screen panel, and the concern of -- my concern and a number of others that were expressed was that there were just enough pieces that hadn't gone quite far enough that it didn't meet some very, very carefully thought out and long discussed guidelines for approval to be added to the screening list. To maintain the credibility of this committee we really do have to maintain a standard I think, and so in discussion after the formal part of the meeting finished, several of us came up with what we thought would be the minimum necessary information to really push this over the top, and some of these I think I mean are actually really done and we are just acknowledging that they haven't been maybe brought to the fore.

At any rate, prospective identification of at least one confirmed case of SCID through newborn screening, and this was something that we all agreed that was really hard to go forward with a recommendation to add something to the panel that had never been identified by newborn screen.

Continuing FALSE positive rate and we selected
actually based on the current data relatively conservative
number of less than 0.1 percent. The Wisconsin program is
doing well, better than this. So, this does not seem to
be a barrier.
One of the pieces where there was some concern
was that this is being piloted in one State and started in
another but hasn't had any other movements to a State
screening lab, so we thought that it was important that
another state should step up and show willingness to
implement SCID screening.
I understand after this conversation, Texas is
actually partnering with Massachusetts and is going to be
piloting in a small scale, but this would be an important
component.
One of the other pieces that was questioned
yesterday was the availability of QC materials and so we

think that we need to be sure that we have those in place
for recommended screening, and Bob Vogt has committed the
CDC to make something available by June of '09, so
relatively short and aggressive time period.
There may be some optimization of those beyond
that, but at least something will be available in the very
near future

The last bullet is not really one that the screening community put together, but one that Dr. Fleischman recommended that we put there to alert folks back here in Washington that appropriate resources should be available to fund things that we are specifically requesting the screening community to provide us. So, that's the list.

DR. HOWELL: Any comments? The purpose of this list was to provide a list of things that the nominators of SCID would work on as quickly as possible to come back to the Committee so that there is no ambiguity about what the, shall we say, the holes in the problem was.

Coleen.

DR. BOYLE: I guess there is two issues for me. I will take the easiest one first. On the third bullet,

my sense from the discussion yesterday was that the two States that were implementing were perhaps the more research oriented States versus the other States, and I guess I am just thinking about the ability of other State screening laboratories to implement this, and just adding one more State to it doesn't really address that issue for me.

I am not exactly sure how to, I am just bringing it back in terms of what that discussion really was.

That's the first point. The second point is for Bullet No. 1, I guess I am thinking of that. In addition to at least one confirmed case, I would want to know something about the denominator there, so, you know, the denominator experience of screening 200,000 children, getting a better sense of the full impact of screening from a population perspective, you know, getting a better sense of all of the cases that are there, SCID cases or the larger definition in terms of what we talked about yesterday. It is not just picking up that one confirmed case, but it's getting a better sense of how that test acts within the context of a population screen.

DR. HOWELL: Kellie, you had a question?

DR. KELM: I guess I just wanted to say, coming from someone who, you know, looking at a screening, and knowing about how FDA works with things in precedence, I guess I just wanted to caution that whatever we say here is the bar, that they need to be here is probably what others may then take as the bar that they have to meet in the future, and so we want to make sure that we set the bar appropriately, or are we going to couch this in such a way that it is only for here and that we would have to consider others complete separately based on prevalence,

et cetera, but, you know, thinking about how many labs have it, I mean so is two going to be the bar in the future? I mean all those things they throw, you might want to think about a minimum, you know, this will be it presumably, possibly.

DR. HOWELL: And how would you word that, Kellie, to get around that? Since you brought it up, you need to solve it .

[Laughter.]

DR. KELM: Well, I am just saying I am not sure and I don't have a feeling if this is what people want the bar to be or do they want this to be unique for this case and that we would have to add some kind of terminology here, that we are limiting it to SCID, and so I don't know what the feeling was. I guess I would have to see if people were comfortable with this or not.

DR. HOWELL: Jerry might comment.

DR. VOCKLEY: I think that what we are seeing here is this isn't the bar, these are the additions to the evidence already presented that gets SCID to the bar. So, it is this plus the other. The discussions that we have already had, which I think -- I mean this was the evidence-based review, identified several gaps, and this is what we identified or what we feel is the minimum

amount of information that we need to fill those gaps.
So, I don't think we are setting an sort of
specific precedent here. If we wanted to couch this in
terms of making this specific to SCID, it is already
there.
DR. TROTTER: I agree. In fact, I would only
agree to these conditions as it applies to SCID based on
our already very thorough review, not in a generalization.
DR. HOWELL: Lots of interest over here. I think

Sharon was first -- Chris was first.
DR. KUS: I guess the difficulty I have is that
it is listed as conditions. No. 3 is willingness of
another State. How do you meet that condition? The fifth
one is appropriate resources available to fund it, how do
you measure that?
DR. VOCKLEY: That one, I conditioned the
condition.
DR. KUS: It shouldn't be a condition. It is
listed as a condition, that's what I am saying.
DR. VOCKLEY: It is there for ease of
presentation.
DR. HANNON: Could I quickly address the third
State issue? We have an RFA out which we hope we will
find a third State. It will come out like the others at

half a million roughly for a year. The RFA will go out this year. We are hoping to pick up a third State.

DR. HOWELL: The list we have here is we have Chris, Fred is next.

DR. CHEN: I am going to raise a question about the FALSE positive rate at 0.1 percent and if there was a reason why that was selected. There is nothing that I have seen in the literature about why that is a particularly good rate or not, but it is 100 FALSE positives if we are dealing with an insensitive one at 100,000, it's 100 FALSE positives for one TRUE positive is what you get at that rate.

I am curious where that came from, and I think if it's going to be on a condition list, we need to have some kind of reason for it.

DR. RINALDO: I would like to comment on that.

I think that what we have learned like from the expansion of neumos green [ph] by tandem mass spectrometry, the truth is that the FALSE positive rate can easily be above 1 percent and can even be close to 3 percent. As a part of one of the collaborative parties, we actually collect the FALSE positive rates and we have now data from about almost 40 States, and in general, although I don't think it can be easily extrapolated, but

for a multiplex platform, we consider an acceptable FALSE positive 8.3 percent.

I think what we have heard so far from Mei Baker and from Frank Comeau it is actually rather outstanding to have a FALSE positive rate in a population screening of

0.01, 0.2 percent. Believe me, it doesn't happen. If you take Pompei, the Taiwan experience that I believe was a key element because it was the only prospective evidence, the FALSE positive rate was 0.9 percent, actually, 0.89 percent.

So, the 0.1 I think is -- I think actually a high bar, and I can tell you in most of the Curran [ph] screening tests, right now will fail miserably, because I was involved. So I think for the newcomers, we are setting a really high standard.

DR. HOWELL: Sharon.

DR. TERRY: So, that was going to be one question and I was going to say I think that's a high standard to set, and again I know we are saying just SCID here, but it would be also in the case of having a second State, and we are again saying just SCID here.

There is a lot of politics around this as we all know, and are we saying SCID has to reach a higher bar than some other conditions that later on we will say

should reach a lower bar.

I think while we are not saying we are setting a precedent, or course, every single thing that this committee does is a precedent for the future, so I think we just want to be careful to give why SCID has to have two or three labs and why SCID has to be less than 0.1 versus other diseases.

DR. HOWELL: Mike.

DR. WATSON: I am not sure what this is. This is sort of conditional condition, which is when you ultimately make the recommendation, you are going to be left with 40 percent of the States not having a molecular capability right now, and this is obviously a molecular diagnostic or screening test, so I think you are going to have to look a bit at the reality of the situation and figure out how to do some gap filling around capabilities of States to actually fulfill your recommendation.

The sense is that you are going to make it eventually, and you don't want to start then with having to deal with the reality of the inability of many States to do it.

DR. HOWELL: Peter.

DR. VAN DYCK: I would just like to say I was concerned that the two labs are using different lab tests,

and I don't know how similar or how different they are,

but I was concerned that we couldn't recommend a single test that States would want to take up if they are willing to test for this condition.

DR. RINALDO: I don't think it's a good idea, I think that you really want to let it be and see what works best and eventually, naturally, there will be a selection. I think you will have a lot of unintended consequences to say now there must be one test, because frankly, I am sure that -- and that was one of the things that was discussed yesterday. I believe that inclusion in the panel of SCID will trigger a lot of industry interest, and so there could be more masses available and eventually, I think it will sort themself out, which one works best and which is the most cost effective. I don't think we really should focus on the expectation of a single test.

DR. HOWELL: Ned.

DR. CALONGE: I wanted to answer or address Fred's issue about the number of -- absolute number of FALSE positives. So, I just went back to the evidence-based presentation, at least in my mind, and if I remember right, the harms, there was no evidence of harms, but they were estimated to be small.

So, the harms associated with a FALSE positive we talked a little bit about and we decided maybe we didn't really examine those enough from the standpoint of bringing the child back for another test.

I didn't see anything about is there anxiety, is there other labeling issues associated with that, but I put that as a minor harm. I think we talked about having to do multiple blood draws on preemies and the issue that, you know, I know it's not a problem because we just transfused them, so we can draw more blood, so that sounded like a relatively minor harm.

So, I think you need to recognize for net benefit, there is kind of this weighing of the harms which are in the treatment area and the FALSE positive area against the benefits which look, you know, did it reach the bar that that 3 2-Jan month gain of treatment, that treatment before the first respiratory infection conferred a benefit to early detection versus late detection.

So, I think we will end up putting in the FALSE positive rate. I am not worried about the rate, it's just how much harm is there for the FALSE positives versus how much benefit with the TRUE positives treatment detection,

and that's why the issue about making sure that when we make the diagnosis we are right was important, because whether we like it or not, we treat people unnecessarily all the time, and I wanted to make sure that we wouldn't be doing that in this case.

So, from the 100 FALSE positives while I think there is some harm there, I think weighing it against the benefit will get us towards the right conclusion.

DR. HOWELL: Jane next. As a matter of policy, we will always have comments from the members of the committee, and the liaison member, before we go to the public.

DR. GETCHELL: Just a few comments.

First of all, the word willingness bothers me a little bit. I would rather see that we demonstrated ability than willingness. Also, on the last bullet where it talks about appropriate resources, I think that needs to be coupled with some idea of the cost of this.

I also wanted to comment on Piero's comment on the method. Yes, it will eventually sort itself out, but I can tell you before I would implement it in Delaware I would want it to be pretty well sorted out.

DR. RINALDO: I agree, and in fact, I was actually

thinking about the willingness, it could be replaced I think. Your suggestion is good, but I actually would have a commitment to a start date.

DR. VOCKLEY: Let me -- I use the word conditions here because it was late and I was just typing, and that is the word that came to mind. I mean what this really is, is this is the additional information that the Committee has requested. These aren't conditions, and the last one is not a condition. The last one is this committee, Alan suggested that this committee make the recommendation that funds be made available for this testing, so that is a fairly generic and I think safe statement to put out here.l

DR. HOWELL: And again when we discussed this yesterday, if you remember, we identified certain areas where we had holes, and the purpose of this document is to list the holes that we thought were present, that the group working in this area will need to answer to come back, and it was really an advice document more than, you know, this is what you need to -- this is what we think the holes are really, and so forth.

DR. LLOYD-PURYEAR: Since this has to be transmitted into letter and there was talk about writing recommendations to the Secretary, these aren't really

clear recommendations to the Secretary, and, well, that is what Kristine [ph] said to me during the break.

DR. RINALDO: But this I think is a condition to return to the meeting.

DR. LLOYD-PURYEAR: Well, but you would need to outline what you are telling -- it is served a dual purpose -- to outline to the research community at large what it is you want them to do, but you are also telling the Secretary that you are saying this, and they are just not -- I don't think it's clear and maybe Mei and Jenifer, well, Jenifer isn't here -- are these clear to you guys what it is you want, or what it is we want, the committee wants?

DR. HOWELL: I would think that the recommendation of the committee would be the recommendation of the level that we have placed it, and we have identified these areas where additional information needs to be acquired, and basically lists those.

Ned.

DR. CALONGE: I was actually thinking about bringing this up yesterday, and I probably should have. Michele, I am trying to understand the issue about when we take action and when a letter goes off, because another option if we thought this was a C+, this

is a 3+, it's almost ready for prime time, we just need some gaps filled in. Would a better answer have been to table the vote, so that we don't send a letter and we try to get this gap information in, and I just didn't know how long it was going to take to get that, so I was comfortable voting, but I at least want to have a think about would it be better to send a letter to the Secretary now saying this is our recommendation because -- or would it be better to say we will table the vote pending the receipt of additional information on the search gaps.

DR. VOCKLEY: We don't have to table the vote.

We don't have to table the vote, but you also don't have to send a letter saying here is our recommendation to the Secretary.

DR. CALONGE: That is what I would like to know.

DR. HOWELL: Clearly, it could sit until -- we are not recommending for screening, and we are not recommending it should not be screened, so perhaps it would be better to let the thing sit until we get the additional information, and so forth.

Alan.

DR. FLEISCHMAN: As I understood the discussion yesterday, and what the minutes I thought would reflect, and I am talking now about the minutes, not a letter, it

would reflect the excellent evidence-based review which did not allow the committee to come to a conclusion that this ought to be recommended for screening, but there was a strong and vocal comment about the critical nature of the disorder and the likelihood that the evidence would be amassed if there were small additional conditions or information or data rather than condition.

So, I think the minutes should be continual, that this discussion should be part of those minutes, that the motion should be to put this into the third category with the idea that the evidence would require these things and the request to the appropriate agencies that resources be available to facilitate this action, so that in a short period of time, the evidence-based review would be sufficient for us to recommend or might be sufficient for us to recommend such screening.

I mean that's -- if the minutes would reflect that, kind of statement, then, I think the agency should take that seriously and the scientists should take that seriously, and we should do everything we can to accomplish that goal.

DR. HOWELL: That's my perception of what the minutes will show.

Piero.

DR. RINALDO: I agree completely. I think taking the step to send a recommendation to the Secretary should really be up to two ends of the spectrum either include or actually there is evidence not to include.

Anything in between should sort of remain at this level. I think the system so far seems to work, we have the evidence review, it clearly pointed out the gaps. This is now triggering an action to respond to the gaps, once the gaps are filled, I think the committee should again look at it and decide if it now has reached the threshold.

So, I don't think we should be recommendation going anywhere at this point. We have reached a certain stage and now we are looking at what it takes to get to the next stage.

DR. HOWELL: I sense the committee feels that there should not be any formal recommendation for the minutes are here, the minutes for discussion I think Alan has summarized what I heard, and Michele still thinks that these recommendations are vague.

Am I quoting you properly?

DR. LLOYD-PURYEAR: The researchers should do 1, 2, 3 I mean this is what you need, and I just don't see it. I mean willingness, ability of another state screening lab to implement, SCID screening, who is going

to implement that, how is that going to be implemented? Who can do that, what are you expecting a researcher to do with that?

DR. TERRY: And also to that point, some of these things, the researcher can't really -- doesn't have control over these variables, so we are sort of expand -- again the present setting of expanding this, so that the nominator then, not only is the researcher and the lay community, blah-blah-blah, but also has to be part of the public health system to get some of this stuff done as well. So we just need to think about how realistic this is for a researcher to do.

DR. VOCKLEY: We are not making these recommendations or saying that only the basic science research community or the public health research community are going to fill these needs.

We just identified areas that had to be filled, and it is obvious from the earlier discussion that the quality control materials are not going to come from the current testing laboratories. This is not designed to -- I mean we actually got probably even more specific than I would have by including CDC in that bullet. I don't think, Michele, that these need to be any more specific. I think what we are asking, what we are suggesting is fairly

specific.

What is not specific is maybe who should do them, but that is I think it has got to be the community that is invested in pushing this forward will have to respond by identifying the partners who are going to get the next state on board.

DR. HOWELL: Sharon.

DR. TERRY: To finish my comment, I think then we need to be saying who is responsible for this, and it is almost a moral imperative then and this is a tough thing. So, the nomination comes forward, and so as a parent I am saying gee, this looks like it's a good thing to get screening for and then as a parent I am saying so what is this committee going to do about getting the rest of this stuff done, or does the disease have to have advocates in the public health system, in the funding sources, in the CDC, I mean it becomes obviously very, very complicated, so I think we can't just sort of like drop this out there and say no one is responsible for any of these things.

DR. HOWELL: Let me make a couple comments, and so forth. Number one, we know two States are currently screening for SCID, and they have intimated, and so forth, that they are going to continue as far as we know, so that unless something very odd happens, we will identify a

patient eventually.

We have just heard from Harry that they are going to fund a State to continue. So, it seems to me that those two things are kind of coming along, and the next is an imperative to the lab to be certain that they stay below, and we have heard that the quality assurance stuff is being made available by the CDC.

So, I think people have either stood up and said they are going to do it, or it has been identified, I believe. Am I the only one that heard that?

DR. VOCKLEY: I agree completely, and Texas has already said that they are participating in collaboration with Massachusetts, so, in fact, the third state has already stepped up and will be starting.

I think these are easily attainable goals and specific enough.

DR. TERRY: So, really, the only one that is pending is the positive identification.

DR. HOWELL: And which we anticipate.

DR. TERRY: And funding, and funding is not a condition, but it is a recommendation.

DR. HOWELL: But it seems to me that one of the things -- this is an ongoing process -- I think that we are a little early in the process to get the stuff that we

need, and so forth. I think the process is underway, I believe, at least I heard it was.

DR. DOUGHERTY: My only question was a letter to the Secretary, would be whether Duane needs this to do the research that he talked about doing or support the research he talked about doing, whether it would help.

DR. HOWELL: The answer is no, I think he is shaking his head and I think the other thing is it's in the minutes of the meeting what we are wanting to do.

DR. ALEXANDER: It's there and I think that the letter to the Secretary would be premature at this point. When we have the evidence, then, we will send him a letter, and we should have that soon with the combination of the activities that we have started to engage in.

DR. HOWELL: We need to wrap this up, and so forth. Peter has a word before we wrap up apparently.

DR. VAN DYCK: I would just like to say I don't think it is the role of the committee or was it never thought to be the role of the committee to decide who should do something or that they should advocate for getting it done in the strictest sense.

We reviewed a reference-based review, we found gaps, and we are stating publicly what we feel those gaps are, and when they are filled, then, we will reconsider

the nomination of the category.

DR. HOWELL: I think that's well placed, and I think this outlines the gaps adequately, and so forth.

Is there further discussion? I mean this is a document that we simply want to append to get back to the group. They are all here, so they know what we would like to see.

DR. CALONGE: I think the title shouldn't be conditions for approval, it should be conditions for reevaluation.

DR. VOCKLEY: Gaps identified in the evidence.

DR. HOWELL: So, we will change that. We will add it to the document and so that the folks will know what we would like, and hopefully, this will rapidly come to a solution, and so forth.

Now, we are going to hear very briefly from the two distinguished people who have been waiting at the microphone.

DR. HINNMAN: Alan Hinnman. It strikes me from the discussions yesterday that the issues weren't necessarily about the willingness of another State, that the issues had to do with reproducibility, which we have two different tests being used now, we don't have evidence of how the tests can be transferred to another area, and

the second issue was capacity of State labs to be able to

carry it out, and it seems to me that an assessment of the capacity of laboratories is one of the evidence gaps that you have as well as evidence that the test is transferrable.

DR. HOWELL: Well put. I think that that is true, and the other issue is the numbers game. We need more numbers to get to that person.

Mei.

DR. BAKER: I just want to quick say people talk about giving a test. I think you need to be clarified with it, because Anne and I mean Massachusetts and Wisconsin virtually use the sand principle. Use it real time. The formatting a little bit different, but it is virtually the same path. For the newborn screening ideally people looking to like RO7. If you have this for the one peer, then, do the second peer.

To me, I think it is a different task. I think we need to keep this in mine, too.

DR. HOWELL: Thank you very much. Is there further discussion about this? Is there any ambiguity? We are going to change some of this so it is not a condition for approval and things of that nature, and so

forth.

DR. VOCKLEY: Wordsmith the minutes. I will be happy to help with that .

DR. LLOYD-PURYEAR: And the recommendation is category 3?

DR. HOWELL: Yes, it's a C.

DR. LLOYD-PURYEAR: Category 3C.

DR. VOCKLEY: With these gaps identified.

DR. LLOYD-PURYEAR: Before we re-evaluate it.

DR. HOWELL: And we would hope that that will happen promptly because we think it is an important condition that we want to see move along.

DR. LLOYD-PURYEAR: We have formally approved them. I had to change them because the legislation changed because the general services administration said I had to move things from the charter to the committee's bylaws. So those two things were done.

DR. HOWELL: Okay.

DR. LLOYD-PURYEAR: Plus, I put in the decision protocol.

DR. HOWELL: These are the same ones we have had, but they have had some changes with the new charter, and

the new charter obviously had some reflections for the Newborn Screening Save Lives Act, and those are legislative things that have been moved in here.

Would you like to comment about those?

DR. CALONGE: With the recognition that they are set in perpetuity because we want to be a group with continuous quality improvement, I would move that we accept these presenters.

DR. HOWELL: Is there a second?

ATTENDEE: Second.

DR. HOWELL: Any further discussion?

[No response.]

DR. HOWELL: Those favoring?

[Chorus of ayes.]

DR. HOWELL: Outstanding. It is unanimously approved.

We will have a telephone meeting in May, and Michelle would like to hear from you about items that you would like on that agenda. Certain things will carry forth from here.

Denise, you have something already in mind, I can see.

DR. DOUGHERTY: Well, I noticed from the

legislation that we have a new requirement, and that is to produce a report to the Secretary of Congress. Now I have forgotten. But even though it is not due for another two years, I would say it is not too early to clarify exactly what it means because it says the Report on Newborn Screening Guidelines, which I don't think we have done under that title.

So I think it would be useful for the committee to think about what that report might include.

DR. HOWELL: We will have that as an agenda item, then, maybe for May.

DR. DOUGHERTY: Yes. We could start in May, but it will take a face-to-face.

DR. HOWELL: Okay. Other things, if you would please submit those.

The dates that we have for the September face-to-face meeting is September 24th and 25th, and I hope that that will work in your calendars. There has been some circulation about that, and hopefully, if you could please put that on your calendar, that is one week after Roshashana, so that we should have people. However, Yom Kippur is the following Monday, but that will be a window between those important holidays.

DR. TERRY: So that is the NCHE meeting.

DR. LLOYD-PURYEAR: You know, we sent this out,
and I'm
sorry. I mean, this is --
DR. TERRY: No. So that will be what it is up
against.
DR. LLOYD-PURYEAR: But they don't come to our
meeting.
DR. HOWELL: Let me make a few other comments.
In your book tucked in the front cover, you have this
document that I think many of you have seen and read that
is from a publication from the President's Council on
Bioethics. It is a focus on newborn screening. It was
published in December of this year, and this group worked
for a very long time on newborn screening.
I think it is interesting. Let me make a few
personal comments now. It is interesting to me that a
Presidential commission looking at newborn screening, not
only failed, but refused to have members of the
congressionally mandated committee on newborn screening,

this committee, appear officially before them, which I
think is somewhat unusual.
Anyway, I think that this is a document that we
may want to discuss at some point in the future. I would
not suggest today.

There are a number of publications that are in the process of being submitted discussing this document, and I think after those are submitted and in press, I think that it will give a time that we can discuss this document and perhaps invite some of the authors of the other documents that I am aware that are in press discussing this document would be my idea, rather than to discuss this as a freestanding document today. I am sure most of you have read this in one form or another.

Does anybody have any comments about it?

[No response.]

DR. HOWELL: We will plan to discuss it, but I think it would be appropriate to have some balanced information about this document at the time we discuss it.

Does anybody disagree with that?

[No response.]

DR. HOWELL: Maybe you can read that on the plane.

Since Piero is officially departing the committee, but we anticipate that he is going to be here much of the time, I am going to ask Jerry to chair the internal working group that looks at nominations and priorities that come before the committee. We would hope that Piero would continue to serve on that committee.

I also am going to ask Harry and Ned if they would participate on this. This is the committee that looks at documents internally when they come, recommendations when they come to the committee, and then get some report to the committee about what should be done with those, whether there is sufficient evidence to go to the work group, et cetera.

I think that we need to be thinking about the future, number one. We will have a preliminary review of Krabbe disease, which is currently understand evidence review, at our May meeting.

Then I think that, as you know, the new charter for this committee requires that a person, an expert in infectious diseases, be appointed to the committee, as well as a person who is an ethicist professionally in the area.

I think that one of the things is that we will need to think as we move forward on expanding our scope a bit. One of the areas that the CDC recently had a major meeting about was CMV. For example, when the ACMG originally considered conditions for newborn screening, infectious diseases were not considered simply because of the expertise of the panel, but I think that there is considerable interest in screening in the newborn period

for certain infectious diseases, and CMV is certainly one of those. So I think we will want to start thinking about expanding a little bit.

There is also considerable interest percolating around such technologies as oxygen saturation in identifying potential fatal heart disease in the newborn period. That has been discussed by the American Heart Association.

We have had discussions with some folks in the past about that, and the British Medical Journal has an article in 2008 from Sweden that is very supportive of that particular technology, but again, that expands out again into a slightly different arena of hospital-based newborn screening that would be situated in the hospital, as opposed to the lab and so forth. So I think we need to be thinking about where we are going as we move along in the future, and I am sure that other people have lots of other great ideas.

We have heard some work today. I was pleased to hear that Piero is doing some work with immunoreactive proteins and comparing it to enzyme assays in tandem mass spectrometry. There has always been a continuing discussion about whether or not you have had an immunoreactive protein that is inactive. So, hopefully,

some of those will come out.

California screens for thalycemia. I think the other question is, are there certain things that certain States are screening for that we ought to think about that have not yet come before this panel and so forth, but those were the only things that are really on my agenda.

Are there other things that should come before this august body before we adjourn?

[No response.]

DR. HOWELL: Silence.

DR. LLOYD-PURYEAR: The last discussion item that Dr. Howell raised of things to go forward with, the Krabbe review is the last review that is in the pipeline. So, if we want the evidence review to take up any other items, we need to think about that quickly.

DR. HOWELL: Let me make one comment about that. As you know, we recently had an excellent evidence review on Pompe disease, and we concluded that it was a very important condition.

There were life-saving treatments, like all treatments for these children. Life saving doesn't mean that it is completely cured, but it clearly is life saving, and there were certain datasets that weren't available, for example.

We did not send in our note back to the Pompe nominator, the areas that we saw holes in. We talked about them. We said we would really like to do that.

DR. LLOYD-PURYEAR: Yes, we did.

DR. HOWELL: Did we?

DR. LLOYD-PURYEAR: Oh, yes.

DR. HOWELL: Michelle says that we did tell them. We did not have a chart, that I hope we will have in this one, that said we want to see this, that, and the other thing. I think that that is an important thing that we do. Hopefully, those studies will proceed with some rapidity, and we will have a national study, and we will have a little bit more information and can revisit that condition too.

Anything further? Chris.

DR. KUS: We had a good discussion about blood-spot banking, and the question I have is what do we do with that. What is the role of this committee relative to that? There were lots of statements recommending guidance and all those kind of things. Do we do anything with that?

DR. HOWELL: Any comments? Peter, did you want to make some comments about the role of this committee and such activities? We certainly will continue to discuss

it, I can assure you.

DR. VAN DYCK: Well, I think the committee should decide whether they have a role or not. I think it is a ripe area for discussion. I don't mean today.

DR. HOWELL: Right. I know you don't mean today.

Coleen, you had some comments?

DR. BOYLE: I guess I was thinking of the same thing. I thought Botkin made some very important recommendations or provided some very important guidance, particularly in terms of how we move forward on filling some of the evidence gaps here.

I think it would be an important issue for the committee to take up as to how we could help move that along to put in place, a biobank that actually could start to address some of those questions.

DR. HOWELL: I think that is the kind of discussion that would benefit greatly from a face-to-face meeting. So perhaps we can put that on the September agenda.

I think that we also need to have increasing public dialogue in this area, which is beyond the scope of this meeting, but hopefully, that can happen.

Piero?

DR. RINALDO: A few comments. The first one, I

think it would be appropriate if we talk about the physical matters for population screening. We actually should look at all, so hearing screening, asymmetry -- because I really think that it will serve as internal controls to each other.

The second one is your comment about the fact that we don't have after Krabbe, another evidence review cooking, it clearly reflects the fact that there are no conditions being nominated.

Now, I think it would be obviously a message to deliver that perhaps it is a good time to nominate something, but at the same time, I really think we have an obligation to remind potential nominators that I think the experience learned from the first two experiences about the need to have a prospective, ongoing population screening, and the need to have identified cases shouldn't be lost.

In other words, I hate to see premature nominations coming forward, just because the time seemed to be right. So I think we have a role.

My last comment is sort of a parting comment. I just want to express really how much of an honor and a privilege it has been to work with you all. It has been really a remarkable professional experience. Thank you.

DR. HOWELL: Thank you, Piero. We expect to see your certificate on your wall when we visit in May.

[Laughter.]

DR. HOWELL: Is there further comments?

[No response.]

DR. HOWELL: Can we have a motion to adjourn? No one wants to leave.

ATTENDEE: Move.

ATTENDEE: Second.

[Laughter.]

DR. HOWELL: Move and a seconded.

[Whereupon, at 2:10 p.m, the meeting was concluded.]

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ecessed, to reconvene on Friday, February 27, 2009.]

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