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GENETIC DISEASES IN NEWBORNS AND CHILDREN
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Rotunda Room
Ronald Reagan Building and
International Trade Center
1300 Pennsylvania Avenue, N.W.
Washington, D.C.
PARTICIPANTS

R. Rodney Howell, M.D., Chairperson
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Executive Secretary

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William J. Becker, D.O., M.P.H.
Amy Brower, Ph.D.
Peter B. Coggins, Ph.D.
Gregory A. Hawkins, Ph.D.
James A. Newton, M.D.
Mary Jane Owen, M.S.W.
Piero Rinaldo, M.D., Ph.D.

LIAISON MEMBERS:

James W. Collins, Jr., M.D., M.P.H.
Joseph Telfair, Dr.P.H., M.S.W., M.P.H.

EX-OFFICIO MEMBERS:

Coleen Boyle, Ph.D., M.S.
Denise Dougherty, Ph.D.
Peter C. van Dyck, M.D., M.P.H., M.S.

ORGANIZATION REPRESENTATIVES:

Norman B. Kahn, Jr., M.D.,
American Academy of Family Physicians
E. Stephen Edwards, M.D., F.A.A.P.,
American Academy of Pediatricians
Nancy Green, M.D.,
March of Dimes Birth Defects Foundation

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Opening Remarks

DR. HOWELL: Ladies and gentlemen, let me welcome you to the sixth meeting of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. We still are looking for a great word to describe this committee, other than the very long word, without much success.

We have some new members with us today that I would like to start by introducing. We have two new members of the committee who have recently been appointed. They are not seated at the tabletoday because their paperwork is not complete and Michelle is very meticulous in following the federal guidelines. But we would like to welcome Dr. Alan Newton, who is sitting in the first row. Dr. Newton is a neonatologist from Montgomery, Alabama and we welcome his expertise in joining the committee. Seated next to him is Mary Jane Owen. Mary Jane is Director of the Disabled Catholics in Action here, in Washington, D.C. She has a long history in working in advocacy for persons with disability. We welcome both of them as new members of the committee.

As you know, we have discussed, and the committee has had a considerable discussion about the importance of adding other members to the committee is liaison members and we are delighted that that process has moved ahead really quite well at this point. We now have at the table a series of outstanding

new liaison representatives. The first is Dr. Norman Kahn, seated here. Norm is Vice President for Science and Education of the American Academy of Family Practice.

Steve Edwards is back under a new banner. Steve has served on the committee and he has now returned to the committee as the official representative for the American Academy of Pediatrics. Steve is a past President of the American Academy of Pediatrics. He has been active in the committee and, Steve, we are delighted to have you back with a new descriptor.

Seated next to Steve is Dr. Nancy Green.

Dr. Green, of course, has been very active in newborn screening for a long time, and is the Medical Director of the March of Dimes, in New York. Nancy, we welcome you here as the official representative of the March of Dimes. We are expecting Tony Gregg, at least I think we are expecting Tony Gregg. He spoke to the committee previously and Tony is here as the official representative of the American College of Obstetrics and Gynecology. He is a geneticist who
spoke about genetic issues and OB/GYN at one of our previous meetings.

The Association of State and Territorial Health Officials has not yet appointed a permanent representative as liaison to this committee but we are delighted today to have Lauren Raskin Ramos representing the Association here today. Thank you very much.

In the member's book is a very thoughtful letter from Jennifer House, President of March of Dimes, who has served extremely well on this committee, thanking us for her ability to serve on the committee. I have written back to Jennifer thanking her for her outstanding service. We will miss her but she has said that she will continue to

be very actively involved in the committee and its activities.

I think that we will come back to this again, but there are other liaison members that we have discussed in the past and we want to discuss probably a little bit more. One is that the Department of Defense, with our multiple military people, have special areas within newborn screening and they have been very active in discussion of their issues in the past and I think that we will want to consider adding a single representative from the Department of Defense, which would not be someone from downtown but someone that represents various military groups in the newborn screening. The other area that we have discussed in the past and we will certainly want to consider further is FDA because the FDA is involved in so many overlapping issues with regard to therapies for rare diseases and things, so I think we will want to come back to that in our business meeting today.

We have a busy agenda today. We are going to start off early this morning with Dr. Atkins who is going to talk about decision-making and examining evidence. We talked about this before but, as you know, Dr. Atkins and his group focus on this area.

We are particularly pleased also to have Dr. Larry Pickering, whom we will introduce later but Dr. Pickering is the Executive Secretary from the Advisory Committee on Immunization Practices, and some of the overlapping issues there are quite prominent and we will be looking forward to hearing on that. Piero and Bill are also going to be on the program, talking about formatting how conditions will be considered for future additions, etc. Brad will give an update on the status of newborn screening.

Friday's agenda is going to be largely for the subcommittees. I think that as we move along we will certainly need to discuss the activities that should have a priority so that we can move ahead on those. The other thing we have to always be clear about is whether or not the issues that are of interest to us really fall in the committee's purview. We would like not to spend a lot of time talking about things that are really not our business, shall we say?

The other thing is that I would like us to consider things that are actionable, things that we really can move ahead and do something about. It is nice to talk about things but it is nice to have things that we can do and accomplish that would help us.

One of the things that many of you have been very much aware of recently, and those of us who live in Miami are acutely aware of, is the disruption that can occur with hurricanes. An article that I have had a chance to review as a pre-print describes the activities dealing with rare diseases and the treatment of rare diseases in New Orleans in the wake of Katrina. The issues that surface there are extraordinary. I mean, when you have not only the patients widely distributed but the availability of special products, the availability of records, you don't know where the patients are, you hardly know where the doctors are, that is a very important thing. As we consider these things we need to think about advance communication and effective communication because that was really a huge problem in the recent hurricane things.

Now, the first order of formal business that we have before us is the minutes of the fifth committee, which was July 21 and 22. They are in the book and we need to review those and have a motion to approve those. Can we have a comment about the minutes and a motion to approve them, or any changes to the minutes? You have not seen that? All right, perhaps we will defer that until you have had a chance to read them. That would be prudent.

Behind the minutes, I might point out--that I am sure you have not seen--is a letter from Dr. House that I referred to earlier and that is just for your information.

As we continue our discussion over the next couple of days, there are a few things that we need to keep in mind. One is that we need to continue to have the discussions that we have had about how we examine evidence. That will obviously come with Dr. Atkins' talk. That will lead into how one decides about conditions that are appropriate for addition in the future and the basis on which those additions might be made and the long-term and persistent issue of what constitutes evidence. One of the key areas that we need to focus on is long-term follow-up, and one of the things that is going to come out of this meeting is that we have meetings of the subcommittee and we have additions to that where people are experts in follow-up, etc.

The other thing that I would like to remind the committee of is that if you read the charge of this committee, which the committee members certainly have, it is that we are supposed to also provide advice to the Secretary on grant programs and, as far as I am aware, that definition of grant programs is broad, not just the grants that would come from HRSA but from any of the agencies under HHS that would be appropriate. What are the needs that we see for grants and what are the important grants that we might want? Let's keep that in mind so that we can continue to have that.

The long-term follow-up thing, one of the things that I would hope we can do is to have some presentations on some of the things that are going on in HRSA with some of their regional cooperative efforts that have some follow-up issues built into them. We need to hear about those.

The other thing that we are supposed to provide advice on is technology development. What are some of the new technologies that are needed? We need to keep that in mind as we move along, and as we move beyond the first part of our efforts which have been focused extremely heavily on the ACMG report, etc. I might point out, as everybody knows, that report has been sent to the Secretary. That is public information. The letter that accompanied it is in your folder. You have seen that letter, the committee members have seen that letter but that is in the folder also.

Are there any comments or questions before we get into the formal part of the agenda?

PARTICIPANT: [Not at microphone; inaudible].

DR. HOWELL: The letter has been sent and I personally am aware of the fact that the Secretary has the letter. The Secretary has read the letter and the Secretary is thinking about the letter and is currently drafting a response to the letter. The letter was actually sent in September. But, to answer your question, we have not yet received a formal response to that but we will anticipate that. Any other comments or questions?

[No response]

Well, why don't we get under way then? David Atkins is not here yet. Why don't we just go on with Larry? Larry, are you willing to start off the thing first thing this morning? We will move to Dr. Pickering. He is here and Dr. Larry Pickering is a distinguished pediatrician and infectious disease expert. The pediatricians in the group know him as the editor of the Red Book which is, shall we say, the bible of the practice of infectious diseases in pediatrics. Larry also serves as the Executive Secretary of the Advisory Committee on Immunization Practices, and he comes to us from the Centers for Disease Control.

Examining the Advisory Committee on Immunization
Practices: ACIP Committee Structure and Decision-Making

DR. PICKERING: If it is okay, I will just sit here because the computer is here. I think this presentation is in the handout. Is that right, Michelle? So, basically, I will just follow along and I don't know how you want to handle questions, as we go along or at the end. Either way is fine with me, however Dr. Howell wants to handle this.

There are four things that I would like to do with this presentation. One is to review the vaccine approval process that the Advisory Committee on Immunization Practices undertakes; secondly, to discuss the responsibilities, the structure and the function of the Advisory Committee on Immunization Practices; thirdly, to review the interaction of the ACIP with the public and private organizations and societies with which we interact; lastly, to summarize the issues facing the ACIP. As I have heard a little bit just in the opening comments this morning and in talking with Dr. Howell previously, I think there is a lot of overlap in what I will say and what activities need to be considered here.

Briefly, this is a slide showing the development of the pediatric vaccine recommendations and policies, specifically where the ACIP enters into the process. Manufacturers will undergo vaccine development and testing and then they will submit a license to the FDA for a biologics license application for licensing of that vaccine. The Advisory Committee on Immunization Practices becomes involved back at this stage because that is when the preparation is really necessary.

Usually ten months later is when the FDA needs to make a decision. So, the FDA will either license a vaccine ten months after the BLA application is submitted or sometime after that. There are expedited reviews but all manufacturers want their vaccines to have expedited reviews so generally it is a ten-month period. The FDA has their vaccines and related biologic products advisory committee. Once it is licensed, once a vaccine is licensed, then it is almost an immediate fact that the Advisory Committee on Immunization Practices needs to make recommendations because once the vaccines are licensed everybody wants to know what to do with them because once they are licensed they can be utilized. So, the ACIP then meets generally right after the licensure. At the next meeting the recommendations will be made. At the same time another committee meets, the Committee on Infectious Diseases of the American Academy of Pediatrics. They make recommendations also for vaccine usage and those recommendations go to the board of directors of the AAP.

Now, one of the potential problems and one of the problems that occurred in the past was discrepancies in recommendations from the two committees. Now that is fairly well adjudicated because there are members of each committee on the other committee so that there is very good communication in harmonizing the recommendations. I will talk a little bit about the immunization schedule that we have. There is very good communication and harmonization with the ACIP, the AAP and the American

Academy of Family Physicians. So, once the recommendations are presented from the ACIP to the CDC, these recommendations are not official until approved by Dr. Gerberding, who is the Director of the CDC, and by Secretary Leavitt, and are published in MMWR. This is somewhat of a problem because the ACIP is an open meeting and when the recommendations are made everybody hears that, including the press, so they assume that that is law. Well, it isn't law until they are approved by the Director of the CDC and published in MMWR and that takes several months.

That causes a little bit of dyspepsia for practitioners because they see these recommendations and, yet, the funding and the actual approval is not immediate. The same thing occurs with the Committee on Infectious Diseases for the Academy. Those recommendations are not official until the board approves them.

Once these recommendations become official, then the uptake and financing occurs. The laws kick in and they are utilized eventually by the public and private sector. So, the real point I think to take home from this slide is the fact that the ACIP has to be involved very early on in this process so that when the licensure occurs the recommendations follow shortly thereafter.

Now, the responsibilities of the ACIP really are twofold, one on this slide and one on the next slide. Since 1964, it provides advice and guidance to the Office of the Secretary and the Director of the CDC on the most effective way to prevent vaccine-preventable diseases. That usually deals with vaccines but it also deals with antigens and other related agents, antisera, immune globulins, antiviral agents and so on. For instance, with the area of immune globulins, at our meeting next week we will consider VZIG, varicella-zoster immune globulin. The sole manufacturer of that compound is not making it anymore so we have to come up with recommendations on what to do with individuals who may need this preparation when we don't have any of it made anymore in the United States. So, these are the types of things that we deal with in addition to vaccines. Of course, we make recommendations about licensed vaccines and non-licensed vaccines as warranted. The latter is very rare.

Since 1993, the second part of what the ACIP does became effective, and that is the funding aspect of vaccines, the Vaccines for Children Program. This is a unique statutory authority that was established in 1993 and it gives the ACIP the authority to determine the vaccines, the number of doses, the schedule and the contraindications for the Vaccines for Children Program. The Vaccines for Children Program is an entitlement program for poor children in this country. It is a 1.5 billion annual entitlement. Shortly after the recommendations are made by the ACIP this committee will also vote on whether it should be included in the Vaccines for Children Program. Usually these two are synonymous.

I am moving to the structure. The ACIP has 15 voting members, including the chair. They serve four-year terms. The CDC committee nominates these individuals. That is sent to the Office of the Secretary, Secretary Leavitt in this case. There are usually two names sent for each position, with a description of what the position entails and why we need somebody in this category and why the individuals that are being nominated have been nominated. Then the Secretary either approves or disapproves these nominees and then they are installed, sometimes somewhat delayed as I see from your meeting here also. The chairman is selected from the current members.

So, that is one aspect of the ACIP. The second major aspect as far as structure are the eight ex-officio members. They attend all the meetings and they represent eight government organizations, which are listed here. Thirdly, we have 22 liaison organizations that send members. Two of the liaison organizations send two members each and that is the American Academy of Pediatrics and the American Academy of Family Physicians. All the other organizations send one. These are, of course, professional societies and organizations that are responsible for vaccine development and immunization programs. I have listed these here and I am not going to go over all of them but you have them in the handout to see.

These individuals play a very important part in ACIP by, number one, serving on the working groups, which I will talk about; secondly, making sure that there is harmonization with what the ACIP recommends and their organizations; thirdly, supporting ACIP recommendations. So, there are a lot of individuals that

attend, very high quality people from all these organizations. I think that is one of the reasons why things flow so smoothly, because of the input of these very important organizations.

The difficulty that we have is that there are a lot of organizations that want to be liaisons to the ACIP and we are somewhat limited in the number that can be liaisons. We are working on putting in writing some structure about what it requires to be a liaison organization.

Now, the function of the ACIP is listed here. We have three meetings annually. It seems like we have 18 meetings annually but there are only three, February, June and October, and ours will be next week. The agenda items--the formulation and construction of the agenda of the ACIP meetings is absolutely critical because there are always time constraints. There is a huge amount of material that must be digested by the ACIP members and discussed at the meeting. So, the agenda items are solicited from many people, the ACIP members, liaisons, CDC staff and others, and there is a standardized form that we utilize. It is submitted and then the committee that reviews all the agenda items, which consists of the ACIP chair, the executive secretary and the CDC steering committee, makes the decisions about what goes onto the agenda. They also make the decisions about the time allotted. Everybody, of course, wants four hours to present their topic and that is not really possible so we have to sometimes make some concessions--the people who want to present have to make some concessions. We follow the FACA rules and procedures. As I said, all the recommendations of the ACIP are published in final form in the MMWR.

Now, the expertise of the ACIP committee members is very important. We need people that are knowledgeable in infectious diseases and immunology, pediatrics, internal medicine and, of course, family physicians span both of those so we need expertise in family medicine, public health, vaccine research and policy. Then, we have one consumer representative that is appointed to the ACIP. One of the 15 members is a consumer rep. One of the very important aspects of the ACIP is the working groups. The working groups' function is absolutely critical to the working of the ACIP. The working groups develop draft policies and options that undergo review and vote by the full ACIP. The working groups do not vote. They do not have the power to vote. Only the ACIP members vote on anything. But they are really the work horses, so to speak, of the ACIP in preparing all the material that will be presented for consideration by the ACIP members. There are many teleconferences that the working groups have in between the meetings, before and during the ACIP meetings. So, the working groups usually will meet the night before or the first night of the meeting to discuss various aspects of their agendas.

The working group guidelines are regularly updated. I have been working on those and I think we will have those done next week to give to all the working groups. The makeup of the working groups is important. This is in our bylaws. Working groups have to have two ACIP members, one of whom serves as the chair and the CDC lead staff who usually is the person that organizes gathering all of the information that the working groups consider. Ex-officio representatives may be on. For instance, an FDA member may be on a certain panel or other ex-officios. The liaisons serve on all working groups. All working groups have at least two liaison representatives, depending on what the subject is. If it is an adolescent vaccine or an adult vaccine we make sure that somebody representing those constituencies serves as a liaison.

Then, there are two types of consultant groups. One is experts from universities or other areas that may be doing research on a certain vaccine. They may be called in to present to the working group. Then manufacturers, of course, come and present data. The working group meetings are closed so a lot of the data that is really confidential from the manufacturers, of course, is not distributed.

We currently have 14 active working groups, which is a huge number. I will show you why we have so many. The vaccine area is very vigorous currently and this is the most working groups we have ever had. It is about at the unmanageable point right now because of the huge number and the work that all of these individuals have to undertake.

Now, this is an example of what the FDA does, of course. They approve vaccines. I have this slide in here to show that this is the approval of the recent Tdap, tetanus, diphtheria and acellular pertussis, vaccine that was licensed in May for use in adolescents and adults. The adolescent aspect was approved at our meeting in June and the adult utilization of this vaccine will be discussed next week.

Now, if the ACIP doesn't become involved until the FDA generates a licensure it would take a long period of time. The point to make here is that we have to become involved in these vaccines way before the FDA licenses them so that the recommendations are all ready because it has to be as smooth a process as possible.

As I said, there are 14 ACIP working groups. There are four permanent work groups and then there are ten that are task oriented. The four permanent ones are listed here. The adult immunization working group--the adult immunization schedule was generated about three years ago and it is updated every year. In fact, it was just published this month. This is very exciting because in the past we really didn't have an adult platform for immunizations but now, with the Tdap vaccine, the acellular pertussis for individuals up to 64 years of age and the zoster vaccine which will be considered soon, there are more immunizations that are becoming available for adults. The general recommendations are updated every three years, and that contains information about the generalities of immunizations like how to store vaccines, how to give vaccines, and so on. This is a document that is applicable to all vaccines.

The harmonized schedule refers here to the pediatric and adolescent harmonized schedule. This is updated every year and is published in January. Again, getting three major groups, the ACIP, the American Academy of Pediatrics and the American Academy of Family Physicians together to agree on a harmonized immunization schedule is remarkable. This first occurred in 1995 and has been very successful since then.

Then, influenza vaccine--because of all the changes that occur in influenza and that are occurring not only in the regular influenza but also what we have been reading about pandemic flu, this is a very active working group that is one of the permanent ones.

These are the task-oriented working groups. When the task is finished the working groups are finished but it seems like we don't finish any tasks. We just keep adding onto them. Bioterrorism is quiet now, thank heavens, the working group. It is interesting because Dr. Howell mentioned earlier the evidence-based aspects of what you do in this committee and we have an evidence-based working group. The reason for that is that the American College of Physicians does not accept the ACIP recommendations because they are supposedly not evidence based. In reality, all ACIP recommendations are evidence based but they are not numbered and lettered like people like. So, the evidence-based working group is formulating some guidelines so that all future ACIP statements will be evidence based and be, hopefully, accepted by the ACIP. So, it is a structure process, which is a good one. It is an interesting process to go through.

The hepatitis working group deals with A and B. The HIV group is quiet. Human papilloma virus is an interesting one because that is causing some real discussion. This vaccine probably will be licensed next year and there are a lot of issues dealing with HBV.

Then, the meningococcal, MMR, varicella, pertussis. Rabies is a new working group and that was formed because we are losing manufacturers of rabies vaccine so a working group was formed to try to deal with this. Rotavirus is a diarrheal disease in children and that working group is active and that vaccine will probably be approved the first of next year. So, all of these working groups are extremely busy.

Now, there are several key documents that the ACIP utilizes and follows. One is the charter that was amended in October of 2004. We have policies and procedures and that also is being updated. And our bylaws, we have to update these every so often. Guidelines for working groups is the guideline that structures what working groups can do; how they should be formed and how they function. The October

2005 version was the most recent one and that is again being updated. We updated our list of working groups. The current chair, Dr. Abramson, and I have been working on that to keep the working groups streamlined and functional and highly effective. Then, the calendar of the ACIP activities.

We also just started a new member orientation book and we have a mentor program for new members that come on the committee so the new member is paired with an old-timer. They sit together at the meeting. They discuss all aspects of what is happening before, during and after the meeting. This really brings new members up to speed fairly rapidly. As you know, anyone who comes on a committee--it is daunting to step in when other people have been doing this for several years. So, this is an attempt to try to resolve that situation.

Now, the management of the ACIP is as follows: The executive secretary leads the CDC management of the ACIP and makes sure that the meetings follow the guidelines, approves the meeting agendas, guides development and revision of procedures, charters and other documents.

Also something that we just started with the last meeting is that I prepare a briefing document for Dr. Gerberding, the head of the CDC. I think this is very important because, as you know, you don't want your leader to be blind-sided by anything. So, outlined in that briefing document is each of the agenda items. There is a seven-question document. All of these are then reviewed and given to Dr. Gerberding so that she knows what is on the agenda; what potential problems may develop; and where she is going to have to respond. We also provide this to all of the ACIP members so that they have a quick overview of what is going to be on the agenda and what they are going to have to consider. Historically, this position was held by the CDC associate director for science but that has been changed recently.

The ACIP currently sits in the National Immunization Program which provides critical management and support services. It might be somewhat under-staffed currently. There are two FTEs. There is an assistant to the director for the immunization policy and this is usually a medical officer; secondly, the ACIP committee program analyst, and then I am the third person that does this. It is not included in this overall financial aspect. So, there is a small staff that supports the ACIP but, in addition to that, we have a lot of CDC members who work on the working groups and provide a lot of the leg work for all of the working groups material that will be presented.

The CDC ACIP steering committee--there is a steering committee that advises me on what to do. I will tell specifically what they do in a moment. We have the federal advisory committee management that provides FACA support so if I ever have any questions or we ever have any questions about what we are doing and whether it is appropriate, they are easily answered. There is a FACA course which is a two-day course that we all need to take that supplies all the rules and guidelines, but they are a very good backup if we need it.

The other things is we have advice from the Office of General Counsel at the CDC. There are a lot of legal issues that come up with our committee, particularly with conflicts of interest, and the general counsel for the CDC is very helpful in answering all of those. Then, we have funding for the ACIP operations.

The steering committee is a very important committee. It coordinates all the ACIP activities across the coordinating center. The CDC is currently undergoing some reorganization, which I won't burden you with, but it undergoing reorganization and basically there will be three or four centers in the coordinating center. Then, there will be one person from each of those centers that will be on the steering committee. They work with the individuals in their specific centers, the CDC lead staff, to make sure that anything that needs to be done is done. It develops consensus on CDC position, ACIP issues, policies and procedures, ACIP meeting agendas and nominees for the ACIP replacement committee members. This steering committee does all of that.

It is convened by the executive secretary. The ACIP chair also participates in the steering committee meetings. The composition, again, is the director of the National Immunization Program, representatives from each of the centers in NCID, the AD for the immunization policy, the program analyst and generally FDA ex-officio members will attend the meetings, many of which are by teleconference. Generally this committee works through a consensus.

Now, other activities--we develop agendas for the meetings. This begins two months in advance of each meeting. So, when we finish our meeting we are already beginning to think about the agenda for the next meeting. The center representatives, as I said, work with the lead staff in the various centers to define the agendas, the length, the speakers for each topic and issues for vote versus discussion. So, something will come up with a vaccine that we may not take a vote on during a meeting but it will be discussed. What we usually try to do is have one or two discussion periods at each meeting before a vote is held on a vaccine. For instance, at this meeting we are going to vote on hepatitis A vaccine. The committee has already been primed at the two previous meetings with a lot of background data about this disease and this condition. All the economic analyses have been presented. So, when they take a vote on an issue there is a fairly good understanding by the committee of all the issues and they are as informed as they can be.

The second big thing that the steering committee does, as I mentioned earlier, is to develop the nomination slate to replace the departing members and the chair. The chair serves usually three years and each member serves four years. So, with 15 members we have about four vacancies every year. This committee then will review the nominees and select a lead and an alternate candidate for each position, as I said, with the qualifications for that position and why these people have been submitted.

Other activities are to refine continually the policies and procedures, including conflict of interest. There has been a lot of interest, of course, in government officials and their conflicts and committee members and their conflicts. It is a very stringent procedure that the ACIP follows. There is a forum for considering how to prioritize development of new recommendations; determine the need for new liaison organizations; and deal with the structure function activities of each of the working groups in specific and in general.

The participants in the United States Immunization Program aren't just government officials and aren't just the ACIP. Industry is involved, academic institutions, private providers and insurers. So, it is a very complex area with which we must deal. The childhood vaccine policy recommending bodies are listed here. Each of these organizations or committees makes recommendations about immunizations and CDC, the ACIP, as I have stated, and the American Academy of Pediatrics and the American Academy of Family Physicians and we have been very fortunate to have the recommendations for both the adult schedule and the pediatric schedule harmonized.

The ACIP, the AAP and the AAFP produce this harmonized schedule, as I have mentioned, on the childhood and adolescent immunization schedule. It was first harmonized in 1994. Before 1994 different schedules were published and that was a disaster because when the AAP or the AAFP went public with one schedule and the ACIP another you had the public sector getting one recommendation, the private sector perhaps another. It was very confusing. That has been dealt with and no longer occurs. The ACIP and the AAFP produce a harmonized adult immunization schedule and the new schedule, for any of you who want to make sure you are up to date on your immunizations, was just published in October. They are updated once a year and they look at the complete schedule, each vaccine in the context of all other vaccines.

This is a slide showing the 2005 recommended childhood and adolescent immunization schedule. This one will undergo significant changes because there have been about three or four new vaccines or vaccine changes that have occurred this year so there will be a lot of changes to the schedule that will be published in 2006. This is the new adult immunization schedule. It has been reformatted so it is a lot easier to use. It basically gives all of the vaccine age groups and underlying conditions for those individuals and, again, in a harmonized fashion.

Now, the evidence consideration in vaccine policy development, the things that are general--these are generalities that we consider are a preventable burden of disease by a specific vaccine or biologic that is being considered; the efficacy and effectiveness in various age groups and populations. As a rule, population-based immunizations are not nearly as effective as age-based immunizations. In other words, hepatitis B, if you recommend it for everybody is much easier to institute than if you recommend it for high risk groups. Safety of the vaccine is a major consideration; interaction with other vaccines; and, of course, now more and more we are getting into the economic benefits of vaccines because of the expense of them.

As I said, this is January of last year. The ACIP put out the recommendations for the harmonized schedule. The American Academy of Pediatrics published it the same month and the AAFP published it the same month in all of their respective journals and publications.

Now, I mentioned just a moment ago the types of ACIP recommendations that we have. Universal use, which are age-based. Rotavirus, for instance, will be recommended at two, four and six months of age--an age-based recommendation. This is the least confusing and the easiest to implement, and the vaccine must benefit all people or all children in that specific age group for which it is recommended. The zoster vaccine to prevent shingles will be recommended--may be recommended for individuals over 60 and it has to benefit everybody within the population for which it is recommended.

Risk-based or medical occupational behavioral risk--it is difficult for providers to identify those who should or should not be vaccinated, and this is much less well implemented than universal immunization. So, this is one of the considerations that is taken into account when a recommendation is made.

This is just to show the success. When you make a recommendation, whether it be for screening or whether it be for a vaccine, you like to see that it is a successful recommendation. This is the recommendation for Haemophilus influenzae invasive disease. In 1985 there were probably 20,000 to 30,000 cases and now this disease has been markedly reduced, not eliminated but close to it in the United States--so, very successful.

I want to move a little bit now to talk about some of the financial aspects, and this is assuring the purchase of recommended vaccines. I think when you do screening it costs money; when you make vaccine recommendations it costs money and this is a major consideration. This is a shared public sector and private sector responsibility. The cost of the vaccines is a significant barrier or potentially could be a significant barrier to vaccination, and the adequate financing of vaccines is critical to successful implementation.

Vaccines are paid for, as shown here, by the private sector about 45 percent; federal through a 317 program. The 317 vaccine program pays for vaccines for children that are poor, the children that are not covered by insurance. The parents earn money but a very little bit. The Vaccines for Children Program, which covers 40 percent, is for children that have no coverage whatsoever and their parents generally have very little to no income. Then there are state programs.
The reason I show this is because the ACIP is involved in approval of the VFC Program. The Vaccines for Children Program was started under the Clinton administration. It is an entitlement program for I think the most vulnerable children in our population. Forty-five percent of young children in the United States, unfortunately, are eligible for VFC. It provides mandatory funding. It is an entitlement program. If the ACIP approves a vaccine, votes a vaccine into the VFC program, then children are entitled to receive it. Inclusion of vaccines into VFC is controlled by the CDC's ACIP. Section 317 has to be approved annually by Congress. It is discretionary funding and there are no restrictions on vaccines or populations but the states utilize this to cover children that are poor and would not have any way of receiving vaccines except through this program. Then, the private health sector, of course, covers the remainder.

Now, the state government role in purchasing vaccines varies substantially by state. I won't get into that because it is a very complex area. Some states have purchase policies in which they guarantee purchase

of all vaccines and states regulate most insurance companies and can mandate inclusion of vaccines into insurers' packages. The thing to really remember is that the VFC Program is an entitlement program for all children in all states.

This is how vaccines are given to children. Twenty-four percent are in mixed public/private; 14 percent are in public health; and 62 percent have private providers, many of whom are enrolled in this VFC Program. The Vaccines for Children Program, which is approved by the ACIP, has about 45,000 providers. Collectively, VFC providers vaccinate about 90 percent of all children. Improving VFC providers' practices improves vaccination for almost all children.

This is an issue that we are facing. I mentioned earlier that the ACIP is busier than it has ever been with 14 working groups. You can see that in 1985 there were seven vaccines that were given to children. In 2005 there were 13 and there are a couple more on the horizon. Some people say, "gee, aren't there too many vaccines?" My response to that is that I don't think there are enough. I think that prevention, which is something that your committee deals with a great deal with the screening tests, we deal a great deal with also. Having seen these diseases in many children and having seen them die from them, I think it is very important to prevent these diseases.

This is interesting. It gets into some of the financing issues. In 1985, this slide shows the federal contract prices for vaccines recommended universally for children and adolescents--from 1985 on the left-hand part of this slide to 2005. In 1985, it was $45 per child. In 2005 it is $570. You can see in that orange area that a huge part of this was due to one vaccine, a pneumococcal conjugate vaccine. This shows and illustrates the fact that financing of vaccines is becoming very complex and is something with which we have to deal.

This is something that we have put on the web site. We put this on the Academy of Pediatrics web site because we couldn't put it on the CDC web site, for many reasons, but it basically is the status of the licensure and recommendations for new vaccines. This allows anybody to go into this web site and see exactly where we stand with regard to new vaccines. I think this is very important for information dissemination. It lists the vaccine on the left-hand column, the manufacturer, when the BLA was submitted to the FDA, what the age indications for the vaccines are, and then whether or not the vaccine has been licensed by the FDA and, if it has been, the date. Then, on the right-hand side is the status of the ACIP recommendations. The ones in blue, of course, you can click on and go directly to the web site that lists those recommendations.

Now, this is important because there is a lot of confusion out there about where various vaccines stand. If you look at, for instance, the top one, Menactra which is a meningococcal vaccine, you can follow on through and see that it has been submitted, licensed, and there are recommendations out there and people can click on those recommendations. So, I think that developing something that keeps everybody--the public, physicians, anyone that wants to know, up to date on the status of what is going to be considered is a very important area.

This is the status of our licensed vaccines we have to deal with. I have grouped them a little bit differently but these are all the new ones that are being considered. All of them have been FDA licensed and the ACIP recommendations are shown here. It is interesting that the second dose varicella vaccine was not recommended by the ACIP at the last meeting. There is a lot of discussion particularly about the economics of this vaccine. It was not approved. It will be discussed again in the February meeting. Several others, of course, are pending.

In conclusion for this rapid journey through the various ACIP activities, routine immunizations, we feel, provide a tremendous benefit to infants, children, adolescents, adults and to society. I am sure you feel the same thing about your screening activities for newborns. Immunizations is a shared public/private responsibility. The ACIP, we feel, is a well-functioning, well-respected FACA committee. And, there are many challenges facing the ACIP, including vaccine financing, vaccine supply and vaccine acceptance

issues. These are critical areas that are going to have to be dealt with in order to ensure a very successful program.

So, that is the extent of what I want to present and I will be glad to answer any questions, Dr. Howell, if you want me to.

[Applause] Questions from the Committee DR. HOWELL: Thank you very much. Do we have some questions for Dr. Pickering? Amy?

DR. BROWER: Thank you. So, the FDA submission seems like a trigger for the process but how do you find out about what is in the works prior to the FDA submission? Is there some notification on what is going to be submitted either from the manufacturers, from researchers or from FDA?

DR. PICKERING: That is a very important question. As I alluded to, we have to know when these are happening. There are a couple of ways to find out. One is from the FDA and they really are constrained about giving out information because of all the rules and regulations. So, getting anything out of the FDA, because of their rules and regulations, is not generally the way we find out information. We do find it out from the manufacturers. Because of all of the people on the committee and all the liaisons, many of whom are doing research in various vaccines, we have a really good handle on what is going on with regard to vaccine development. The manufacturers are very helpful in letting us know when they submit or when they are going to submit.

For instance, there is one specific organism that a vaccine is being developed for and Dr. Abramson and I received a call from the manufacturer saying that they were going to submit in December. Because of that, we will form a working group and have that already begun. So, I think the answer to your question, in brief, is that the manufacturers generally are the major persons that let us know and we work closely with them with regard to this issue. Secondly, with the whole community in vaccines also, because of the research that they are doing, we will sort of have an idea about what is coming down the line. Some of that, of course, we can't make public because it is confidential but we at least know or have an idea when we can form specific working groups.

DR. BROWER: Thank you. Just to follow-up to that, how do you decide which ones you are going to look at in a formal working group? Let's say there are ten things that people are working on in a year, do you look at all ten or do you have some process that says, okay, out of these ten these are the five that are really going to take the next steps in the next X amount of time?

DR. PICKERING: I think there are several levels to that question. One is that if a vaccine is going to be submitted to the FDA we have to consider it for the public sector. We don't do anything with the Department of Defense. They have their own mechanism. This is only for the general public. So, if the FDA has a submission we have to look at it and we will either form a new working group if it is for a new vaccine or try to fold it into an already existing working group.

Secondly, how to prioritize what is presented and when, that is a decision the steering committee makes. Generally we have been able to get most of the activities that the CDC lead staff and the working group want on the ACIP agendas. They are never happy with the amount of time that they receive but are happy to be on the agenda and that is the compromise that we sometimes have to make.

It is really critical--because you bring up another point, it is really critical that the ACIP members be communicated with as frequently as possible so they know exactly what is going on. They have to have a good baseline of data about the safety, the efficacy, the immunogenicity of all vaccines going into the meetings so that they can make informed decisions. That is why we have generally presentations for a couple of meetings about a specific area before a vote is made so that they are brought up to speed.

DR. EDWARDS: I guess the thing that surprised me about your presentation is just the logistics of your meeting. I had not realized that you had 22 liaison groups and 15 members and staff, and others. So, are there like 50 or so people sitting around the table and only the 15 members vote? Is that correct?

DR. PICKERING: That is correct.

DR. EDWARDS: But do you have 50 or so people sitting around the table discussing?

DR. PICKERING: We have an inner table and an outer table. The inner table is the ACIP members and the government ex-officios who can be called upon to vote if we don't have a quorum of ACIP members. Then, around the outer table are all the liaisons. The people, of course, who speak are the ACIP members and the liaisons. Generally we will have the public and the press, and there are usually 200 or so people representing the public and the press that are also there. They also have an opportunity to speak in two public comment periods, one on each day, and if there is time, 53 after each of the discussions are held. So, it is a fairly large meeting of about 300-400 people.

DR. TELFAIR: Dr. Pickering, the harmonization of the schedule has been an important public service over the last decade. I was struck by the fact that you mentioned that at least one of the liaison organizations has not participated in that harmonization through some criticism of the evidence-based nature of the recommendations. Could you explain that in a little bit more detail? It would seem that this harmonized schedule would be important for everyone to buy into.

DR. PICKERING: Yes, that is a good question. The childhood schedule, of course, is harmonized and bought into and published in your journal and the pediatric journal and ACIP MMWR. The American College of Physicians is a very evidence-based group, very evidence-based group, and they feel that the ACIP recommendations, although they are evidence based, need to be more officially evidence based. So, that is why the evidence-based working group was formed. But the real benefit I think is to really provide some continuity between each of the recommendations that is made and utilize the same evidence-based recommendations for each of those recommendations that are made from the ACIP. So, that is why that was formed. I think there are people from the American College of Physicians, of course, on the evidence-based working group. That is moving along very well and I think will be discussed at the next meeting and fairly soon will be officially implemented.

DR. TELFAIR: May I just ask a quick follow-up question? Do you expect the ACIP to change its policy on what it considers evidence based, based on the recommendation of that working group?

DR. PICKERING: There may be some changes. As you know, there are different organizations that follow different evidence-based grading. AAFP is a very evidence-based organization. AAP is evidence based. So, there are some differences. There may be some changes in how we currently rank various studies and that is under discussion by the working group. But it will be made in conjunction with the working group which has representatives from all of those various organizations.

DR. RINALDO: Dr. Pickering, somewhat following the question from Dr. Edwards, I too was impressed by the size of this committee. But I also was a little surprised to see, and perhaps I missed it, no formal representation of the association of microbiologists. Can you elaborate on that?

DR. PICKERING: Yes, the American Society of Microbiology is not one of the liaison groups, probably because their organization deals more with development of vaccines rather than vaccine policy. There are representatives, of course, of ASM--they are not representing ASM but ASM members that are on various liaison groups but that is one organization that is not a liaison organization and they have not applied to be a liaison organization.

DR. RINALDO: If I can follow-up, as you know, we have worked with consideration of certain infectious diseases as part of a screening panel, and really in the end we had to table it because we were unable to

engage infectious disease people. We are still debating if it was our fault or perhaps they were not too receptive on the other end.

DR. PICKERING: We do have as two of our liaison representatives the Infectious Disease Society of America so that group is represented, and they are the clinicians that do infectious diseases. So, there is good input from that group. Then, the National Foundation for Infectious Diseases is also a liaison representative. So, we have good input. As you know, many members of IDSA are also members of the ASM. The overlap is really fairly significant. So I think, although not officially represented, there is good representation of members who are ASM members.

DR. RASKIN RAMOS: Thank you in particular for mentioning the Vaccine for Children Program and other ways that we are trying to ensure equitable access to vaccines. It is my impression that, kind of despite these programs, some states are still having difficulty supplying all vaccines for all children. So, I think a word on that would be helpful for this group, and maybe also a word on congressional appropriation and the role that that has.

DR. PICKERING: Yes, the financing of vaccines is really done under several umbrellas. One is Vaccines for Children which is an entitlement program and once the vaccine is recommended by ACIP and voted on for the VFC, all children get that. I mean, that is an entitlement program. So, that is good. The issue that you raise is an important one because it covers the next group which is the 317 funds. The 317 funds cover children, as I said, that are poor. The parents may not have insurance and they are below the mean income level. This is a program that is approved yearly by Congress and the funding has not quite kept up with the amount that is needed to vaccinate these children. Therefore, the states have to make decisions. They have to make a decision when a new vaccine is licensed and approved whether or not they continue with immunizing against some of the vaccines that they are currently immunizing against or whether they substitute one of the new ones. State funds can be used to supplement 317 funds but it is a very difficult situation. Of course, the insurance companies also cover certain individuals. Sometimes there is a little bit of a delay between approval and when the insurance companies will officially cover them.

This is a major issue that we have to deal with, the funding of vaccines for children in our country. It is a major issue. I won't speak for Congress but, hopefully, they will recognize the importance of children in their deliberations.

DR. GREEN: The issue of adequate evidence has come up in this committee a number of times and will continue to do so, obviously. So, I was wondering, you said this was an evolution for your committee but do you go through a sort of specific flow chart kind of strict paradigm or is it a more generic consideration? Particularly if you have specific criteria, maybe it would be helpful to share that with this committee.

DR. PICKERING: Yes, it is both. It started out generically discussing what everybody else was doing and what should be incorporated into it. Now there are specific tables and figures that are being developed. I would be happy to share those with you. I will talk to the chair of the committee and, when appropriate, we can get that information to you. I can work with Michelle on doing that, yes.

DR. BOYLE: I just wanted to get back to the Vaccines for Children Program and I guess its influence on the advice that the ACIP gives. Obviously drawing parallels to what this committee is trying to do, it is also giving advice to the Secretary about newborn screening-related issues, particularly about what types of tests or what conditions children should be screened for. A question clearly continues to come up in terms of financing and barriers out of these programs. Just perhaps going back a little bit in history, you know, to 1993 or prior to that, what influence has the Vaccines for Children Program had in terms of carrying through the mandate or actually making your advice a reality?

DR. PICKERING: I think it has been a huge benefit for children because the most vulnerable group of children in our society is now covered, and is covered as a mandate. So, vaccines that are recommended for children, these individuals will receive as part of the VFC Program. I think personally it is a wonderful program that really ensures that the disadvantaged children in our society have the opportunity to become fully immunized. It would be nice if we had such programs for a lot of the preventive services for children. That is my personal opinion as a pediatrician and a father and grandfather.

DR. EDWARDS: I wonder if you would be willing to give us your personal opinion. As you know, you are here because we are interested in the model of the ACIP as far as if it projects and if it would be appropriate for newborn screening testing. So, what is your personal opinion about this model and its appropriateness for looking at new newborn screening tests? Having worked with the ACIP, do you personally think that this is an appropriate model for us to consider?

DR. PICKERING: Yes, I think so, Dr. Edwards. I talked to Dr. Howell about several of the newborn screening activities and what your considerations are and several of them seem to be the same. I mean, it is sort of a parallel track with different issues and I think the things that the ACIP really benefits from, which would probably benefit the newborn screening, would be the gathering of experts in the area to really provide advice; secondly, the strong interaction that we have with the public/private sector, other government organizations, as well as private organizations, the 22 liaisons that we have; the openness of the meetings so we get good input from the general public on the activities that are ongoing; and the real structure so that it is a structured area, structured activities and meetings that we have that everybody has input into. And, the way that it runs, I think it runs fairly smoothly for the complexity of what we have. So, I think, in summary, there are a lot of similarities and having such a committee for newborn screening, at least from what I know, would be very beneficial.

DR. BECKER: If I could expand on that, I have spent a lot of the time assimilating your conversation and wrote down a list of about half a dozen similarities and differences between them, and you have already illustrated several of them--the stakeholders being very similar; there are many different groups making different recommendations about either vaccines or newborn screening. You have working groups, we have working groups. Yours are probably more evolved. Ours are just getting started. I loved your slide that said that it is a shared public/private responsibility. I think that is probably true for newborn screening. Financing, of course, is a challenge for both of us.

Then, some of the differences--ACIP has developed a way to disseminate their recommendations via publication through MMWR. That is something that we don't currently have or maybe have not gone as far. You obviously have a lot more liaison organizations than we have and there may be some financial constraints there. I like the new member orientation and that may be a note. I saw Michelle writing it down as well when you brought it up.

You have tried to solve some of the financing issues with the Vaccine for Children, the entitlement program, and that may be something this committee wants to take on because, obviously, we have a lot of under-served, under-insured, uninsured people needing newborn screening.

Then, I also particularly liked the communication avenues that you have. Our meetings, as you correctly pointed out, are open as well as yours, but also putting in information on the status of recommendations on web sites, the AAP's web site, I think could be important because right now it is my understanding that really our communication is the announcement of the meetings really on the web. Then I think the minutes are published. Is that right?

DR. PICKERING: Yes, they are.

DR. BECKER: Yes. You know, I think the status of our recommendations, or the status of where the letter is to the Secretary, or the status of the ACMG report--you know, it may be unclear as to where some of

those things are. So, I think there are a lot of similarities. I think there are a few differences. But I think it is a model well worth considering as we move forward.

I guess the one difference--and please don't have heart failure, Michelle, is the oversight. Clearly, ACIP's oversight is more geared down CDC's pathway whereas oversight of this group is more under I guess the auspices of HRSA. But since we are all HHS I guess we can say that.

DR. PICKERING: Thank you. That was a very nice summary. I appreciate it and I think one thing, the dissemination of information, all of the recommendations are published in MMWR but, believe it or not, not everybody reads MMWR as I keep telling people at the CDC. So, we have our liaison organizations which are very, very helpful in disseminating information so that when an MMWR publication comes out, the AAP, the AAFP, all of the nursing organizations, everybody lets everyone else know by linking to those web sites and that is extremely helpful. All the states also do disseminate the information so we really have a very good network to get these data out.

DR. BOYLE: I just wanted to follow-up on Bill's list of commonalities and differences. I guess one thing I see as very different between newborn screening and the vaccine program--and correct me if you see it differently, is that vaccine is sort of a one-shot deal. You know, the child gets the vaccine and you are done with the program. Whereas, with newborn screening it is a continuum of activities. You know, it is not just screening the children. It is the follow-up of all positive screens. It is the care and the management of the child and that can go on for that individual's lifetime. In many ways, you know, we have been focusing on the screening piece of it but it is much more complex which, you know, makes the parallels for me a little bit difficult between the two groups.

DR. PICKERING: Yes, Coleen, that is a good point but, on the other hand, we have a new birth cohort every year of four million children so they have to be immunized. We have a very extensive surveillance system for these diseases that have to be monitored. I mean, we are continuously evaluating outbreaks of measles, and outbreaks of pertussis, and outbreaks of this and that. So, these diseases, unfortunately, don't go away. Polio has gone away, except now we have some polio cases--not cases but polio isolates in Minnesota. Smallpox has gone away. That is the one that has. But the other ones haven't. So, it is a little bit different but we have to do surveillance because these vaccine diseases, if we stop or if there is a downfall in immunizations like there are in certain areas of the country, they will come back and then we have our four million kids, as you know, that you have to screen and we have to immunize every year. So, it is ongoing. There is no question, it is ongoing. There is no letup in this area whatsoever.

DR. HOWELL: We have a lot more questions. Let me pick up on Coleen's thing for those of us who work in newborn screening, I have a slide you would like and it says "newborn screening is not a test." I think the system is the key thing. But Piero has some exciting comment here.

DR. RINALDO: Actually, Coleen, a key component of the immunization process is actually to monitor and detect adverse events following immunization, which I think really is one thing that certainly has caught the attention of the public. In fact, that actually leads to my question and that is that there is somewhat of a similarity with newborn screening. Often we hear about strong opposition to immunizations and vaccinations. So, I would like to hear how you handle those.

DR. PICKERING: With a lot of patience. Yes, there are various individuals in our society that feel, for one reason or another, that vaccines shouldn't be given to children. So, the thing that we have to do there is be very patient and continually educate about the benefits of vaccines--education of healthcare professionals, education of parents and patients if they are older and need their immunizations.

But also you raised a point, and I am glad you did and I appreciate it, about the immunization safety program. We have a very vigorous immunization safety office which now had been moved into Dr.

Gerberding's office under the direction of the associate director for science. It monitors very carefully the safety of all of our vaccines through several well-established mechanisms. There are some very effective measures that are set up to ensure that after a vaccine is licensed and approved the safety of it is followed and monitored.

DR. RINALDO: So, in a sense there is follow-up.

DR. PICKERING: Absolutely, yes, very vigorous follow-up.

DR. HOWELL: On your list of people I didn't see a lot of families on your committees. How do they have input as you are developing the vaccines and so forth? Because, again, the thing that we read most about in the papers are the opposition to vaccination.

DR. PICKERING: You mean the general public? Yes, that is an issue that we really have grappled with because we want as much input from the general public as possible. It is interesting, we have one community representative on the 15-member committee so he--it is a he this time--he will serve on some of the working groups, particularly the working groups where there may be some contentious issues. We have open comments at the public meetings and we listen, of course, to any public statements that people want to make. We have people come to the meetings where all the time we will have general public represented at the meetings.

When we looked at the meningococcal vaccine we had the three parents groups of children who had been maimed or died from that organism at the meeting, stressing the importance. When we changed from oral polio to IPV we had parents and children who had been affected by vaccine preventable poliomyelitis and had acquired polio from the vaccine. They were there to stress the importance of the change. We have parents who are against certain vaccines who will come and speak. All these comments are taken into consideration and are very seriously considered because we want to make sure that concerns that are expressed are listened to.

DR. HOWELL: The cost of developing vaccines, and so forth, at the current time is a lot of that development federally funded? Is it funded through the drug houses, etc? Because I guess one of the big problems is that drug manufacturers have a real problem in turning a profit in making vaccines. Is that correct? Is that a major problem? DR. PICKERING: Well, that is also a very contentious issue. I think that the development of a vaccine is very, very expensive and not all of them, of course, make it to the market and some, like the rotavirus vaccine, are recalled after they have been approved because of the potential safety problems that we find. I think the development of a vaccine is borne a lot by the vaccine manufacturers but also federal funding is very important in development of various vaccines. How much manufacturers make, and so on, I am not really the appropriate person to answer that question.

DR. HOWELL: The other thing is the age of the ACIP. In other words, it is my impression that the committee has been in effect for a long time.

DR. PICKERING: Yes.

DR. HOWELL: When did it start? DR. PICKERING: I think in the '60s. DR. HOWELL: So, it is 40 years old basically.

DR. PICKERING: Yes.

DR. HOWELL: Which I think has created an opportunity for a lot of evolution and a lot of situations, and so forth.

DR. PICKERING: It may have been in the '70s.

DR. HOWELL: But it is a mature committee now.

DR. HAWKINS: On education, who does the development of material. Does it come from the private sector? Does it come from the states? The federal government? And where does the funding come from to develop this material and how is it disseminated to the public?

DR. PICKERING: It comes from all. If it is a multiple choice, it would be all of the above. Many states have very good educational programs and develop excellent educational material that can be utilized. Secondly, the CDC has very good communications people that will develop educational material that is open to the public. Anyone can utilize it. It is in the public domain. And it is developed in several areas. One is specific information that is put on the web--questions and answers about vaccines that are continually developed. Then, lastly, posters, CDs and so on that are developed and available for distribution. Lastly, the private sector--all of the organizations, the AAFP, the AAP, will develop educational information about vaccines that is distributed to their members and also to the public.

DR. HAWKINS: You may have answered this but who kind of guarantees the uniformity of information? Is that controlled by the CDC?

DR. PICKERING: Well, no, the CDC can't control what other groups do but generally the CDC will be looked to for a lot of the information. CDC works very closely with the states so if a state comes up with some good information we will try to get it disseminated. But for much of the basic information the CDC is looked to for development of that information about various vaccines. For instance, now we have influenza. As you know, there is a lot going on in influenza so the CDC has established a web site, www.cdc.gov/flu, where all of the influenza information from the CDC is placed and that is available then and people utilize that, both in the public and private sector. The same thing happened with Katrina where all of the information, not only for vaccines but for other areas, was centralized in that one location to try to make information available to people for general utilization.

DR. HOWELL: I want to go back to the evidence base again because that has been one of the issues that we have wrestled with a great deal. I gather that you are not going to acquire new evidence but you are basically going to categorize material you have on hand. Is that what I understand?

DR. PICKERING: Yes. Yes, really, Dr. Howell, the evidence that is gathered is considered in an evidence-based manner. I mean, it is amazing how many people look at the data that are gathered and then the recommendations. There are so many layers of clearance, which is one of the problems why it takes so long in getting these things out because they have to be cleared by the working groups; they have to be looked at by liaison groups, and so on. So, all of that is done. There won't be any real change in how data are gathered or evaluated; it will just be change in the ranking of the recommendations.

DR. BOYLE: Just to elaborate a little more on the specifics. Who gathers the data in the working group? I am more curious about the functions of the working group only because I am chairing a subcommittee now and feeling like we are not making the progress I would like us to make. So, how do the working groups work?

DR. PICKERING: Well, let's take as an example hepatitis. Okay? There is a hepatitis branch at the CDC so when the hepatitis group was formed the lead CDC staff will be a senior person from the hepatitis group. Then, that individual will select other appropriate CDC staff not only from the hepatitis group but also from the National Immunization Program or from other areas of the CDC so that all people are represented. Then, as the working group is formed, the ACIP members are selected by the chair of the committee to serve on this working group. There have to be two but there may be more. The hepatitis working group has seven members on it, which is probably a bit much but they have seven ACIP working

group members. Then, the liaisons that have expertise or needs in this area are also added on and then individuals from the universities or individuals that are doing research, as well as manufacturers are brought in to bring the information in.

But the real person that keeps things going is the lead CDC staff because they keep monitoring so if the ACIP chair of the committee wants something, the lead staff will gather that. A lot of the brunt of the work falls on those individuals.

DR. HOWELL: The bottom line, as I said, our committee is very young and we have a very modest budget. Larry's committee is not only mature--do you know what the budget is from your committee?

DR. PICKERING: Yes, I do but I have forgotten it. I am just now getting into the budget aspects because we are going to try to increase it. I can get you the specific number but I can't remember what it is. I apologize.

DR. HOWELL: It is clearly vastly greater than the budget we have.

DR. BOYLE: It actually says the budget here. I don't know if that is accurate. In the ACIP charter.

DR. PICKERING: It is probably in there. DR. BOYLE: Yes. I mean, it doesn't sound like a lot to me. I was surprised.

DR. PICKERING: It isn't. Basically I can tell you what it pays for.

DR. BOYLE: It is the second blue tab in the back.

DR. PICKERING: It pays for a couple of staff and a lot of that is for travel for the ACIP members.

DR. BOYLE: Right, it says 109,000 for the travel expenses and compensation, and annual person years of staff of 2.1, about 300,000. I am surprised it is that little actually.

DR. LLOYD-PURYEAR: That is not including all the CDC staff time that is in there.

DR. PICKERING: Yes.

DR. LLOYD-PURYEAR: I assume it is not including if you have to commission papers and research.

DR. PICKERING: No, the CDC staff will do that on their own. It does include the hotel, the meeting site, transcriptions, stenographers and the travel of the people on the ACIP.

DR. HOWELL: Just the voting members?

DR. PICKERING: Absolutely, just the voting members. Occasionally work groups will want to travel an expert in to discuss something. So, if somebody, say, from Stanford is to come in who is an expert in an area, then the ACIP will pay for that individual but we try to keep that minimized.

DR. HOWELL: Any further questions? One of the things that I failed to mention at the beginning of this meeting, and I apologize, is that Dr. Duane Alexander sends his apologies. He is representing the NIH at a meeting in Europe. And, Derek has let us know that he has a family emergency and will not likely be here but might be here later in the meeting.

I think that in view of where we, we are ahead of our schedule which is always wonderful, let's take a break now and let's return at 10:45 and we will hear from Dr. Atkins at that time, who is here.

[Brief recess]

DR. HOWELL: Ladies and gentlemen, Let's come back to our respective chairs, and so forth, and we will continue with our program. As we have already said several times this morning, this committee has been keenly interested in identifying evidence-based material that would underlie our recommendations for newborn screening, and we are pleased to have with us today Dr. David Atkins, from the Center for Outcomes and Evidence from the Agency for Healthcare Research and Quality. Dr. Atkins is going to address us concerning the role of explicit and evidence-based processes for making recommendations regarding newborn screening. Dr. Atkins?

The Role of Explicit and Evidence-Based

Processes for Making Recommendations

Regarding Newborn Screening

DR. ATKINS: I want to apologize for getting held up this morning but I think it was very useful for Larry to go first because I think he described a very well-established process that, despite being well established, is continuing to evolve. I think that this committee is early in its life and I think what I am going to talk about is sort of explicit evidence-based processes, largely from the perspective of a group like the U.S. Preventive Services Task Force. The reality is it is a continuing evolution so you learn as you go about how to make your processes both functional and feasible but also clear to your audience, and there is always a balance and tradeoff so it is sort of natural that as you learn and deal with new topics the process will evolve.

So, I am going to sort of pick up where Larry left off about a process that is now beginning to pay a little closer attention to the mechanics of how it looks at evidence and thinks through what kind of gold standard process might look like, not saying that that is what this committee would want to do, but that sort of very evidence-based approach that ACP has, and think about to what extent that could be applied to a difficult area like newborn screening, and think about what the roles of this committee would be versus what the approach of sifting through the evidence may be in a way that then can be presented to the committee.

So, I think the point I am going to try to emphasize is that I think it is useful to separate out the two processes, and have a process that sifts through the evidence in a systematic and well-described way but then produces a synthesis of that, not with conclusions, that is then presented to the committee. Then, the important role of judgment, because the evidence never makes all the decisions for you, and the role of the committee then is to say have they looked at all the evidence we need to know? Have they done it well? Then, given the evidence and given the judgment and the professional expertise we bring, what seems to be the right decision? So, more clearly separating out that process I think is a direction that has been helpful for the groups that I have worked with and I think would be helpful to this committee. So, that is just to acknowledge that this material sort of reflects a number of different sources.

Our agency works with evidence-based practice centers so we have had a lot of experience in synthesizing evidence. Those groups don't make recommendations. They produce that evidence for groups like guideline committees of the AAP or the American Heart Association that then take that evidence and turn it into recommendations.

I want to apologize. I ran off some copies late last night and managed to make single-sided copies of double-sided documents. So, they are running off copies and both the audience and the members will have copies of my slides by the end of the day.

Just to emphasize, the multiple goals of having a process that is both more explicit and more evidence-based--and when I say more evidence-based I don't mean to imply that the process right now is not evidence-based, but having a more explicit description of what was done, and how it was done, and how it got you to where you go I think is the sort of evolution of a process that I think is on the table.

So, one is to be credible. You want to convince people that your conclusions are right. The second, which is just as important, is this issue of being transparent. So, even if people don't agree with what conclusion you made they understand how you got there. You would like to make sure you have a process that is reproducible, that you wouldn't have reached a completely different conclusion if a couple of other experts had done the review or some other university had done it.

Then the fourth point, which is very important, is that even though you acknowledge that we don't have enough evidence, you want to specify what is missing because you want to direct the ongoing research to fill those gaps so that you never sort of say we are done with this topic but you say this is as far as we could get; if someone could answer these questions then we could make a more conclusive recommendation.

At the bottom is this idea that there is some sort of right decision and you would like to get as close to that as possible. That is an ideal that we can never completely reach. We will always have situations where, as new information comes out, we will need to revisit topics. But those are where you are trying to get to as you develop your process.

I don't want to belabor some of these sort of process steps of what goes into it. I think I talked a little about it last time when I was sort of talking about the different roles of evidence and judgment where the evidence is poor. But to quickly walk through that, in making the process more explicit it is helpful to kind of break it out into these different steps. There are roles for the committee in different parts of this step.

The first is to identify what the goal is and who these recommendations apply to. I think that is fairly straightforward. The second is to say, okay, what are we going to start with? What topics are we going to look at? What are the outcomes that we care about? Have we thought about every outcome that people care about? And to specify those ahead of time.

The fourth, which I will spend a little more time on is, okay, given that that is what we care about, what is the evidence that we think is relevant? So, you focus your attention on the step that is meaningful to answering that question and you don't get distracted by evidence that might be less relevant or misleading. Then to synthesize that and say, okay, given all we could find to answer this question, this is how confident we are in our answer and then it is the role of the committee to say this is what the evidence is and, given that evidence, this is the kind of recommendation we make. Given that there are going to be different qualities of evidence, what are the different grades of recommendations one might make? What I will talk about is that there might be more than just a yes/no kind of recommendation.

So, just to emphasize that using a more explicit and evidence-based process does not require evidence from RCTs. The Preventive Services Task Force is sort of often criticized that they will only recommend something if they have RCTs. RCTs certainly give you the highest internal validity evidence but it is obviously not feasible in this field or in many other fields. Sorry, RCT is randomized controlled trial.

So, I want to be clear that there is a small group who sort of say, well, evidence-based processes are meaningless because they require a standard of evidence that we can't achieve. I want to emphasize that that is not true. You just need to be clear that you have different strengths of evidence and you have to be clear what constitutes sufficient evidence for the decision-making you are involved in. Again, it doesn't

exclude the input from things other than peer-reviewed literature so you can have a process to include expert opinion and other stakeholders. Lastly, it doesn't prohibit you saying the evidence isn't great but we need to make a recommendation.

I think my focus is really on being explicit rather than on any kind of definition of what constitutes an evidence-based process. So, I think when Larry was talking about the ACP being very evidence-based, I think it is true and I think for some topics they do set the bar pretty high because they deal with lots of issues where you can demand randomized trial evidence. But I think what they are really talking about is being a little bit more explicit and transparent in what you require and how do you get to the conclusions.

What it does specify is what questions do you really need to answer in order to make a recommendation. What is the process by which you look through the evidence and how do you ensure that different people are doing it the same way? The reason for specifying that process in detail is to reduce the perception that undetected sort of bias or conflict of interest or just random variation can affect the outcome. The more specific you are about the kind of evidence and questions, the more confident people are that it didn't really matter whether it was a group of people at HRSA or whether it was a group of people at University of North Carolina or at CDC, they would all put together the information in a comparable way.

Lastly, the other point is to specify what the role of evidence is versus these other factors--I don't mean to say they aren't evidence but they are a different type of evidence so the role of expert opinion and patient preference, prevailing standard, etc.--to separate out the relative contribution of those things into the recommendation. So, you can make recommendations based on either of those or a combination of both but you should be clear what the recommendations are based on because you also want to explain to your audience how you got there, and also then it tells you, as new information comes in, that maybe the conclusions will change.

This is a sort of framework that I probably showed last time but it is just a useful sort of way of pointing out two things, one, thinking about the outcomes--it does three things. One is what are the outcomes of screening. Coleen pointed out that newborn screening is not just screening. It is the first step in a process by which you are hoping to improve outcomes for the infant. I could have put in another slide in here, that you have to control the diagnosis. So, you screen; you diagnose; you treat; and you hope that that is going to improve the outcomes. Along the way there are some potential adverse events that one needs to keep an eye on.

The arrows are just to sort of imply different types of evidence one might have. So, one might have direct evidence from a screening program that has been implemented by a state looking at outcomes in children. In the absence of that, one needs to look at sort of discrete questions. You know, these are all the issues that were in the ACMG report as specific factors. But having a framework like this can sort of help you put that information in a way that makes it easier to sort of synthesize what you know, what the gaps are, and have you really established that the screening will have the outcome that is more important to you, which is healthier babies.

I am not going to belabor the target population and audience. I think it is fairly straightforward. But I think it is important just to remember that the audience is broad, and it is typical that one doesn't realize how broad your audience is until you get out there with recommendations. So, obviously, the audience includes state screening programs and clinicians, but it is not just the pediatricians but it is the family physicians and nurse practitioners who are going to have to deal with parents who come in with questions about tests or need to think about referrals. It is other public health practitioners who are involved in a general decision-making process of which newborn screening is a part of. So, it is typical that your audience is broader than you initially realized and it is important to figure out how to include them in the process because I think the experience of many committees is that you start with a sort of more narrow focus and you come to some conclusions and then you realize there are other people who care about what you say and they may have different perspectives to bring to bear.

Identifying topics for consideration--clearly, the issue you are going to have to deal with going forward is you have completed a report on a number of conditions. That is sort of set at one point in time and now there are going to be new issues that are popping up.

The good news is that you don't have to deal with the whole universe at once, but you need a process for figuring out, okay, what is the next thing on our table.

I think what the groups I have worked with have done, both the U.S. Preventive Services Task Force and our agency, when we get nominations requesting that we do a review on something is that we have some criteria to say this is what would make it a useful topic to address. So, you need to have some minimum threshold of there is enough information out there to be worth looking at. You don't want to spend time sifting through everything and find out that there is nothing there. You obviously need to have an available test that has to be relevant to a sort of policy issue. So, I think the criteria things everybody knows but it is useful to sort of specify those.

You can have an open nomination process. I think Larry mentioned that there is an open process for ACIP. Clearly, there are people who are close to the issue who would know about things that are getting through different FDA processes or that states are grappling with. So, you can have a sort of open process where people can nominate things. It is useful to go out proactively to groups who are in the best position to know and make sure that they are soliciting. The problem is not that you are not going to get enough nominations, the challenge is, okay, given these how are we going to sift through them.

So, then you need a process to assess each topic against those criteria. That is not a trivial process. It doesn't require looking at every article that is out there but it requires some level of searching for the most important information and doing some preliminary look to say is there enough here to be worth trying to sift through? Is there a potential that this is going to be a useful process? So, one needs a process for that and I guess the take-home point I would make is don't underestimate the effort involved in that and don't assume it is something each of you can do in your spare time on weekends. We use a group to do that with topic nominations that come into our evidence-based practice centers. They can turn around things in a matter of a couple of weeks. They do sort of searches, not exhaustive searches but they look for major types of evidence. They look for existing reviews out there.

I mean, the problem for you is you are dealing in a field where you are the kind of leaders in it. There are not a lot of other people that are necessarily going to crank out these reviews ahead of you. Maybe that is not true, but I think we often have the luxury of saying, gee, we don't need to look at this topic. Someone else has already looked at it over in Europe or somewhere else. Then, that ought to come to a committee to say, okay, we have considered these 12 topics for nomination and, based on these criteria, we will start looking at these three or four.

Specify the outcomes of interest. Again, these things are sort of fact sheets in the ACMG report but I think it is important, if you look back on this framework, just to pay attention to the fact--and this is something that the Task Force emphasizes a lot dealing with screening tests, that the screening is the first step of a process and you have to really look at all the outcomes of that process and not just the one you are hoping to achieve but the other sort of unanticipated and potentially harmful outcomes along the way. You also need to look at not just how it is going to work in that ideal patient but how it is going to work as part of a screening program. So, in any screening program there are issues about how the program runs and how it functions.

The Task Force had some discussion about do you have to have proof that it works out in the real world before you make a recommendation. The Task Force said, well, that would be sort of an impossible standard, the example being colon cancer screening. So, it clearly can work in well-designed trials of screening. We know that out in the real world it is probably not going to work as well, but to say we are not going to recommend it until people start to do it and show it works gets you in a trap. So, one doesn't necessarily require showing that every state in the country can do this and do it perfectly right out of the

box, but one needs to be aware that the way things work in the real world isn't going to be the way they work in an ideal setting, and understand how that is going to affect your confidence that things are ready roll out now versus needing more information.

Again just to go back to those outcomes, clearly morbidity and mortality in infants is the main outcome. You want to capture also the impact of those kids on their families and on society. But in a program that is aimed at all kids you also have to be thinking about what are the potential outcomes for healthy kids, and are there harms that we need to be aware of and make sure that we want to minimize. The question marks are on there because I think different committees will define their scope differently. Okay? So, I am not saying the emphasis one puts on each of these is always equal.

But the last one is efficient use of resources, the whole issue of what are the costs of actually doing this through a program. What would be the impacts in an environment of constrained budgets of putting new money into new programs? Is that going to have effects on other things? This committee may not want to grapple with this because you can't anticipate what is going to happen in state programs. But I think it has to be somewhere in your consciousness.

I think the area where one can evolve the process to be more explicit is being clear. And I want to emphasize that it is the role for this committee to come to some clear agreement about this, what is the evidence that you think is relevant to answer the question. You need to give marching instructions to people who are going to go and look for evidence about the kind of things you care about. Obviously, the issue is that the evidence is limited for many rare newborn conditions so you don't have the luxury of saying only go out and find randomized trials done in 98 large populations; don't waste your time on anything else. You have to go and look more broadly. So, you need to say, okay, what is a reasonable way to broaden that evidence without getting into types of studies that you don't think help your decision.

I can't give you a simple answer to that but it is something that the group should think through together to say let's look at the range of studies that are out there. Which are the ones that really help us answer the questions we want? Are there types of studies--you know, individual case reports, editorials, things like that that really don't answer the question? They reflect someone's opinion on something or other study designs that have fundamental flaws so that you say they are just going to take us off track. Then you give those sort of instructions to a group whoever it is, but my point is it is not going to be this committee to say go find us this kind of evidence and put it together in a way that we can figure out can we answer these questions.

So, this is just to say, you know, the committee's role is to set the bar. I am not going to say where that bar should be. I think I come from an experience working with a group who admittedly sets that bar fairly high. In part it is because we look at all sorts of screening tests, a lot of them in adults, and the general feeling was we aren't yet doing a good enough job doing all the screening tests that work and where the Task Force is comfortable saying we don't know yet because, if we didn't have many things to recommend we might say, gee, we want to lower that bar and we don't want to wait for the ideal evidence.

There is also tension. If you set the bar too high, then there is a chance of waiting longer than you need to recommend something that is helpful. If you set it too low, you end up recommending something before it is ready; before it really is fully effective. There might be harms involved; a waste of resources. It is the committee's role to say this is where we set the bar and then, to torture the analogy, it is the role of the people putting together the evidence to say, you know, has the person made a fair jump--the analogy doesn't work very well. Anyway, you set sort of the ground rules. Someone else goes and puts it together and comes back to you and you say, okay, they have cleared the bar or they haven't, or they need to take a re-jump.

Judging the quality of evidence--there are many frameworks out there to set issues of quality standards. Again, I think given the challenges of these types of evidence you have to deal with I am not suggesting

that any of them are going to work ideally for you because they tend to be a little more oriented towards a hierarchy that emphasizes randomized trials. But what I want to point out is that there are sort of three steps to the process that sometimes get overlooked.

The first is taking each study one by one and saying, all right, given what we care about and what we know about different types of study designs, is this a good study or a bad study or somewhere in between? Okay, given that you have a number of studies that address this issue--prevalence. You want to say what is the prevalence of this condition? You say, well, to answer prevalence it has to be this kind of study. You find four or five of those and then you want to put those together. Okay, given that we have four or five studies, does that give me a reliable enough handle on what is the prevalence in the general population?

So, you need a process to evaluate studies one by one, to put them together and say altogether we have pretty good evidence on this one question. Then you need some process to put it all together at the end to say, all right, we have answered these different questions and putting it all together how confident are we that we should recommend this test? That is a judgment that in recommending it you are going to be doing overall good to the population.

In terms of quality of individual studies, again, it is the study design and for different questions you are going to be looking for different study designs. So, to answer the question about diagnosis, diagnostic accuracy or prevalence you are not going to look for trials anyway. So, there are specific study designs that research has shown give you the best answer on diagnostic accuracy or on prevalence and there are certain flaws to look out for in looking at those studies. So, one can specify for different types of questions in more detail the kinds of studies that one wants to look for and the kinds of issues to look for. The elements are going to vary both by topic and by the questions within the topic.

Again, when we talk about quality of study, we are really saying has the study design and the way it was executed an analyzed minimized the potential for selection measurement and confounding biases? That is sort of epidemiologist talk but to translate that into English, it is how confident can we be that our estimate of the effect is right?

So, just to be a little more specific about what we are talking about--treatment. So, if you are looking at studies of treatment, how effective is the treatment of this condition? We can find it and we are finding it because we think we can treat kids and make them better. So, what kind of treatment? You don't have randomized trials of treatment. These conditions are too rare and there are ethical issues in randomizing kids not to get treatment.

So, the real question is without that kind of randomized or even a control group, how sure can I be that the effects I see, if they seem to be favorable, have to do with the treatment? So, that means that since you don't have controlled studies what are the sources of bias in the absence of having a control group? Obviously, that is connected to how sure are we what the clinical course would have been without treatment. So, if we can be 100 percent confident that without treatment that control group, which we don't have, would have all died in this period of time or all had this kind of morbidity, then we can compare that to the effect we saw on treatment.

But you need to think through how do we know that, what is the source of our confidence that that would have been the clinical course. Again, one needs to think as you expand screening is the population you are not treating really the same as the population that we were basing our prognosis on. So, if you have a group of kids, all with one disorder, all of whom died or all of whom had this prognosis, were they really the same kids that you would find with a universal screening program?

Those are all issues which I know everyone on this committee is familiar with, but that is sort of a way of breaking it down, saying, okay, when I am looking at treatment studies these are issues I need to be

aware of and assess in some kind of systematic way so that I can at the end draw some judgment about whether I have established a benefit of treatment.

When looking at diagnosis obviously the question is do we have a test that is good at diagnosing the kids we want? Obviously, the population that it is applied to is an important issue. So, in the study that this test was tried out in, are they generally representative of the study that is going to get this test when a state starts implementing screening? Secondly, is the test applied in a way that is representative of what is going to happen?

So, if the study is done from an expert laboratory as part of a research study, what is going to happen when you try to take those results out to a state screening program, and how is the variability that is introduced there going to affect the results? There may be issues in the consensus about the gold standard for diagnosis. So, you have a screening test and then you try to confirm a diagnosis and there are various ways to confirm that. Is everyone in agreement about what that gold standard is? And, has the study used that kind of gold standard?

Then, what you really want to be able to do at the end of it all is get some estimates of what is the sensitivity and specificity and positive predictive value. You want to know, of all those kids who turn up positive on that screen, how many of them actually have the disease because they are the ones that are going to get subjected to follow-up testing, potentially to treatment if the diagnosis is made accurately. The positive predictive value of mammogram is about two percent. So, of 50 women who have an abnormal mammogram, only one of them has cancer. You know, two percent sounds terrible but we accept that because we have ways of confirming the diagnosis non-invasively. A proportion of them need a biopsy. And, we know what the benefit of screening is. So there is no sort of one single level that makes a test good or not but you need to sort of think through what are the implications of this testing, how many kids get caught up in that initial net; how we sift through the ones we want to capture from the ones that we don't care so much about.

Putting the evidence together, not to belabor it but the issues of what epidemiologists call internal validity of the individual studies. Then, the second question is they may be good but do they really answer the question we care about? They may give you a really good answer about a population which really doesn't help us in figuring out the real question of is this going to work in the real world.

Then, are the principles of other results, you know, comparable? Is there enough? Then, what I want to emphasize is this issue of directness. So, given that we want to say does screening improve this outcome, lower morbidity and mortality for kids, does the information we have make that link pretty directly or do we have to sort of infer that link by answering little pieces of the question? Maybe the more links there are in the chain, the lower confidence one has that one has gotten it completely right because if there are little problems each way in the link in the performance of the screening test, the diagnosis and then in the treatment, then you are not so sure that after that all plays out it is going to work exactly as you intend. The more real-world evidence with screening programs you have, the more confidence you have that you have that sort of direct evidence.

The Preventive Services Task Force I think distinguishes itself from many other groups in making sort of recommendations about adult screening and it attention to harms. Sometimes people think we pay too much attention to harms but I think the important thing is to at least acknowledge it. I think the Task Force has realized we need to hold harms to the same level and standard as benefits. So, just because someone thinks there might be harms, what is the evidence that there really are harms? So, it is important to set the same bar for how sure we are that there are harms.

But the reality is that all screening tests have harms, whether it is screening for prostate cancer or screening for glaucoma. Harms may not be important but they are there whether they are as trivial as, you know, a false-positive test and you need to come back and have your cholesterol rechecked to

something where the harms are more direct, such as an abnormal ultrasound where you need to get a laparotomy to find that you don't really have ovarian cancer.

So, there are false positives that you need to think about and they can be due to a number of factors, such as the technology limitations of the test, just errors in that process. Then, there is this issue of do we really even know what that positive test is, you know, where are the cases that we really want to find? So, we might be finding some people who have positive disease but we are really not sure we needed to find them, the example being mammography screening. You find a lot of women with ductal carcinoma in situ. Some of them are going to benefit from detection because treatment may, you know, make a difference. There are probably a lot of other women for whom ductal carcinoma in situ is a benign condition and they would have been better off not finding it. So, it doesn't negate the value of screening but you need to think about those issues and consequences.

Then, harms also include the psychological harms; the parents; downstream testing; the possibility that maybe you are going to treat some kids who didn't need to be treated; and the potential that you will be spending money without benefit.

Again, not to say how much weight one needs to put on these or not to exaggerate them, but I think it is especially important when you have conditions that are rare and for which the benefits are constrained by the fact that they are rare you need to pay attention to the harms because if there are some real harms it is possible that they could offset small benefits. Again, just to say you need to think about that in the real world where things don't work ideally.

This most important to the committee, given the boundaries you laid out, this is the kind of evidence that is important and these are the ways we would like you to put it together and have recommendations that are clearly linked to that. So, again, I have talked about the things the recommendations should reflect; how confident you are that this recommendation will do more good than harm. And, it relates to how good the evidence is; what the tradeoffs are. If there are no harms, then you may accept the other evidence of benefits. If there are real harms, you might set the bar higher for benefits. If there are difficulties in making a program work in the real world, that is another factor. Then, there are other issues like patient preferences and expert opinion that might come into play.

So, the Task Force has A, B, C recommendations, two sort of different levels of positive recommendations and one that is sort of insufficient. Then, I will show you some more specific wording about that.

But to talk a little bit about what are the considerations, I said an explicit process doesn't mean you can't bring in other factors beyond the sort of peer-reviewed evidence and the kinds of things that might be relevant to a recommendation that are concerns about equity. You know, how do we protect disabled kids and disadvantaged kids? Prevailing practice is probably less of an issue with newborn screening than some adult screening--the importance to parents and society; issues about feasibility; what weight do we give to issues of cost and resources. One can consider those evidence but when I say there are other considerations, they are considerations separate from the question about is this test going to work or are we sure that it is going to work.

One point about economic evaluation, I am not saying that that has to be a role of this committee but I think if you are going to introduce the issue of cost it ought to be done in a rigorous and a credible way. My experience in looking at even published cost effectiveness analyses on screening tests is that often they are done in a not rigorous way. I think we all recognize it is the 500 lb. guerrilla out there in the current healthcare environment so if we are going to talk about it, how can we avoid either being misled by superficial or misleading cost analyses?

I think the point to make is that you can't tell the cost impact from the cost of a test alone. You might have expensive tests that actually are cost effective because they have very good benefits. You might have a

very cheap test that is very expensive because it generates lots of false positives and lots of downstream testing. You know, the cost of a PSA, prostate specific antigen, is not very high but the costs of screening with PSA are much higher than the cost of the test itself because the false-positive rate can be up to 20 percent. So, if you decide that cost is an issue you will need a process for saying, okay, this cost would be too rigorous a cost analysis.

Obviously, obtaining input from the public is important but you need to balance interests from affected children with the people who represent interests of all children, and it is hard to get representative samples of that, and that may not be critical. You may want to get articulate people to give you a sense of how important this is to the kids who are affected and people who are thinking more globally about the best ways to protect the interests of kids.

You heard at the last meeting about ways to get expert opinion in a more formal way from the FDA. Again, when one has poor evidence--calling it insufficient is a little clearer--it is not that we know that things don't work; we just don't have enough to answer the question. But you may feel you need to make a decision and experts might be the best thing to turn to on that. The important thing is that if you are going to rely on expert opinion you want to make sure you do that in the least biased way possible and find some way of getting a balanced group of experts. You don't want to only get those people who feel strongly. They might feel strongly for something or strongly against something and their judgment might certainly not be representative.

This is my own personal opinion, that content experts can be very good at answering those specific important questions of is this test accurate. They may not be the best people for saying, okay, this is how I put it all together because their focus is often on a very specific issue. So, either they are very good at understanding diagnostic issues or they are very focused on treatment issues but asking them to put it all together may not be as helpful. But ask them to answer, okay, on this specific question tell us your best judgment.

So this committee is going to have to deal with making recommendations in the face of poor evidence and there are various ways to do that. We have talked about experts. One might make extrapolations from other data and say, gosh, we don't really have the data we want but we think this other condition is comparable enough, or it might be extrapolations from an intermediate endpoint. So, you have studies of treatment that haven't really followed kids out to morbidity but they followed them to some intermediate metabolic endpoint that you are confident is a measure of effectiveness.

You might say this problem is so big or so important that we don't want to wait for perfect evidence and we are going to recommend based on that, or we are not sure of the benefits through evidence but we know it is safe and so we are going to guess that the benefits are likely to outweigh harms or clinical tradition.

The Task Force, in the face of poor evidence, takes a fairly strong point, the primum non nocere--first do no harm principle. So, they say we are not going to recommend anything unless we have what we consider sufficient evidence to recommend it. Again, the Task Force has the luxury of having reasonable quality data. With the conditions we look at generally it is reasonable to expect adequate quality data but that might be too high a bar for this area. But you need to understand that that is sort of one approach to say we are not going to recommend anything for routine use until you have shown that it actually does what you expect. The other is to say there are times when we need to make policy recommendations short of the evidence that we would like to have, and these are the kinds of things that we would consider.

This is just my own sort of thinking about are there options other than recommend/non-recommend. So, one could say you have some threshold for recommending a test. You have sufficient evidence on these parameters, similar to the parameters in the ACMG report. There may be some level where one has some evidence but there is some uncertainty about some component of it or uncertainty about putting it all together and you want to get more information, and you think there is enough promise there that you

don't want to just sort of defer recommendation, and that there be a category of recommending it as an option to states but actively recommending it collect pilot data. So, one could think about what the policy options are that are available but just recognize that there may be a middle option between making a recommendation versus deferring any kind of recommendation.

I guess my personal opinion is having that option may help you avoid the pressure to do something in the face of important uncertainty. So, we feel like we want to do something and we don't want to just say come back to us in five years when you might have better data. Yet, it may not be the best policy option to recommend everybody do this all at once.

We deal with a lot of issues of conflict of interest, which one can define as sort of is this person predisposed to a certain outcome, something that makes it hard for them to step back and look at the data objectively? It is important to think about perceived as well as real conflict. The point I want to make is that paying attention to conflict of interest doesn't mean you can't have anybody who has anything that smells like a conflict of interest. You want people who are smart and who have opinions, but you want to be sure you deal with that by disclosure, by whether you think there is such a conflict that it is going to pose a challenge and they might recuse themselves on a certain issue and, most importantly, by balance.

So, you might have people with different kind of conflicts but if you balance them on the committee and you disclose them, that is not a problem. I think it is more important when you ask people to review the evidence. When we work with that evidence at evidence-based practice centers we try to make sure that the lead authors on those don't have anything that would look like a conflict of interest, whereas in the groups that give us advice on that we need people with different opinions and they are often going to be conflicted. So, you want to incorporate content expertise. These are complicated scientific issues and you need people who are smart about this. Yet, you have to realize that there is a line between someone being so invested in a topic--and sometimes they may be the only person who has published in the literature so they are probably not the best person to evaluate their own studies. So, you need to find a way to sort of balance people who can know enough about it to understand the studies but have enough distance that they can fairly say, you know, that study is quoted everywhere but it has this problem.

In making recommendations, again, having these standards for evidence and for recommendations I think is useful. We have people on the Preventive Services Task Force who have methodology backgrounds. All of them have some sort of background. On all committees it is useful to have one or two people who are experts in kind of research design because they bring that perspective to sometimes complicated analyses.

The role of the committee is ensuring that all stakeholders are involved in the process, thinking inclusively about your audience, and having a formal process for outside review so that you don't just put it out there for anyone who bites but you think, okay, we really need to get these kind of perspectives on this issue and make sure that you are getting those even if some are people who you think would weigh in or wouldn't weigh in.

I am going to close with just these comments, just to separate out what I think the appropriate or most useful role of the committee is versus what you would want to task to some other body to do. So, the role of the committee is to provide that representation of key stakeholders; to lay the ground rules to say for us to make a recommendation we need to be able to demonstrate this; to lay out what questions you want answered. Again, the advantage is you are looking at a set of topics where these questions are going to be generally similar from topic to topic, the kinds of parameters that were in the ACMG report. Then, your job is to take a synthesis of the evidence that someone else prepares and say has this done what we wanted them to do? Are there other considerations beyond what they can tell us from the evidence that we think play into it? And, then to make recommendations.

The other body that you tasked to do the evidence review is responsible for following the ground rules; doing the kind of exhaustive search that no one on this committee has the time to do and apply those

ground rules in a systematic way to weigh the evidence. Again, what we have found in the evidence-based practice centers is that it requires this combination of expertise in research design and systematic review. I mean, just slogging through evidence in an efficient way is a learned art as well. Then, they are also responsible for when they get criticism from a peer review for addressing them in a way that satisfies the committee.

I think that is all I have to say. I took a little longer than I wanted but we have time for questions.

Questions from the Committee

DR. HOWELL: Thank you very much, David, for that very nice presentation. I am sure there are questions by the group. Norm?

DR. KAHN: Dr. Atkins, thank you very much for your presentation. I don't know if you were able to get here in time to hear Dr. Pickering's presentation from the Advisory Committee on Immunization Practices. One of the issues that came up was that while that committee uses an evidence-based process, there are one or more groups that don't feel that the process is evidence based enough. For the process that you have just outlined, are the groups that criticize this process as well as not being evidence based enough, or is this considered the gold standard? DR. ATKINS: Yes, there are people who think it is a little bit too intensive or it sets the bar too high. That is why I tried to emphasize the issue is less about where one sets the bar than it is in being explicit about how you want to answer those questions and how you decide whether you have gotten over the bar or not. Is Larry still here? So, my inference--I don't really know--is that ACP's objections to the ACIP process may be less that they aren't looking at evidence so they aren't, you know, thinking about harms and benefits but that they just haven't codified the process in a way whereby they will say, okay, we are going to answer this question with this kind of evidence so that the reports prepared for them don't, you know, have a clear structure to them. I think everybody sort of knows what the issues are in terms of making these recommendations, but having a somewhat more codified process where you march through the steps serves the issues of transparency, but the fact is that if you don't have a codified process you can get it wrong. You know, you can think you are thinking about other things but you have forgotten an important issue.

DR. HOWELL: Piero?

DR. RINALDO: I think the process you are applying is, you know, very logical and very rational. There is one point that really was one of the critical issues in the development of those recommendations, specifically the ACMG report. That was how you deal with what I might call the branching points. In other words, the evidence to test for a certain disease is strong but the same biochemical markers actually can lead to the diagnosis of something else where there might be five, ten cases known in the world. So, we are not even close to be any time soon near to a reasonable level of evidence. That is really where a lot of the discussion, and perhaps controversy, was about people saying why do you bring in the so-called secondary targets when there are, you know, just a handful of cases described? That is really my question for you, if you can give us any guidance, in retrospect in a sense, because there is the possibility of diagnosing something we know so little about, should that be used against or be a deterrent to screen for something where the evidence is strong? Because that is really the fundamental concept of the screening by a multiplex platform--in my case mass spectrometry--that all these things are interconnected and you really cannot take them apart.

DR. ATKINS: Yes, I think that is an important point. I was talking with Mike Watson about that in the break. I think there is a challenge. We wrestle with it to some extent in some of the adult screening issues

that in order to get the folks you want, you catch some other patient in that and you are not sure that you have done them any good and maybe you have done them some harm, and does that mean you can't even go and look for the kids you want? I think it is important at least to acknowledge that and to recognize that the decision point is screening or not screening, that it will have these kind of unanticipated downstream consequences. Whether one says those are so great that even though we could have this other group of kids we are not going to do it, that is a judgment call. I think definitely what it does, it points one to recommendations to say in order to minimize those consequences one might want to do some certain policy. So, I don't think our Task Force does it enough, but to take the DCRS example, with prostate PSA screening. In order to find out the prostate cancers you set the threshold so low you find other things.

So, there can be ways one gives guidance both on how one implements the screening and recommendations about the follow-up in a way to try to maximize the benefit for the ones you want, and find ways to minimize the harm to the others. I think there is no simple answer to it but one needs to at least acknowledge it and think, okay, if we do this test on 10,000 kids, at the end of it what happens? We have this group that we really wanted to find; we have this group we didn't necessarily want to find but we can't avoid it. What happens to those kids? Is it a neutral effect? Is it an adverse effect? So, you can at least sort of think about weighing more explicitly but I think our Task Force is more and more comfortable with saying that we are not going to do something where we know we can help just because it is going to do that, but one needs to think about, okay, how can we minimize those consequences.

DR. RINALDO: There could be also benefits for detection of rare or less well-known diseases.

I don't really see why it should be assumed--

DR. ATKINS: Sure. So, if you have clear benefits to one group and you have another group for whom you are not sure whether it is a benefit or not, you can acknowledge--the point is do you recommend the test? You then may want to give guidance about what to do about all the things.

So, I guess to summarize, it may not affect your decision-making about whether to recommend a test. It might definitely identify issues--to take the ACIP analogy--that you need to develop guidance to clarify the different populations.

DR. HOWELL: Coleen?

DR. BOYLE: I will be quick. In your closing you sort of recommended--you made some suggestions, not recommended--you made some suggestions in terms of the role of the committee and then the role of what you called in the beginning the process to sift through the evidence.

You sort of suggested that those be fairly separate activities in terms of what the committee does and what the body or the group does in terms of gathering that evidence and bringing it back to the committee.

I think that at least in our last discussions, because of sort of the limitations in funding and other things that go behind this

committee, we were thinking of sort of doing all those things ourselves. I guess I would just like your thoughts in terms of whether or not we can do that and still be sort of objective in that process, and how that might contaminate the evidence in some way.

DR. ATKINS: So, is that right? Actually, in one of the earlier directions of the Task Force we did do that. We tapped the Task Force members to do that. I think we probably got to the right answer. I think what they produced probably wouldn't pass mustard with today's standards. It can be a big undertaking. So,

one issue is the practical time commitment involved. Your question is really more about objectivity. I guess what we learned trough the evidence-based practice centers project is that there is a learning curve to doing it and you get efficiency by having one group do it over and over again.

So, my concern would be less that any of you would be biased in reviewing it but that you will spend a lot of time just kind of learning how to do it, and then for the next topic someone else would do it. So, I think that there is a value in working with a group. We talked a little bit with Michelle and Peter. We have different groups who do this either for pharmaceuticals or devices or for other treatments. That might be a mechanism for doing it. But it is good to work with one group. They understand. They also understand by working with the committee what the committee wants.

I didn't want to over-emphasize this separation. I think the committee often works with them. You know, there is some interaction with them to say should we look at this or not; is this how you meant this question to be? There is not a wall between them.

DR. HOWELL: I don't think we finalized that but I think that we had thought about having an external group help with the review and I think we will have to look at that further. Let me ask you a little bit about conflict of interest again because, obviously, most of the people that have looked at recommendations and made recommendations and focused on these committees have been people who have been interested in newborn screening--the groups, and so forth, and the families that have affected children, and relatives, and so forth, so the groups that have basically dealt with this have been people that have this as a main interest. Now, one of the criticisms, of course, is that the group is biased because they all have conflicts of interest. Can you comment about that?

DR. ATKINS: Well, I think obviously conflict of interest is more grey than black and white. I think the important thing is to have disclosure but then to recognize at what point does a conflict rise to the point where you really don't think that person could reach a different conclusion no matter what evidence you put them with. So, I think you can have patient/parent representatives on the committee. You might want them to recuse themselves about a recommendation about a condition their kid is affected with but you might say they can be a part of the process on other conditions. Again, given that you need that kind of input and that those folks are going to be predisposed probably more one way than the other, you really want to exclude them but you might want to say, okay, they are bringing one kind of perspective to the table. What are other perspectives? You really want all the people to have kind of leanings in one way and not representing everybody else. But I think inherently if you represent all your audiences you should balance those out. So, there are people who are going to be more concerned with issues of cost and feasibility, you know, someone from a state program--you know, how am I ever going to do this? Then, there are going to be people who are more concerned with the potential good you can do and leave it to someone else to figure out how to implement it. So, I think you want to disclose things. You want some process to decide when does a conflict of interest rise to a level that you want to have those people either not be on the committee or recuse themselves under individual issues. Then you want to balance the potential sort of leanings on the committee.

DR. HOWELL: Amy?

DR. BROWER: This is just really a comment and I want to get your thoughts on the comment. You did a great job, Dr. Atkins, of differentiating the differences between what we are considering where we have rare disorders and what you look at, which is really common adult chronic disorders. One concern I have is the timing of the testing. Often with newborn screening we have one capture point to test. For adult screening, you know, you have your yearly check or every five years, and there may be other ways to detect those different screening methodologies but we only have one capture point. So, I just wanted us to all kind of consider that. Often it is a time sensitive issue, that we really have one data point that we are able to capture all the information.

DR. ATKINS: Yes, I think that is an important point. You know, in an adult world one could say, you know, have an informed decision between patients and their clinicians. That is what we sort of recommend with PSA. You know, there are lots of people getting it, here is what you ought to know and you make a choice. That is not feasible with newborn screening so there are issues of equity that you want to be sure every kid gets the same kind of treatment. So, I think things are different. I don't think it changes the fact that the decision point is you are either going to screen all kids or not, and you need to think about other consequences of that decision and how many things one ought to screen for.

DR. HOWELL: This is becoming complicated because some of the things that are being thought about obviously can't be detected in the immediate newborn period. I am thinking of Wilson disease and some of the infants with in utero viral infections who later become hard of hearing and are not at birth. So, life becomes even more complex. Bill?

DR. BECKER: Yes, thanks for the presentation. In the description of the models that you have, you have the committee that makes the decisions and the recommendations and the evidence-based, as you could call them, working group actually reviewing the evidence. You mentioned that that working group would be the place where criticisms of the evidence would be reviewed and comments provided back to the committee. In newborn screening, or at least in screening processes in general and I think newborn screening would fit with this, I see questions about the evidence almost at every step along the line. Obviously, there are going to be questions about the evidence in the process of making the recommendations and I think you described that process very well. In the implementation of a program, or in this case newborn screening, oftentimes you get concern being expressed. It is almost fear of the overall impact by the programs or the clinical community and again you get questions about the evidence that could be fed back to the review process. Then, because every good public health program needs to do evaluation and feedback of all their programs, particularly using the PSA model, we are now beginning to again generate questions about the evidence and there is beginning to be some literature out there questioning whether PSA screening is of value and again feeds back questions about the evidence to the body that is going to evaluate it. At what point does the evidence review group have to work or interact with the full committee to try to resolve questions about the evidence that are occurring pretty much at every point down the line?

DR. ATKINS: The issue I heard is about evidence-based recommendations and then kind of real-world implementation questions. I mean, I think both of those ought to be captured in the original evidence review because you need to think about whether this is going to work in the real world. You may not be able to answer that question at the time you make a recommendation but you at least need to put that on the table. Again, you know, I talked about different levels of evidence but now that I think about it you might actually want different levels of sort of positive recommendation or something. You know, PKU is not only recommended but it has been out there and there is lots of experience doing it and it is kind of like we don't need to reassess it, although there may be some issues. Then there may be some things that work and are recommended but you realize we are just learning about implementation issues and you might have a flag that we need to come back and look at kind of implementation issues and maybe tweak what we have said about it. Then, there are questions even earlier in the process about what information you really need to collect, what you don't have yet that would help you answer the questions that you can't answer. So, I think as much as possible those things ought to be captured in sort of the original evidence reviews. But then there is the question, okay, given in this sort of development phase of a screening test when do you need to come back to an issue, and which issues you don't need to come back to, which ones you need to come back sooner rather than later because you realize, you know, that there is going to be new information as people get experience that may change your recommendation.

DR. VAN DYCK: I think that is a good question. I see the process as the working group, the evidence-based working group gets a job from the committee. They perform that job, turn the evidence over. There is some interaction but then the committee makes a recommendation and the evidence-based working group, as I see it, has fulfilled their task and they are done. Then, as new evidence comes or as more criticism might be raised, as you suggest, that then comes to the committee who then has to make

a decision when to take something back to the evidence-based working group. But I don't see the evidence-based working group having a continuing role in a job order, if you want to think of it as that compact, that is ongoing. It is time limited--do the job; get out of it; go on to something else.

DR. ATKINS: And I guess it is a question for this committee how much they want to get into the implementation type questions, or do they want to leave that to another group of people to sort of work though from the perspective of state labs? Is their job just sort of go or no-go? Then, how you go and how you maximize benefits and limit harms, make it more efficient--you know, that is someone else's job and not the committee's.

DR. HOWELL: Dr. Green?

DR. GREEN: I just wanted to make one follow-up comment that Amy had made about the single time point, just to point out, as I am sure many of the people on the committee are already aware, that as you suggested, David, but to sort of expand a little bit on what you talked about, there are different levels of implementation. There isn't a single time point. You know, it is not all or none. There can be anonymous incidence studies done and also pilot studies, as was done in Massachusetts, with various phases of reevaluation. So, I don't think the committee should feel pressured into thinking it is all or none decisions. And, I think that is what you highlighted but maybe you want to make some more comments about that.

DR. ATKINS: Yes, I think that is a good point. So that, you know, states were making kind of individual level decisions before this committee existed and were doing pilots or intermittent screening at different levels of the curve and to some extent that is an advantage because you can collect information before you make a go or no-go decision. But I think now that the committee is in existence and has higher visibility, more people are going to be looking to it to kind of help states with those decisions. So, one option is to, you know, not make a recommendation and let states kind of do their own thing. I don't know whether states are going to do that. I guess what I am saying is my sense is that there has been a lot of sort of individual variation and learning from that variation. But one of the aims of this committee was to, you know, raise the floor to reduce the amount of variation there and the question is might it also limit the sort of more leading edge variation that states might be doing to gain more information. I can't answer that question but you might want a process to say even though we are not saying go yet, we are encouraging people to get some pilot information or learn about it.

DR. GREEN: Just to follow-up, I agree but I am just saying that the committee may decide that there aren't sufficient data to make decisions to test universally or not--

DR. ATKINS: Yes.

DR. GREEN: --since it is such a big responsibility but, rather, to suggest either state basis or regional basis to do pilot programs--

DR. ATKINS: Right.

DR. GREEN: --with a built in evaluation program. I mean, you are right about freeing up the floor but there is always going to be a pushing up of the ceiling as well.

DR. ATKINS: Right.

DR. GREEN: So, all I am saying the point is that there are different levels of recommendations that we can make--

DR. ATKINS: Right.

DR. GREEN: --about where screening should be.

DR. ATKINS: Yes, though I think the committee ought to be as clear as possible. There may be some things where you really want to say don't do this, you know, there are clear problems in this. Then, there are some things where we say we just don't know and we are comfortable with states going their own way, and some of them are going to choose to do things. Then, there may be some places where you want to actively encourage states to do that. So, the committee can think through what kind of different levels of guidance they want to give.

DR. HOWELL:Thank you very much, Dr. Atkins. We are running a bit ahead of schedule, which is always encouraging. The committee, as usual, has a working lunch so we will take advantage of that. The committee, the ex-officio members, the liaison members, the subcommittee members will all have lunch in the concourse level, in Meridian B, and we will return at 1:30. Thank you very much.

A F T E R N O O N P R O C E E D I N G S

DR. HOWELL:Let's find our seats, please. We have a lot of things to cover this afternoon so we will get started with our afternoon business. One of the clear charges that this committee has would be to look at the process of conditions, tests, technologies that might be added to a newborn screening panel in the future and, at the same time, one could visualize looking at some of the current recommendations in that light and might decide that a condition might fall off the list, etc., but basically the process of nomination is an important one that we want to think about a great deal. The material that we have heard today about evidence and the other things, etc., we will use that but Bill Becker and Piero Rinaldo are going to tell us about nominations for conditions, testing and technologies. Piero, are you going to lead off?

DR. BECKER: Rod, before Piero begins, Piero has done an extraordinary job on this and put all the Power Points together and all the congratulations go to him; all the criticisms can go to me.

DR. HOWELL: We will remember that. I hope somebody taped that! Nomination Process for Conditions, Tests and Technologies for Evaluation by ACHDGDNC

DR. RINALDO: Although I remember very well that in April, when we were here, we talked about this and I think it would be easy to blame process because really I haven't given much thought to this, except for the last 48 hours, but I think it is a good idea. You have to start somewhere so this is really a collection of thoughts about the process. You remember that we were discussing about how we were going to do this, and I have sort of a set of assumptions. I realize now that certainly it would have been very helpful to hear presentations from this morning about how to do this, but I think certainly these can be easily modified. This is assumptions. Again, it is very much a personal view. There should be a relatively simple nomination process. I think we heard about the vaccination issues this morning, and also from Dr. Atkins. The assessment should have similarity to the one used by the expert group to establish a uniform panel. Again, I put in fairness and consistency. After all, we are talking about adding conditions or at least, as was definedc using a certain process. So again, for the sake of fairness and consistency, there should be some consistency; some similarity. That doesn't mean that there will be reliance exclusively on the ACMG criteria. There are many others. That is just one of the options. The other one is that it somewhat makes sense to really utilize similar tools based on the experience learned during that process. The approval should be through progressive steps. We talked briefly about what the role would be of HRSA, this committee, the subcommittees and the ad hoc working group. Again, the key component will be the formation of ad hoc working groups with representation of each subcommittee. The final recommendation for inclusion or deferral will rest with the full committee. So, these are general assumptions. Now, when we met here Amy, I and others were frantically trying to put something together and we came up with this process, that was briefly presented here and discussed, as the activities of each subcommittee. With only one conference call Dr. Duane Alexander made the comment that it was a little "loopy." I think he is

absolutely right. There seems to be a loop here at the beginning and the end, and there was no clear understanding of the beginning or the end point. So, I thought it was a very legitimate comment so I tried first to modify this graph, and I got frustrated and decided to start from scratch. I realize that at least from the back of the room it might be almost impossible to follow. I hope that all the committee members do have a copy that I brought with me, about 20 copies. So, the process would start with a proponent and the nomination of a condition. This will obviously start with defining a process where whoever feels that one nominating a condition for inclusion in the uniform panel will submit something--whether we call them questioners or forms--that will go to HRSA. This is now sort of a recurrent process. I hope not to make anybody seasick but basically going back and forth, and HRSA might decide--how they do that is obviously entirely their purview--that this is really not a reasonable nomination. As such, they can design their own process to really get feedback to the proponent and say, you know, this is not going to be considered at this time. At the same time, HRSA may say that there is merit--and Dr. Howell has been asking for a better name and I give up so I still use the abbreviation but I believe we will have to do something about it because it is really not easy to even say it. But that alphabet soup really represents this committee. The committee might decide--and, again how this will happen is entirely really ahead of us in defining as a process--not to pursue it and again go back to the same system for getting feedback to the proponent. It may decide to give it to the subcommittees. There was a discussion a few months ago that one committee, the laboratory subcommittee should focus on the merits of the proposed test and, at the same time the follow-up in treatment subcommittee should focus more on the merits of the treatment process--and again make recommendations and basically say that it is not applicable. We haven't done it so we really don't know what the kinks and problems could be in this process but it is possible the subcommittee would be in agreement not to go any further. On the other hand, it might come back here to the full committee and we may say it should go forward. At that point there is still a possibility--remember, this is a 30,000 ft. sort of path, if you want, but there might still be a point where a decision is made not to continue despite a positive recommendation from the subcommittee. Earlier this morning Dr. Becker was making the point that really we should be very careful, especially when we deal with conditions that we really don't know too well, and he made an example with infectious diseases. So, perhaps we should err on the side of caution and bring things to the ad hoc working group when we feel that we really are not knowledgeable enough to deal with certain conditions, and infectious diseases could be an example. At that point, that could be a green light to go and form a working group. The working group will be formed. It will include liaisons for each of the subcommittees. And, it will come up with a report and presentation to the full committee. This was actually a point discussed before lunch by Dr. Atkins. It really is a point in time; it is not something that will be perpetuated forever. They really had us to do a job and the job has somewhat of an endpoint. There will be a report and presentation to the committee. The committee then, at that point, can still decide on whatever is the recommendation, to endorse or not endorse it. It depends on whether it is positive or negative, or recommend for inclusion of the condition in the uniform panel. Again, I think we really don't know how to do all this. So, I just want to focus a little bit on very preliminary possibilities for submission of nominations. The proponent, of course, could be almost anybody. I don't know if we need to discuss this here. This is just a list of people that came to mind. It could be a provider of newborn screening services; be a representative of a professional organization; representative of a patient support group. It could be a clinician, scientist. It could be industry or for-profit organization. It could be a patient himself or herself, a family member or advocate. Clearly there is overlap here. Or it could be any other that is not listed yet. Again, I think once there is a consensus that should really come from almost anybody. I think this is a moot issue. When we were here in April, from what I can find from my notes and my memory, we were talking about a questionnaire but really there was no specific issue that we were talking about. And, we were talking about two forms, one relative to the screening test; the other about treatment options. I am here to sort of bring up somewhat modified parses and, again, it is very much open for discussion and all the changes you want to do. But I think perhaps we should start talking about at least four components. It could be more; it could be less. There should obviously be a cover letter, giving latitude to the proponent to say why they want to do it and what is the reason. There should be some emphasis, perhaps with some limits--again, this is not really a global 360 evaluation of the evidence; it is more about getting a sense. After all, if I grant tenure to people on the basis of three best papers I think that we should be able to identify the five best papers related to a specific issue. That doesn't mean there are not more. That is just what are the most significant ones.

I just want to elaborate a little bit on these two things, about a score card and a fact sheet. It goes back to an assumption I made in the beginning that perhaps there is something that can be taken from the work

done by the HRSA expert group to raise at least a tentative document or file that is supposed to suggest how to evaluate and consider additional conditions. Again, I realize it is not readable. I hope you have it in front of you. This is sort of taking the form that was used but very greatly simplified. In red, here, it reads, this form is to be filled as a requirement for evaluation by HRSA, the committee, the subcommittees and ad hoc working groups of a condition not included in the 2005 HRSA ACMG uniform panel. There is basic information about the proponent. Again, a check list where the groups are asking the proponent to identify the provider, the organizations, scientists or industry--very simple instructions here. Here is basically the full address of Dr. Puryear as to where to send it. The second page is the infamous or famous criteria, however you want to call it. The more we digest this, the more the dust settles. I really think that these criteria cover in a very effective and objective way all the issues that need to be addressed in the evaluation of a condition for possible inclusion in the uniform screening program because, after all, we will always be talking about a condition, a test, or a treatment. I don't think there is anything that goes beyond this point. So, there is a page just with a reminder of what the criteria are and the different scoring categories. Actually, in that document it was part of what you might call a calibration page. You know, there are five conditions here, MCAD, PKU, CH, sickle cell anemia and CAH, and these are the scores that were derived by the survey and, say take a shot at it and see where you would stand; how you would grade the conditions. These will lead to a final page, and that is the final page where, again, there are blanks and you score your condition. Again, you can consider it as an optional exercise. I don't know if this is optional or required, but the fact is it could be used even as an exercise to warm up a discussion at this committee level, at a subcommittee level, at the ad hoc working group. I would be interested to know how the members of these ad hoc working groups, either people who clearly are involved with the conditions or non-stakeholders, would really score the condition. Again, this is probably just one piece of what will likely be a very large body of evidence in the assessment. The other thing that I felt would be useful is to actually take the fact sheets that were part of the report and modify them. Again, I realize this is just for the efficiency of presenting it. You can see this box being blown up. I really don't want to put any limits. I think in the nomination process some constraints and conciseness might be helpful. Obviously, this is not readable but there are here some specific
clues given. Again, you know, this is a condition and the little writing here says include also data. The same for the phenotype. It says include typical age of onset. Of course, there is the whole section about the test. Really at the top of my head I was thinking that there should be clearly--and that is the addition here--it says pilot study. In might be actually a regular program already ongoing. We know that there are states testing for, say, toxoplasmosis or HIV. I really think if we are looking specially at the newer conditions, the little writing here says location, duration, size and preliminary results of past or ongoing pilot studies must be provided. Here it says cases per FT per day or cases per instrument per day, as applicable. Cost of test: Actual cost and estimated testing fee. I mean, there are all sorts of things and, again, this is just general indications. This is the treatment section; a reference section. This document can be converted to Word or
any other more user-friendly program. I like it because this box can basically be formatted. You just type in and it looks pretty neat and also gives you a sense of when you are exceeding your space but, again, the format of this file should be the last of our concerns. Again, there is the section about where to send it and I really did a very simple checklist. You can look at it. It is basically the four elements, submission checklist, score card, fact sheets, copy of references listed on this form. Again, without the benefit of the presentation that we heard this morning, in my mind the things that still need to be determined are how to get word out for this, how we really launch our call for proposals. Probably there are a number of professional organizations. I think that would be a great benefit of the increasing presence and role of the liaisons on this committee. You can easily see whenever the time comes that people can be invited to bring forward nominations. Again, this morning we learned a lot from
ACIP and others. I really like to hear that there are guidelines for adult working groups and for the grading of the agents so I really don't think we should reinvent the wheel but just take as much as possible from people who have the experience. Again just a few thoughts, what if we have two subcommittees in disagreement? What if a subcommittee says yes, there is a test and the other one says but there is no treatment, or the opposite situation? So, I think these are the scenarios that we will probably just have to deal with as we go. Again, in my mind, probably I have a better idea for ad hoc working groups. What is the selection process? What is the size? What is the timeline? How do we select liaisons for these subcommittees? These are, you know, process details that we really have to address and work up and perhaps there are guidelines. Then, you know, there are a days when I think that once we start we could

get a very large number of nominations and that would really create
a problem of its own about logistics and support if we have fairly valid nominations. We heard this morning that prioritization of these nominations is perhaps one of the most critical things and we will have to deal with that as a committee. Then, even when everything is done there will be issues--well, you know, you do it annually, you do it on evolving conditions whenever you find something that is really considered justified to add. These are just a very few of the questions in my mind. But, again, I put this together very much as a starting point for discussion and modifications. That is all I have. DR. BECKER: I think the strength of this draft is that it is consistent with what we heard from the ACIP process. There are a couple of differences that we can probably point out in the committee discussions on this. The one point that I heard through Larry's presentation about the ACIP process was consistency, consistency of the evaluation and consistency of the process. And, if we use the same tool that was used to make the recommendations for the ACMG core panel--you know, Piero is exactly correct, the condition itself; is there a test; is it treatable. There are some other issues about costs built into the scoring system that was used. But we are applying the same metrics or the same yardstick to candidate conditions that we would have already applied or that are already contained in the report, the ACMG report that we have recommended to the HHS Secretary. So, I think that is the strength of the process. I think the first thing--Piero, if you could put the flow diagram back up--is that it may be useful for the committee to consider the overall process and see if there are comments, concerns or suggestions to be made about that.

Questions from the Committee

DR. COGGINS: Piero, I just have one question about the test process. I mean, this is to look at adding new conditions to the panel but in your process and your flow chart there was a section for test and it would be a good idea to have a test if you are going to recommend a condition to be added. But in the existing panel of conditions is there any mechanism within your proposed process that would consider new technology, new analytes, new markers which may be a better way of screening for some of these conditions or the existing conditions?

DR. RINALDO: First, I hope we will stop calling it mine. I rather hope it is ours. You know, in a sense this is the same dilemma. I remember the question I asked Dr. Atkins, the one really leading factor in all these evidence-based processes really is that things are independent. How do you handle a situation where you can have a platform or things that can handle multiple diseases? So, this is a process--you are absolutely correct--that is driven by a condition. There is really no way, or at least there is nothing now that says how you handle a request to bring up a platform that could deal with multiple diseases. So, you are correct. There is probably a need for a different set of forms. You know, the committee I think will agree that it could actually be a platform or another multiple test procedure. You know, considering what we have heard, the chances are this is likely to happen. So, you are absolutely correct, Peter. That is not covered and it should be in. It can fairly easily be covered.

DR. HOWELL: Denise?

DR. DOUGHERTY:A couple of things on this. I think, you know, we are beginning to get to some systematized way to do this and think about the criteria. I guess I would just like us to explore a few things that I heard from David Atkins this morning. One is about the ad hoc working group and I would like you to explore that a little more. I think I heard David say that what the U.S. Preventive Services Task Force has learned over time is that you don't get a new group of people for every nomination. It improves consistency. People build skills because looking at this kind of data is a skill, and there are forms to do it, and so forth. So, I was wondering who you thought that group would be and whether it would be new for every condition. The other couple of things are the subcommittees and their work because that sounds like a lot of work to do because this literature is not that easily accessible. I am just wondering whether you think that ARC and CDC would do it as the follow-up treatment subcommittee. The other one is where in here do we set up the criteria to give to the ad hoc working group? They are the true evidence reviewers. These forms here are just a start and people can circle what they think, their subjective impression. So, the scores in the end are not really going to matter. It is the stuff that comes after these scores that matters. So, at what point do we consider criteria? Again I am thinking of David Atkins' talk

about separating some things out, separating cost from effectiveness; looking at these things in different areas, not just having one overall score.

DR. RINALDO: On the first question I think it is probably worth mentioning the "to be determined." I heard a comment that 14 working groups was overwhelming for that committee. The reality is--I could be very wrong on this, but I wouldn't be surprised if in a relatively short period of time we might not have close to ten legitimate nominations. So then what? Do we empanel a full-time working group? I am looking at Michelle and Peter and I have no idea. That is really on one end. The other important thing that was said this morning was that there is a staff person that truly is the driving force of these working groups. Then, again, it basically goes back in their court about, you know, how many dedicated people it is possible to have because that really in a sense will give us a message of where we set the bar. There could be conditions that could actually be very legitimate but then, again, there is the process of prioritization. Obviously, we have to hear from HRSA what the resources are to really pursue this because they might be very limited. So, if we can empanel only one working
group at a time that would be a very different story because then probably we would have to set up a holding process which would have a periodic deadline where you say, well, if you want to be considered, you know, sixth or seventh you should apply by May or June 6. These are all the details that I think we will need to talk about.

DR. DOUGHERTY: Well, I guess I am thinking again of what David was saying. I am sorry, I didn't hear Larry Pickering's talk. I think rather than have ad hoc working groups made up of members of the committee or staff, you know, there are many mechanisms in the federal government. Those evidence-based practice centers exist and there could be a task order contract, as it is called. So, you have the expertise in place and then when you get a nomination you give them the task of evaluating the literature. So, I am not too worried about that issue, more about whether the working group, the evidence reviewers here are independent of the committee. I think that is the more important thing.

DR. VAN DYCK: Michelle, I and others have had a lot of discussions with FDA and the CDC around immunization, and with David. Actually, the immunization committee tends to do it in a fashion that Piero has suggested, the way I understand it best. They form ad hoc working groups around each area that are made up and led by either a CDC staff member or members from the committee itself, with the rest of the committee populated by liaison members and outside experts. So, it tends to be different from what David uses in the Prevention Services Task Force, which is more an independent outside contracted evidence-based committee that is put together and tends to be the same regardless of the condition, or with minor changes depending on the condition, so that there is continuity and sameness of the people that are doing the evidence-based review. It is probably more expensive to do the contract one than the internal one but there may be gains. I think the committee needs to discuss that but I think we are tending to lean more towards the
independent or the quasi-independent contracted evidence-based review committee in our thoughts. But that is just to give the committee an idea kind of where we are leaning, but that depends, again, on how much money and costs. We think these will be less expensive because there is less literature and it will take less time. So, we may have to end up doing one or two to get an idea of what the time requirement is and how expensive they really are.

DR. DOUGHERTY: Thank you. That sounds good. But there are other components in this and I don't know how you want to proceed with the discussion. Should we go through it component by component and kind of explore what it would really mean?

DR. HOWELL: Bill and Piero, what would you like to do? We have a lot of time allotted to this, as you see, this afternoon. This should not be a brief discussion but a substantive one.

DR. BECKER: Agreed. Certainly, as Piero mentioned, there are a lot of criteria to be determined. I guess by putting this diagram up on the screen we cab first start engaging the committee in a discussion about the overall process first, and then maybe flesh out a few of the pertinent details, such as what Denise has brought up.

One area that I think is slightly different from what I understood from the ACIP conversation and perhaps in some ways could simplify this diagram is that I thought I heard Larry say basically if they got a nomination that seemed to fit the application criteria that they use, their committee didn't make any initial decision on it. They immediately assigned it to an ad hoc working group.

So, what this would do then is I don't see HRSA making a decision to decline unless it just doesn't meet the nomination criteria or, you know, the forms aren't correctly filled out. They are probably not going to make a decision, nor should we ask them or expect them to make a decision about the disorder. Okay? If the paperwork is not filled out--

DR. HOWELL: I would interpret that the same way. I would assume that that is a purely administrative rejection--

DR. BECKER: Yes.

DR. HOWELL: --that the forms are not complete or something. Is that correct?

DR. RINALDO:It is inevitable, especially when you have a wide catchment area, that there will be nominations that probably don't have much scientific or medical merit and those I think would be fairly easy to weed out.

DR. BECKER: So, that gives HRSA certainly the criteria that they would need. If they have a nomination that is properly presented, then it goes to the full advisory committee. We clearly could make the nomination or we could decide that it is declined to be reviewed. But I got the sense from Larry's presentation that ACIP did not tend to do that. In fact, they go directly to the ad hoc working group, which would simplify this sort of structure right here. They go straight to the ad hoc working group. Larry explained it that way as well. The ad hoc working group doesn't make a decision yea or nay. They present the evidence back to the advisory committee who then says yes or no. It sounds like the Task Force has a similar process.

DR. RINALDO:If I can add something, the reason why it is shown this way is because this was a conclusion at the last meeting here.

DR. BECKER: That is correct.

DR. RINALDO: But nothing is carved in stone. It can be easily changed.

DR. HOWELL: Nancy has a comment.

DR. GREEN: I think this is basically a very sound structure. I guess there are a couple of areas of clarification that might be helpful. I mean, it seems like there is sort of a fast process and a slow process. Right? So, the fast is kind of at the top, if you will, sort of by checklists at least at the HRSA level, sort of the entry into the door. You know, does this fit the purview of newborn screening at all or is it something probably irrelevant? For example, given the name of the committee, I would appreciate a clarification about the infectious disease model. If you consider vertical transmission to be heritable, then I guess it fits in. The other difference from the ACIP is that it seems to me that the pace is different. So, it would have to accommodate different numbers. In other words, for a company to develop a vaccine it is obviously a slow process, whereas, you know, I could generate 25 disorders right now and you wouldn't want to consider each one separately. So, that is why I think sort of a fast process to get ultimately to the ad hoc group--fast, meaning not extremely deliberative versus a more deliberative process, sort of in a secondary swing.

DR. RINALDO: About what you just said, you know, everybody can quickly make a list of 25 conditions. The point is you have to have 25 tests. So, I don't know, probably we are not on the same order of magnitude to developing a vaccine. But, you know, developing and validating a test is not a trivial matter. So, that is where I think the selection, initial selection, really can be actually quite streamlined because if there is no test that is the end of the story. The treatment can probably be trickier because I think that is where it becomes much more subjective. So, that group I think has a tougher job. But for the treatment I think it can be a much more complex issue. But I just want to make a comment. I don't think people can just, you know, enthusiastically start filling nominations and having them taken seriously. You know, it takes a certain level of information.

DR. BROWER: Just to follow-up on that, what we have heard from industry is that they want to know the conditions that need a test. So, if there are some conditions that have been nominated to HRSA and would move forward clinically but there is no test, I think that would be an interesting list to publish for industry to work on for their next targets.

DR. HOWELL: Coleen?

DR. BOYLE: Just two comments on the pathway here. One is that I am not quite sure--and maybe Denise said this as well and I know we had that in our "loopy" effort last time and I still feel like it is "loopy." but it is just kind of elongated this time--I wasn't quite sure what the subcommittees would do with that and whether that is an extra step. So, that is just one issue. I am not asking you to answer this. I feel us, as a committee, need to decide this. Then, this is just my concern about creating more working groups and ad hoc groups for each condition and whether we can put some sense of order on that. Because we wouldn't want to have a working group per condition and I don't know if we can group them in terms of types of conditions, and maybe that might be a way of speeding up the issue. So, just some thoughts on that. I really liked Peter's idea of actually moving away from ACIP. It doesn't look like Larry is still here in the room, but I think they are being moved more into being more transparent and more in line with U.S. Preventive Services Task Force. So, I think that we should heed those issues there in terms of developing our own.

DR. RINALDO; My recollection is that there was a consensus in April that we will delegate to the subcommittees, each subcommittee, to really report back to the full committee on go/no-go specifics about a test and the treatment. Now, if we want to bypass and streamline it, again based on what we have learned today, you know, it is perfectly fine with me. I was just following the process that we agreed--

DR. BOYLE: And I am just re-thinking that and thinking that that would be, again, a lot of work to charge that subcommittee with. You know, do they take what has been given to them by nomination process? Do they do a quick review of that? You know, how forward does that have to be to be fair in that process? Some people come with a lot of resources behind them in putting together the nomination process, others don't.

DR. RINALDO: That I think is the nature--

DR. BOYLE: I am not asking you to defend it; I am just posing the question.

DR. RINALDO: What I think is, to me, the fact of keeping nomination material relatively concise has a benefit to allow for a readily quick review on the part of the committee or the subcommittees. So, I don't think it would be an enormous amount of work.

DR. HOWELL: Peter has a comment and then Denise.

DR. VAN DYCK: I think I can either speak for or against the subcommittee. If we end up getting a lot of nominations, the HRSA step clearly isn't involved in that other than to make them as complete as possible. But there is going to have to be some priority setting. So, if you get 10 or 12 or 15 that subcommittee loop may be useful in a relatively quick evaluation in a priority setting process that would come back, and each of those two subcommittees might have a little different idea on the priorities. It could then loop back around to the full committee to set a final list of priorities that would end up going then for the
evidence-based review. On the other hand, if you don't get a lot of conditions I think it is probably an unnecessary step and the committee can handle it.

So, I can speak for either way and it kind of depends on what comes in. Again, you could make the argument that you still don't need it even if you get a lot of conditions and the whole committee should deal with it all.

DR. RINALDO: I can just take this out and just put an arrow here and we will be done.

DR. DOUGHERTY: But I think we need to get back to first principles at some point and I think, Piero, you are assuming or you are suggesting that we use the same kind of scoring and this kind of sheet. I really thought that it was pretty clear, even when we agreed to send a letter to the Secretary, that we really needed to look again at that set of criteria. I think what David Atkins has said is that, you know, the domains that are here are the right domains. It is just that we may not have the right kind of criteria, and without
the right criteria it is all folly if we are all following the wrong criteria.

DR. RINALDO: Respectfully, I disagree. I really believe those criteria are sensitive, are complete, and they really cover all the aspects that need to be addressed. For one thing, you know, if you think of it as well put together in the end by more than 100 people--and believe me, I understand and I follow and I analyze your concerns of our discussion but the truth is when we look at the big picture of the people who find them appropriate and the people who don't, the balance is overwhelmingly--overwhelmingly in favor of people who found that, and look at the endorsement by professional organizations just to start. So, to say that these are faulty criteria, I then will ask you to specifically point to me, one by one, where the problems are because I really don't think--and nobody has made a cogent argument, credible argument about the fallacy of those criteria.

DR. DOUGHERTY: I agree. I think that this committee needs to have that discussion of these criteria and the scoring one by one. I really agree with that because that is the starting point and if we can't agree on those criteria, then we are telling everybody to go about and approach that--I mean, the letter from the committee says the best we could do at this time but we realize that it needs to evolve. So, I don't think saying that we need to be consistent with a process that we said needs to evolve is the right approach to go. So, I really urge that we have that discussion. We have not had that discussion as a committee.

DR. HOWELL: Denise, you commented about criteria and domains. How would domains differ from criteria?

DR. DOUGHERTY: Well, a domain would be, say, the incidence of a condition, the burden of the disease.

DR. HOWELL: And it is also listed obviously on the sheet as a criteria.

DR. DOUGHERTY: Well, the criteria really are for inclusion of the scores really that are given based on these breakouts.

DR. VAN DYCK:I think we are getting into discussion and we are not all thinking of the same thing when we talk about a process or a criteria or a domain. I know there is a lot of sensitivity around the scoring and

the process that was done initially. I am not sure there is a lot of controversy around the criteria or the domains.

DR. DOUGHERTY: Not the domains.

DR. VAN DYCK: Right.

DR. DOUGHERTY: But the scoring process--

DR. VAN DYCK: And that is what I said, the scoring and the process which I see as different than development of the criteria or the domains. Because there is so my sensitivity, and the green sheet brings up sensitivity, it seems to me it may be better to start with the suggestions David made on what he called criteria and domains and then see how these fit into those. Because my sense is that most of them are going to fit and the difficulty is going to come around, well, do we really score that 100 or 50, or does it even matter how we score it?

DR. DOUGHERTY: Do you score it at all?

DR. VAN DYCK: Exactly. Does it really matter?

DR. DOUGHERTY: The evidence-based practice centers don't come with a score.

DR. VAN DYCK: Right. So, I think it is important to make clear what we call a criteria and what we call a process and the transparency of the process. To me, criteria are the lists of elements under a domain, and a domain can be treatment or screening or diagnosis, and then there are criteria elements under those which we think would be important in the process.

DR. DOUGHERTY: That is perfect. My concern was that we were proceeding with a process where the underlying feature was were these criteria and scoring approach, which is what I thought I heard Piero say.

DR. RINALDO: Okay, let's put it this way, I thought it was relevant to have a term of comparison because, for one thing, you know, we will be reevaluating things that were a part of that process and were included in the uniform panel because there was a perception of not being a test. Now, only in a matter of a few years we have seen this changing. So, to me, there would be value in being able to have a point of reference to see how things have changed over time.

Now, it could very well be, you know, for what Peter called sensitivity, let's say that, you know, we sort of cut clean with the past and say the uniform panel is something. The question for you, and I think it is something that Peter brought up--your concerns are about the wording of the criteria or the actual scores. Perhaps we can together then redefine the scores and, you know, things that were said--0-100, if you want to go from 72-1039 it is perfectly okay with me. The point that bothers me will that allow us to do--well, it could be done just looking back in those databases and changing the numbers and eventually it could be--but the real issue is about
the relative weight of a criteria and if you feel there is a way to improve it, by all means. But I think this is where I think a lot of really unfair assessment of these criteria--it seems like you had a problem with the scoring and the relative weight, yet there was a blanket negative statement about the criteria themselves. This is the first time I hear you articulating that. If that is correct, please tell me my understanding is correct. You are saying you don't have any problem or you have no major problem with the criteria, the 19 criteria and the different levels, but your problem is in how they are scored. Is that the point you are making? Because that is what I thought I understood just now.

DR. DOUGHERTY: What I would like to see is what Peter has suggested, that we go to the kinds of big categories that David Atkins suggested and then we agree on which are the most important domains that this committee wants to look at.

DR. RINALDO: But it is the same thing.
183 Please believe me. I listened very carefully to

Dr. Atkins today. There is nothing different, nothing.

DR. VAN DYCK: But, Piero, the committee wasn't involved in that process before. Now the committee has a chance to put its stamp on something, and what is most likely to happen I think is that you are going to end up with 17 or 21 or 19 criteria that tend to mimic what has been done. I mean, right people and thoughtful people are generally going to end up in the same place, but there is more ownership and there is more buy-in and it is a thoughtful process that is transparent to the public, and all the rest. But it is not negating the quality of anything that has been done. In fact, it can affirm the quality of what has been done if we end up in somewhat the same place.

DR. RINALDO: You know, there is one thing I would like to have engraved on my tomb, "there is always room for improvement." [Laughter]
184 And I believe that. So, the point is, take the criteria and say for our criteria I want to modify with specific suggestions. I think Peter is absolutely correct. It was a different body that had to really step into this later although there is some overlap. But if we can make it now new and improved criteria for inclusion in newborn screening, I am very happy to get involved and engaged in that conversation. But we have to be specific and also I think, at the same time, in all fairness--we all have heard and I have read about pretty blanket criticisms about these criteria but I don't really see where the evidence for this criticism lies.

DR. HOWELL: Denise has the last word I think.

DR. DOUGHERTY: Well, I just would actually like the committee to vote or discuss that point. Are we going to reexamine and come up with new criteria or not? I think the committee needs to decide on that.

DR. HOWELL: Can we have some comments?
185 Coleen, you have some words?

DR. BOYLE: Yes, I guess I am a little confused here. To me, this is a nomination process and I feel like we are making it a little bit complicated in terms of the nomination process. I know we need a process to help cull it but I guess, you know, I wouldn't want to make it so complicated that people stumble all over themselves in doing this. So, I actually feel like we need to have a simpler process. I find what you have proposed--actually the format from the fact sheet I think is a very nice guide to people and, you know, if they had literature cited for each one of these major sections--I would probably say the relevant literature for each one of these, I think that would be very helpful and a very useful way of making a nomination process. But I don't want to overwhelm people in this process. I want them to nominate their tests and their conditions and, you know, have it be, as people said, transparent and explicit. I guess I personally am feeling a little overwhelmed with the first step of this process
186 already.

DR. DOUGHERTY: Could I just say that I agree with you that it should be much simpler for somebody making a nomination, but I still think that we shouldn't be giving different buckets of criteria or domains, whatever we want to call them, to people making the nomination than what will eventually be used to review the evidence. So, I think that it needs to run in parallel. Does that make sense? That we can't just tell them, well, we are going to use entirely different criteria to evaluate the evidence and make a decision than what we have asked you to provide for us.

DR. HOWELL: Greg has a comment.

DR. HAWKINS: I think Coleen kind of hit it for me when she made that comment about the nomination process being simple. The first thing I look at, I look at the uniform panel conditions as if I was a parent and I followed the disease and I wanted to nominate it. I think I simply might have trouble filling out this form myself. So, my question is after the nomination whether this form
187 should be for the ad hoc committee to use to review, and for someone with more knowledge--everyone on the ad hoc committee uses this to review the disease that has been submitted. Then, this criteria is for the ad hoc committee and it moves it to the process. So, basically we have a very simple nomination process coming from anybody and everybody. Then, like I said, it gets the technical review by the people who are really going to do the technical review. I think this becomes very complicated for anybody who is just going to submit a disease.

DR. RINALDO: That is fine. You realize that the score card and the fact sheets are the same, identical criteria. Actually, one point that was made this morning actually I thought was supportive--I wrote it down, that the panel should define the standards to judge evidence and then evaluate the evidence against the standard. I really thought it was a very illuminating presentation because I think for once we are beginning to define the roles. So, perhaps Greg is
188 absolutely correct. We can forget the score card as a tool for nomination and make it just the fact sheet with no scores, but I think in the fine print define and do mention that we need to know about this, the specific items, like when we ask for throughput, a definition of throughput, and then work as a committee in refining the criteria. That will be our process of refining the standards for the working group, and say these are the criteria, modified criteria and scoring criteria that we think should be used in the assessment, and based on your review of the evidence you can score it. So, I agree. That is exactly why we are having this conversation, to find a way to improve things.

DR. HOWELL: On the basis of that very sanguine comment we are going to take a break. We will return at 2:45. We still have considerable time to discuss this issue before we hear from Brad at the end of the day about the status of the states. So, let's take 15 minutes and we will return. [Brief recess]
189

DR. HOWELL: Ladies and gentlemen, we have more time to discuss the issues at hand, and so forth. Who would like to lead off with commentary after the coffee break about things you would like to discuss about how to handle future nominations for additions to the committee? Steve?

DR. EDWARDS: I would like to suggest that we consider modification on this front page. For example, on that first step, the fist box you come to, that our group be given the option to refer directly to the ad hoc working group. That would not absolutely have to be done but it would be an option for our group because, you know, each one of these steps is four months because we are meeting, making a decision and referring it to somebody else, and I can see that initially, after going from HRSA to us, it could be clear to the group that we are ready for it to go to the ad hoc working groups. So, I would like to see that listed as an option. In other words, a bypass would be an option.

DR. HOWELL: Piero, would you be good
190 enough to put that back up on the screen, please, because the audience has a little diagram that only the people with magnifying glasses can read? So, maybe if we saw that, that would be helpful to see what Steve is talking about. You are suggesting to go to HRSA, to the committee and then directly--

DR. EDWARDS: That that be an option, an option also would be to refer to the subcommittee, yes.

DR. HOWELL: Right.

DR. EDWARDS: I am saying that that would be an option because there may be situations where we would really want the subcommittees to look at it--I am just suggesting that it be an option.

DR. HOWELL: Right. Any comment about that? In other words, an option to go directly to the working group, bypassing the committees.

DR. RINALDO: Is tomorrow morning soon enough?

DR. HOWELL: That would work!

DR. EDWARDS: I would support that because
191 I think that is the point Peter was trying to make. You know, until we really get into this and know whether we are going to need a thousand working groups--and I am just exaggerating, guys-- [Laughter] --or whether or not, you know, in the committee's view the work may be more appropriate for the subcommittees at a certain point out. I think the committee having the option of referring it directly to an ad hoc working group or to one of its existing subcommittees make perfect sense.

DR. HOWELL: Any comments about that? Denise, you must have a comment. You always have a comment!

DR. DOUGHERTY: I guess I am still stuck about whether we are discussing the entire process, whether there is a pre-process of getting some criteria that we all agree on. Because giving it to somebody without any criteria is going to result in a lot of disagreement, and so forth. So, I am kind of puzzled about which part of this we are talking about and what comes first and then what
192 the steps are after that.

DR. HOWELL: Amy, you seem to have wisdom over there!

DR. BROWER: No, I think it is good to talk about the process that Stephen brought up and then we can talk about the criteria as well. I don't think we have to do it in order.

DR. HOWELL: Coleen?

DR. BOYLE: I was going to make a suggestion that we talked about off-line during our break. That was that maybe a smaller group of us--because I feel this is a hard thing to do around the table here, but we could actually talk about what I would call the criteria, which are listed in the ACMG forms and maybe try to come back to the larger group at our next meeting, which is in January--

DR. LLOYD-PURYEAR: No, February.

DR. BOYLE: February? And present sort of our revised--whatever we would consider as a consensus from that smaller group to you all. So, to try to address Denise's issues and I think what
193 we heard from the two talks this morning, that we clearly need to have set criteria by which to evaluate this and those criteria need to be transparent to all of us and to everybody on the outside in terms of the nomination process, and those are the criteria by which the condition would be evaluated at every step of the process, even though at every step there might be a different level of review of that. Am I making myself clear?

DR. EDWARDS: I have a clarification question on that. My question to myself is, is the problem the criteria or the scoring system or both? Because I think if it is the scoring system it is different than the criteria. It is hard for me to look at the criteria and then say that there is something wrong with them. I think that most of the objection that we have heard earlier was related to the scoring system for the criteria, not the criteria themselves.

DR. BOYLE: My suggestion, and again I hope I am echoing Peter's wise words before, is that I think that we, as a committee, need to take

194 a look at the criteria, all of them, and feel comfortable with them. Some of them perhaps could be modified; some of them could be reduced. I don't know, I just feel like we need to take a look at them. The second part of your question, I feel uncomfortable with the categories in the scores and I think we need to talk about those issues just so that we as a group own them and feel comfortable with them--the criteria and then whatever we do with the criteria.

DR. DOUGHERTY: Yes, and I think one of the issues is the balancing and I think that is what David was talking about today. Do we emphasize the evidence--the false positives, false negatives and then the effectiveness of treatment, and then have cost as an additional consideration? How is the committee going to weight the different groups of criteria in its decision-making? Maybe not a formal weighting but, you know, are we going to go 51 for a test that costs less than a dollar and everything else, you know, is worth 49 percent
195 of our decision? That kind of weighting I think we need to really think about.

DR. RINALDO: Denise, I just want to follow-up on one thing you just said. I really think what we call evidence really actually becomes a double-edged sword because you just talked about false positives, false negatives and, I will tell you that that is the difference between bad evidence and good evidence. I will tell you that when you try to judge, say, a test based on the fact that somebody has a higher rate of false positives, it is really not an evaluation of the test or the condition. You are evaluating the performance of whoever is putting up those data. That is, by the way, the other issue that I hope eventually we will get to talk about because, I will tell you there is a lot of evidence up there that is garbage and it has to be basically, you know, recognized as such.

DR. HOWELL: Norman?

DR. KAHN: Mr. Chairman, I am going to try to limit my comments to what I think is the most
196 superficial of the questions on the table, which is the process of nominating new conditions, not the process of deciding whether the new condition should be included. I think that the process of nominating new conditions involves

Dr. Edwards' suggestion of the option for bypassing, which is fine. The second one that I wanted to raise was if we really want to make it easy for people to nominate, where no judgments are passed, no criteria are involved, just somebody wants to nominate a condition for our consideration, then I am questioning why we should have the nominator fill out the green criteria form at all. That should be what our ad hoc work group works on. So, just limiting it to the level of the nomination process, I would offer that the option is a good idea and that it should be an easy, simple process that just allows people to nominate without having to go through all the criteria. Once we get down tot he next level of discussion, which is how do we make a determination that we
197 want to accept the nomination, then we are going to have to start talking about the criteria, the weighting, the process of the work groups, etc., and I think that is another level of discussion.

DR. HOWELL: I think I heard a brief comment before lunch that there was a sentiment that supported your position to have a simple document for the nominator. Did I hear that or not?

DR. VAN DYCK: I think there was some general feeling like that before the break. Can I discuss that?

DR. HOWELL: Please, by all means.

DR. VAN DYCK: I think it is important to have a simple nomination process too, but simple does not mean scant and inadequate. If I were nominating a process I would want to know what criteria were going to eventually be used to make a judgment on my nomination. I think that is only fair. If I know what those criteria are, and there are 19 and they are made clear enough, it seems to me I would like to have the opportunity to address
198 those. It doesn't have to be in the form of a busy green sheet with scores, but it certainly can be in a

simple, uncluttered kind of process. But I think we and HRSA and we as a committee have to have enough information that we can make some reasonable judgment about using our resources to send this on to the ad hoc working group, or whatever we call it. So, I am for a simple process. I am for a simple looking process. But I am also for a process that at least has enough information in it, and in a format that will eventually match a more complicated evaluation, the criteria.

DR. HOWELL: Greg?

DR. HAWKINS: I think maybe what we should discuss too is, if you have more of a simple nomination form, it is going to come to HRSA first. That is their criteria for saying this is not approved. Maybe there are some of these things that we thought would go to the ad hoc committee that could be basically short-circuited. I mean, if there is no test it shouldn't probably go any
199 further because there is nothing you can really do. Maybe that is something that some of these criteria can be in the very first box where some are eliminated before moving on to the process. So, some of the criteria for selecting could be spread across the whole process. I don't know if anybody has any feeling for that.

DR. HOWELL: Norman?

DR. KAHN: I appreciate the flow of this discussion. I think what I was reacting to was the assumption, and it is just an assumption, that we were thinking about requiring the nominator to complete a page that looks like this. That is what I was reacting to because, to me, it is too much for a nomination process and it is far too subjective. The nominators are going to be proponents and you ask subjective questions like "burden" and consequences like "profound" and so on. Proponents are going to define those differently than an objective group. But I think what

Dr. Van Dyck is suggesting is that there be some kind of screen
200 that allows us to determine whether this is a high enough priority to be on our radar screen that we should be dealing with. Greg is suggesting that maybe one of those screens is whether there is a test or not. Maybe there are a few things that the nominators do need to fulfill in order to have their nomination accepted.

DR. RINALDO: Can I make a comment?

DR. HOWELL: Please.

DR. RINALDO: I believe that was the conclusion just before the break. So, would you still feel that the other, what we call the fact sheet--again, using the nomenclature used in the ACMG report--is too much? Because I have to say that it seems to me that it is a very different ball game when you try to collect data from experts and stakeholders. It is often, you know, a very tedious and demanding process to convince people to fill a survey, which is true for any survey. Here I think we are talking about somebody that clearly has a very strong motivation. So, I am not sure I really agree in principle with the fact that people
201 would be deterred just by filling. I realize that the green is evoking, you know, an allergic reaction. So, forget those forms. Let's think a little bit more about the black and white. If we look at the black and white form, I really think that the proponent, somebody who decides to assume the role of a proponent is a person that really is assuming responsibility of providing the seed of the evidence. Because, otherwise, we really could be swamped by people who nominate any sort of things without really having the burden of proof, that is, a meritorious proposal. So, I think personally--again, there is no attachment on my part to those forms. You can change it, destroy it, as you will. But the point is we are asking 19 questions and I don't think that is too much to ask.

DR. HOWELL: Nancy, you have a comment?

DR. GREEN: I think that actually we are circling around an area of consensus, which is a nice position to be in. So, I would like to
202 suggest that we take this white, as opposed to the green--no relation, and have a small group sort of twiddle with it and then present it perhaps in advance of the next meeting for consideration for approval at the next meeting. I think, Piero, that it is probably close to what we are all saying about ease of submission for consumers, you know, for a wide variety of proponents, and that the basic categories are sound.

DR. HOWELL: Coleen, you have a comment?

DR. BOYLE: To follow-up with what Peter said, I want to make sure that what we present to the public as being the criteria with which we evaluate their proposal for nomination is the same criteria that we use throughout the process. That means to me that whatever this form says and whatever shape it ends up in, those would be our criteria.

DR. RINALDO: I would actually like to make a suggestion then. Considering that we have a fairly loose agenda for tomorrow, would the rest of the committee think it would be good use of our
203 time to go over that, one by one, and consider changes, additions, omissions? After all, somebody said it before, we operate on four-month steps so to say, well, let's do it the next time we are really just basically staying idle for four months.

DR. BOYLE: We didn't say that, Piero. We said that we would have a subgroup over the next four months that would come back and could even share things through e-mail.

DR. RINALDO: What about doing it tomorrow?

DR. HOWELL: We have full subcommittees.

DR. GREEN: Some of us are representatives of a larger organization so we aren't able to necessarily weigh in on this without consultation.

DR. HOWELL: I might point out that we have additional time today to look at criteria, which we can certainly do. We have 45 minutes still allocated in this period if you want to look at individual criteria. I think that there has been general consensus that we don't want to talk about the scoring system so we will put that aside.
204 But would you like to go down and look at criteria at this point of time, or would you like to discuss something else? Bill?

DR. BECKER: Does the discussion of the criteria impact what the committee might decide about the process that is sort of on the table, the overall process for the nomination of a candidate condition?

DR. HOWELL: I think the answer is yes because I think that if you have a person nominating a condition they will need to know the criteria that will be utilized to evaluate it, and they should know that up front.

DR. BECKER: That is not really my question though. Does that then change whether it is going to go to HRSA then to us, then whether we are going to take it to subcommittees and ad hoc working groups?

DR. HOWELL: Oh, I don't think that. The form I think would be evaluated.

DR. BECKER: Right. That is really my point. There are kind of two issues really on the
205 table. It is the overall process that we really haven't decided yet and then the sub-issue of, once we have decided that overall process, how to actually get a nomination into the queue.

DR. HOWELL: Piero has carefully put a side bar here with a great, big green arrow--he likes green, as you know. Can you comment about that? What about this chart, and so forth? Are you relatively comfortable? Do you want to modify this flow as far as the flow? Denise?

DR. DOUGHERTY: I guess I would like to know what the nature of the ad hoc working group is.

DR. HOWELL: Comments about ad hoc working groups?

DR. VAN DYCK: Can I make a general comment?

DR. HOWELL: Please.

DR. VAN DYCK: If we have 30 or 45 minutes left here I think it would be better to do the flow chart since there is not a direct connection between the flow chart and the criteria, and get the flow chart worked through. I think it is unfair to try to determine the criteria in that constricted a time period because I think the people who are really concerned about it want to look at David's presentation and his slides and Bill's slides and have a thoughtful process to do this, and I think probably a little more time is worth there and, in order to speed it up--I mean, that can be met within a month or two. We can have e-mails to people. They can get buy-offs from their organizations and make suggestions, and then we can come back to the next meeting and we can do it, and be done with it. I just feel if we try to do it in the next 35 minutes we are going to be doing it again at the next meeting for another period of time. It is going to take until the next meeting to do it anyway. So, I would rather get the flow chart done and then look at the points in the flow chart where we need to have criteria to move something on through the next box, and then develop those or assign those to the subcommittee to do in the next couple of months. That is only a suggestion.

DR. HOWELL: We had a question from Denise about that.

DR. VAN DYCK: Well, we had a suggestion on the floor.

DR. HOWELL: We had a question from Denise about the ad hoc working group, about the nature of that.

DR. VAN DYCK: Well, I said what I said before, that we were leaning towards having a contracted group that would do this on a regular basis for us and have some consistency. That is what we are leaning towards, but I think it is worth having discussion. That means there would not be people from the committee on it. It means that it is more of an independent process, separate from the committee. It would be a contracted working group that is doing this independently. Then they would make a verbal and written presentation to the committee and be questioned and asked, and have a back and forth period in public. I mean, that is the structure of that. Then we
would take that information and deliberate on it and make a final recommendation from that. That is what we are thinking about, just because I keep getting asked.

DR. KAHN: Well, representing an organization that participates in both the U.S. Preventive Services Task Force and the Advisory Committee on Immunization Practices, I would be very supportive of Dr. van Dyck's leanings.

DR. BOYLE: With that scenario we wouldn't need a subcommittee review.

DR. RINALDO: So, this model would basically just sort of take the subcommittees out of the equation. So, we would just operate as a full committee.

DR. VAN DYCK: It is still an option. The other thing that is different is the ad hoc working group box and it gets a different name, I mean in the way I am thinking about it. It becomes an independent evidence-based review committee, or whatever.

DR. BOYLE: So, we could still have subcommittees. The lab subcommittee could review the laboratory testing--

DR. VAN DYCK: If the committee chose to have that extra step because of whatever extenuating circumstance there was--

DR. BOYLE: Right.

DR. VAN DYCK: --and I can envision a couple of them, then that is an option. But that is an option that occurs before the committee makes a final decision to send the nomination to the evidence-based review committee.

DR. BOYLE: I mean, one of the things you could do is reverse the order of the subcommittees, where whatever passes through the initial HRSA screen came to our subcommittees for review and then to the full committee. I don't know. I am just thinking there are a lot of steps here.

DR. RINALDO: That would imply somewhat that the subcommittee activity is independent of the main committee. We have occasional conference calls but, again, this is a different process. If we are comfortable with it, why not? But in reality, we meet as a full committee only when we meet as a committee so that is why separating it might really be more artificial than real.

DR. BECKER: I think I would favor having the full committee retain the option, with deliberations, of either sending it directly to a structured ad hoc working group or an evidence-based review group, as Peter described, or through a slightly different pathway through the existing committee subcommittees. I have another comment about the process but I will step back.

DR. HOWELL: Steve?

DR. EDWARDS: My only concern about the option is that I think that there should be some representation from this committee on that evaluating group. I don't think it should be dominant but if you look at the model for the ACIP, the ACIP has representatives from a number of different groups on there and I don't think this one should be excluded. I don't think it should be dominated by this group but I think there should be some representation from this group. For one
thing, it would be helpful in explaining the decisions of the group to our group. But I would like to see some contact between our group and that evaluating group.

DR. HOWELL: Norman?

DR. KAHN: My own opinion would be that liaisons for the purpose of communication and clarification are certainly useful, but I would really minimize that. I think one of the strengths of the U.S. Preventive Services Task Force is the independence of the evidence-based practice centers. The full decision-making authority is retained with the group to which the ad hoc working group reports. The ad hoc working group makes no decisions. They just do all the evidence-based reviews and they report to this committee in this particular case. In the case of U.S. Preventive Services Task Force they report to the U.S. Preventive Services Task Force. It is that group or it is this group which retains full decision-making responsibility. So, in answer to the question just what is that ad hoc work group, I am listening to a discussion which says that that would be in a model very much like the U.S. Preventive Services Task Force which contracts out in the task order contract to an independent evidence-based work group which does the evidence review. That is then presented to this group, and this is the group that makes the

decision. In so doing, while we may retain the option to go to our subcommittees--and we may exercise that option at some point in time--if the external work group is truly independent and truly does a good job in their review, my guess is we would be using that large, green arrow a lot.

DR. RINALDO: I have a recollection that when we were discussing the formation and membership of the subcommittees one of the reasons--and tell me if I am mistaken, but I thought we were sort of adding members also with the expectation that there would be a role for these ad hoc working groups. So, I am wondering if that is a change, but it could very well be the
case.

DR. HOWELL: Bill?

DR. BECKER: I think Norman actually described what the potential role could be for the working group as being liaison or communication source from the full committee to that working group. But I think the point he is really trying to make is in terms of the voting body of that ad hoc working group. Any liaisons from the full committee would not be voting members of the ad hoc working group. They would be there to provide support, which I think is probably appropriate. That seems like a reasonable structure to me.

DR. DOUGHERTY: Just to clarify, the ad hoc working group or the independent evidence review doesn't vote.

DR. BECKER: That is the model by whatever mechanism they make their decision, yes.

DR. RINALDO: Again, some of you may have done this, and again I really look to people with prior experience, I think if I read the report from an evidence-based group I would expect to see the process leaning either in a negative or a positive direction because if it is an entirely neutral, descriptive process I really don't know how helpful it is going to be. That is why we are calling it an ad hoc working group with the idea that they would make a recommendation that could be endorsed or not endorsed. But to say we reviewed 150 papers and 50 say yes and 50 say no and 50 say maybe, then what kind of progress did we make?

DR. HOWELL: Dr. Edwards had suggested that this evidence review group have membership from the committee to serve as a liaison, a minority membership. Norman spoke against that, and so forth. Can we have any further comments about that?

DR. VAN DYCK: I would like to clarify what membership means. I have heard liaison; I have heard membership; I have heard voting or non-voting. I think we need to describe just what the role of a person would be. I have no problem with some person being there as communication. I don't think it is necessary.

DR. HOWELL: You had specifically mentioned that it would be a minority person who would serve as a liaison.

DR. EDWARDS: Not a minority person, but a minority of the committee. Just a couple of persons as liaisons to the committee is what I had in mind. DR. HOWELL: What would you like? Comments about that recommendation or any recommendation? Bill?

DR. BECKER: Rod, I think Piero's question is still on the table about what the nature--I am going to call it a report--from the ad hoc working group would be back to the full advisory committee for the advisory committee's action--

DR. HOWELL: Right.

DR. BECKER: --which is where the appropriate action needs to be taken. I guess I want to ask Norman, the nature of the working groups for I guess it is ACIP--what is the nature of the report that they bring back?

DR. KAHN: Well, there are two different sets of working groups and they are very different, and their level of support is very different between ACIP and the U.S. Preventive Services Task Force. We heard presentations from both of them. One of the criticisms of the U.S. Preventive Services Task Force, as Dr. Atkins pointed out, is that their bar is very high. The evidence-based practice centers are independent. There is a lot of political history about why that took place. But the outcome is that people do a thorough evidence review of the question at hand, and they do it over and over. They use the same criteria over and over. There is consistency in their reporting. So, the report that comes back to the full group--in our case us; in their case the U.S. Preventive Services Task Force--the report comes back in a standard format. It always uses the same criteria. It always uses the same weighting scheme. And, the Task Force is able to deliberate the tough questions, the subjectivity, the rating, the ranking, the prioritization, etc., and make up its mind. That is not exactly the same way the
ACIP does it. But I heard Dr. van Dyck suggest that he was leaning more toward the U.S. Preventive Services Task Force does it, which I am supporting.

DR. DOUGHERTY: let me just read from one of David's slides and maybe, Norman, you can help me here. It is the slide on page five and it is about PSA screening. It says this is the rationale for the recommendation that the Preventive Services Task Force gave for PSA: Insufficient evidence; we can't tell you one way or the other what to do. So, a report would say, in its conclusion, we found good evidence that PSA screening can detect early stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes. Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies and potential complications of treatment, and some cancers that may...blah, blah, blah. So, it gives you the evidence for what they found in their systematic review of how the screening test does, and then also gives you what the benefits of that screening might be in terms of outcomes from treatment, and also will tell you about the harms that may occur because of the screening test or the treatment or the diagnostic procedures. That is what it does. The Task Force will take that evidence review and decide whether it thinks the harms outweigh the benefits or, you know, it should get a D recommendation, which means don't do it, or an I recommendation, which means it is up to the clinician to decide.

DR. BOYLE: Actually, you missed David's talk. I think you were here at the end. But he said that we could come up with our own criteria, or whatever we call those--ratings, rankings.

DR. DOUGHERTY: Weighting schemes.

DR. BOYLE: Well, not weighting schemes but recommendations.

DR. DOUGHERTY: That is right. It doesn't have to be insufficient. It could be the pilot test. Norm, does that fit with your understanding of what the evidence review does?

DR. KHAN: Yes. Maybe this is unnecessary but I don't want us to assume that this one paragraph on page five is all that comes out of the working group. No, that is a gross summary, a very superficial summary of what comes out of the working group.

DR. HOWELL: So people have a good idea of what would come out of this contracted work group. Do you want to discuss that anymore? Do you have additional questions on that?

DR. BECKER: No, I am back to the big diagram. DR. HOWELL: But we still have the question that Steve has raised about whether or not it would be appropriate on this particular contracted group to have membership from the committee. DR. BOYLE: I have some suggestions there, Steve. I have actually participated in the sort of data gathering part of some of the U.S. Preventive Services Task Force topic

areas. You know, we have actually contracted with them to do something and provided them with experts to gather information and data from. I have also participated as an expert on that. So, I feel like you can guide that process. It is not like you hand it over and it is goodbye and see you in six months. I mean, there could be some of us that may be designated as helping oversee that process and maybe that is what you are talking about.

DR. EDWARDS: Communication.

DR. BOYLE: Communication, that is sort of what it is. I mean, it is providing them with guidance. I see that as a clear role for our committee. Obviously, we can't all do all of them.

DR. HOWELL: Did you focus on an individual issue or was it a more global issue, and was your group looking at a variety of issues or did you have individual--

DR. BOYLE: I have had experience with both. I have been an expert for a particular issue, such as speech or language disorders so I have been an expert. Then, on the other end, when we have taken on more global issues from my own division's standpoint, then it is a much broader
issue.

DR. HOWELL: Any comments about Coleen's comment? Amy, what are your thoughts?

DR. BROWER: I agree with Coleen.

DR. HOWELL: Greg?

DR. HAWKINS: I agree.

DR. HOWELL: There seems to be a sense around the table that there would be an interest in having participation from certain members of the committee with the evidence review group. Peter doesn't see a problem with that either, and so forth. Back to the list, back to the chart. What does that little top box say, Piero, that you have between the green arrow?

DR. RINALDO: I can change it. If we are going to call it evidence review basically it will be committee approval to form or to empanel an evidence review group.

DR. HOWELL: Further comments about the chart and the flow, etc.?

DR. BECKER: I would suggest one additional modification. If we decide that a candidate condition is to be considered by one of our subcommittees, if we are following down that pathway, the current draft has the subcommittee potentially taking two actions. One is recommending not to send the proposal to for an evidence review and that has the dashed red line all the way back to the start. Then the second box, of course as you can see, is the recommendation to the full advisory committee to form an ad hoc working group. My suggestion would be that the subcommittee, whether it decided to recommend for or against, should only make its report back to the full advisory committee. There shouldn't be that dashed line all the way back to the start. The subcommittee should always be reporting back to the full committee. The full committee should be the body to recommend for or against.

DR. HOWELL: Done!

DR. EDWARDS: I would agree with that. I think there is an additional reason for doing that. What if one subcommittee recommends quashing it and
the other one recommends sending it back? So, I think it definitely needs to come to the committee to get away from that dilemma.

DR. HOWELL: Any further comments about the flow chart? Is everyone happy with the flow chart?

DR. BECKER: I would move that we accept this as our process.

DR. HOWELL: Is there a second?

DR. KAHN: Second.

DR. HOWELL: You can't second. Is there a second? Hearing no discussion, those in favor of accepting this as the process for introducing new things, let's see your hands. [Show of hands] Oh, it is unanimous. Thank you very much, and so forth.

DR. GREEN: Rod, excuse me, we can't vote but we want to thank Piero and Bill for making the flow chart.

DR. HOWELL: We still have a little time before we move to Brad's talk about the state of the states, and so forth. What do you think we could be most productive in as far as spending time? Coleen?

DR. BOYLE: I do have an issue but I can save it.

DR. HOWELL: Well, bring it up.

DR. BOYLE: Well, I guess I talked about this a little bit over lunch. I feel like the work of our main committee is very different from the work of our subcommittees. I feel like we have started to come together in terms of the full committee. I guess I was hoping, like we heard from ACIP, that the work of the full committee and some of the intricacies and aspects of it would carried out by whatever subcommittees we have charged. Right now I feel like our subcommittees, at least the one I am overseeing, is really doing very different work. Also I feel like it is a little overwhelming as well. It is a huge amount of challenging issues. So, I am not quite sure how to align those two and I am hoping that that could be a discussion for the full committee.

DR. HOWELL: Would any of the other subcommittee people, chairpersons like Amy, like to weigh in on that?

DR. BROWER: I think the subcommittees are just getting started. We just got our charges approved or charters approved. So, I think tomorrow we are going to try to get some milestones and some timelines built for the subcommittees, at least the laboratory subcommittee, that we can report back to the committee as a whole. So, I do think they do seem different right now but it is because we are getting started and because as a full committee we are really starting with the ACMG uniform panel and had to address that first. So, I think in the future they will be more connected.

DR. BECKER: Yes, I would agree with Amy's comments. There probably is a little bit of a disconnect just because of the nature of the tasks being assigned--disconnect between the full committee and the subcommittees. Obviously though, the full committee is the body that ties these tasks back together and sort of unifies them. But
I agree with Amy's comments that the process is still forming. I guess we are still in the fetal stage. I think some of those things will work themselves out. Now, Coleen's comment about potentially some of them being overwhelming, that may be something that the full committee needs to discuss. There may be a role that the committee could play to guide any one of the subcommittees in maybe prioritizing some of the activities. Certainly, any one of us could have a very full plate and it may be helpful to the subcommittees to guide them by some prioritization process.

DR. DOUGHERTY: I am on Coleen's committee. I think another challenge that we have or that I am feeling is I went back and tried to find documents on what the barriers are to having an integrated health system for follow-up and treatment, and found that a lot has been written about that. You know, you can go back to many, many reports provided to HRSA and others. The ACMG report listed a number of barriers; others have.
So, if we just come up with all the barriers that have already been listed and maybe come up with some recommendations for overcoming those challenges, then what? Is it really worth our effort? Is the committee going to do something about that? Because these things have all been said before. I mean, the AAP screening committee, in 2000, said a lot of the same things about barriers to follow-up and treatment. It has all been said before and people are aware of problems, and I am not sure that we can come up with any solution, recommendation that is going to be that dramatically different and not cost a lot of money. So, I am just wondering what the outcome of our work would be, what the committee will do whatever work we do.

DR. HOWELL: Amy?

DR. BROWER: Not to tell your subcommittee what to do, but I know that we feel like in the laboratory committee we have a chance to do something new with data collection, and now that we have a uniform panel, that we can help laboratories
in how they implement the uniform panel; how they are going the test; how we are measuring the testing. I would imagine, being on some of the regional collaborative meetings, long-term follow-up is a huge issue with those regional collaboratives and they are all either tied into Brad Therrell's database or looking at their own way to collect data. So, I guess I am really data focused because, as a committee, we are really starting with a uniform panel in newborn screening and how does that impact laboratory follow-up and treatment and education. I am being a little bit narrow in the focus but that is kind of how we framed our subcommittee as a start.

DR. DOUGHERTY: So, you will come up with some data recommendations, and so forth, and give them to this committee. Then, what if nothing happens? Will you feel as if you have wasted your time?

DR. HOWELL: You know, I think there are a couple of things to point out. One is that this committee is obviously an advisory committee to the
Secretary and we can provide information to the Secretary. But don't forget that we are also, as I mentioned earlier today, to advise on specific grant programs. I think we should pick that opportunity up. Not that we can solve the problems of the world, but there may be certain areas. I am very excited about the regional collaborative program as far as follow-up and what that can be, but it will need a lot of stuff to help it go, and so forth. But we really ought to hear about those, and so forth. Then we ought to make recommendations about specific things that could be helpful. Coleen?

DR. BOYLE: I was just hearing what Amy had to say in terms of maybe focusing on the recommended panel and, you know, things that might be happening because of that new panel and the implementation of it for follow-up and treatment. I guess I am trying to harmonize the groups and I am also trying to harmonize what we are doing in the larger committee with what we are doing in the subcommittees. I feel like they need to come
together somehow and they are not for me yet. I know part of it is the newness and we are starting to get going but I also want to be considerate of the people on the committee and the new members to it. So, I do feel like this needs to be a discussion. We need to have more time to discuss this, now that we are sort of making some progress with the nomination process, so that we don't continue to spin our wheels.

DR. HOWELL: Obviously, we will continue to discuss that. Steve?

DR. EDWARDS: I think there is one dangling issue in this discussion we have had, and that was the point that Coleen raised about the criteria. I haven't heard us make an assignment of evaluating those criteria. I

heard it was going to be done and maybe you want to do that separately, but that is a dangling issue that I think needs to be resolved before we get away from this discussion.

DR. HOWELL: How would you like to focus on evaluating the criteria? Do you have some suggestions that the committee would like to focus on?

DR. DOUGHERTY: I was going to say why don't you ask for volunteers?

DR. HOWELL: Okay. Why don't we ask Denise, Coleen and Piero who spent a great deal of time on the green criteria to put your heads together and come back and see what you can think about those, and so forth?

DR. RINALDO: Can we start after dinner?

DR. HOWELL: What did you say?

DR. RINALDO: We can start after dinner.

DR. HOWELL: Absolutely. You can start any time you choose. I think Nancy Green is interested in participated and I think that would be a great addition, and so forth. And Amy?

DR. BROWER: No, but can I just request if they could do a review and have something for us as a full committee to review before the next meeting so we come ready to sort of have active discussion?

DR. HOWELL: Yes. I think that would be very, very helpful. So, you put your heads together when you would like to do it, but I think it would be good to have something for us well before the next meeting.

DR. BROWER: And maybe I should be part of it, or at least somebody from the technology side, just because it is test and technology.

DR. HOWELL: Well, I see the two technology sides looking at each other! You or Amy. Peter? Okay, we have Peter. So, that group is going to look at these criteria and come back. Peter?

DR. VAN DYCK: Can I make a suggestion? I see three criteria sets. If you follow the flow chart, there is There is the nomination form itself. Then the HRSA acceptance or rejection that needs a set of criteria for what is looked at, and then for the evaluation by the evidence-based work group. Hopefully, there will be some similarities between all that.

DR. HOWELL: Hopefully, there will be quite a lot.

DR. VAN DYCK: Yes.

DR. HOWELL: Excellent! Amy?

DR. LLOYD-PURYEAR: May I just make sure, so it is Coleen, Denise, Piero, Nancy and Peter Coggins.

DR. HOWELL: Right.

DR. DR. LLOYD-PURYEAR: Then we are going to assign staff.

DR. HOWELL: And this group will convene by what mechanism they choose and have something to us so that we can consider it before the next meeting.

DR. BROWER: And because the nomination form is supposed to be kind of a low burden but have some specific information, I think it might make sense to ask one of the parents that are already on the subcommittees to maybe be part of this just to add a little bit of review before our next full committee.

DR. HOWELL: I would encourage you to add whoever you would like to help in that regard.

DR. RINALDO: Do you see this where we can manage it long distance or should it be face to face? Like, should we get together and do it?

DR. GREEN: Piero, my suggestion is that we start with your excellent white sheet because I think that covers a lot of it. So, I think we could try to do it long distance. I don't think it is going to be burdensome.

DR. DOUGHERTY: Could I suggest that we might start, if people can join, before we have dinner?

DR. LLOYD-PURYEAR: Or after dinner.

DR. DOUGHERTY: Not after dinner, no way, not even after the first pre-dinner drink. Five o'clock?

DR. HOWELL: We are going to now move briskly--unless there is some urgent issue we are going to move briskly to hear from Brad about the state of the states and his latest information. I think everybody in the room knows

Dr. Bradford Therrell, from the University of Texas Health Center in San Antonio. Status of the States

DR. THERRELL: Thank you, Rod. Thank you,
committee, for the opportunity to be here again. What I am going to do for the next few minutes is just to review quickly what is going on in the states and talk a little bit about the hurricane disaster action.

Last time there was an indication that you might like to see some of the past maps and how they relate to the current maps so we went back and we checked old presentations and tried to pull out some maps about a year apart so you can kind of see how things were going.

This is a map that we gave in October, 2000. You can see that at this point--and this is going to be consistent throughout--we were talking about eight disorders, more than eight disorders, not the 29 that you talk about now. These disorders included things that could and could not be screened by mass spec. So, you see the ones with the very high number, Wisconsin and North Carolina were using mass spec at that time. These are the mandates, not just the things that were optionally available. But you can see that at that
time we had three programs that only mandated three disorders, and we had eight programs that were mandating more than eight.

This is a year later, almost a year later. Things are changing just a little bit and you are only going to see minor changes each year I think. Now we move to 2003. I didn't have a presentation from 2002 that I could put my hands on. But by March of 2003 you can see that things were really beginning to crank up a little bit and now we had a number of states, 16, that were more than eight and we had decreased the number of three disorders down to two states.

Here we are in 2004 where now we were discussing--just discussing the ACMG criteria and people are reacting to it. Actually, they were reacting to it before it became the discussion at ACMG and HRSA. But

you can see that now we had 28 states screening for more than eight disorders and only one state that mandated three disorders.

This is today. You can see that we now have 36 states that mandate more than eight disorders, and most of those mandate a heck of a lot more than eight. We have no states that now mandate three disorders.

This is counting the other way, so if you started looking at these by the ACMG criteria, you would add two to everybody because everybody counted hemoglobulinopathies as one and ACMG counts it as three. But this just gives you an idea of what has happened over time. So, I would like to see if you have any questions before I move on with this. This is the kind of thing you indicated you wanted to see.

Piero and I were talking at lunch about could we go back and look at more specific data over the past five years or ten years, and that is really difficult because as we put new data on this we sort of erase old data. Now, we have got it somewhere in the thousand. We could probably go back and find some things like that. So, if you want to give me some suggestions as to what you would like to see next time, maybe we can come up with something. Now I am going to switch
gears--yes?

DR. GREEN: Could you just clarify, all those states that are non-maroon, is that what that is?

DR. THERRELL: Non-purple?

DR. GREEN: Yes, dark purple. So, the remaining X states, how many of those employ mass spectrometry, or how many don't?

DR. THERRELL: How many don't? About half of them, just off the top of my head. There is about half of them that have something going on with mass spec. Either they are contracting them out or they are thinking about doing it themselves. If you go to our web site and take a look at it, we can get every state and exactly what they are doing. This really didn't change very much from the last meeting so I didn't go to a lot of effort here.

DR. GREEN: About 30-something?

DR. THERRELL: Yes, about 36 or 37 states have mass spec.

DR. DOUGHERTY: Brad, could I ask another
question?

DR. THERRELL: Yes.

DR. DOUGHERTY: Since you were talking about differences in counting, are you going to count the 24 secondary conditions in the future or 29?

DR. THERRELL: We have them on our web site actually. Whether or not we make maps to show you is another question but, you know, I can bring you sort of summations from our web site every time. But we have listed on our web site the core conditions and whether every state is mandated to screen for it and aren't yet screening for it; whether they offer it as an option to the entire population; or whether they offer it as an option to a selected part of the population. We have an indicator for every state for every one of the core conditions and every one of the secondary conditions. Then, we also list those other conditions that states may be screening for which are not included in the core or the secondary conditions and there are a number of those. So, that is a pretty extensive chart and list. It is three pages on our web site and you can download them. Maybe what we should do is just pass those out each time to the committee as a three-page handout, or something. But it is difficult to gather maps.

DR. DOUGHERTY: Yes, I am sure. But, I mean, if the idea is to be tracking what states are doing after the core conditions and the secondary conditions then it might be useful to see that.

DR. THERRELL: Yes, and we have it. We are actually in some negotiations right now with March of Dimes about keeping maps by condition of the core conditions and, you know, having ongoing maps available on the webs so you can go to any one of the core conditions and look at the map and see all the states that are screening for those. When you get to the secondary conditions you are talking about 25 more maps and I am not sure that is productive. We have it listed on the web site and I think that is where we are right now but we can respond to you, if you want.

DR. DOUGHERTY: I mean, I am just raising it as an issue about what would be most useful for tracking the conditions in the future. That is all.

DR. EDWARDS: I would have thought that everybody who did the basic core conditions would be doing the secondary conditions because it was my understanding that they had to evaluate for the secondary conditions in order to completely eliminate the core conditions.

DR. THERRELL: There is not 100 percent consensus that everything in the secondary grouping can be detected in a manner that they wanted listed by their state. Okay? So, some advisory committees have actually opted to not listed particular things because when they list those things, it then becomes assumed that they are detecting all cases of that and they felt like that was not the way they wanted to list it. So, not every state lists everything in the secondary group.

DR. RINALDO: I really want to thank Dr. Edwards. The point is you need to really appreciate that, with the exception of two conditions, everything included in the secondary target list is part of a differential diagnosis of one of the primary conditions. So, you may not like it but the best example is where we have 11 states screening for ADSOL deficiency and only seven states screening for functional protein deficiency, biochemically and clinically the same disease, the same biochemical markers. So, that again goes back to my statement before about bad evidence. That just means that the people making these decisions just really don't have a complete appreciation of what they are talking about. You cannot separate the primary targets from the secondary targets. They are one from a testing perspective because you cannot tell. You will see elevation of a marker and it could be six different diseases. Now, the Germans are the ones who are saying, or some of them, that they would like to develop a method that if it is not one of the
primary diseases they would rather suppress the evidence. I personally have a lot of ethical and moral problems with that kind of statement but, you know, it certainly is not unheard of and, again, it should be pursued as part of the evidence. But you cannot make a distinction at the time you detect among normal results. It could be one or many diseases. So, it doesn't really matter if it is a primary or a secondary target.

DR. DOUGHERTY: In the future what will they mean?

DR. THERRELL: I mean, I think those are good questions and all I will say is that if you want to have a good argument go to a state that doesn't list them all and ask them. There is not consensus across the country.

DR. RINALDO: I would love to ask them for the evidence.

DR. BOYLE: Brad, before you go on, I am sorry, I am starting to fade out a little bit and you may have said this, I apologize. Just to get to the work of the committee here in terms of tracking our recommendation to the Secretary and
adopting the ACMG panel, can we then see these maps based on that and how many states are actually screening for those conditions? That would be helpful.

DR. THERRELL: I am going to show you a map at the end. I just wanted to kind of separate it. This is the old way we collected the maps and we have a new map that I showed last time and I will show it again. Because of how do you count things, we stopped counting at 30, and this is a long time ago. We just wanted to compare apples to apples and wanted to show you with time how the apples have compared to the new apples. Okay? The next few slides are what is going on in the states in the last 90 days I guess, since the last time you had a meeting. So, what we do is we sent out a message to all of the programs, the laboratory component and the follow-up component, and we ask them to report in to us if they have had any significant activity in the last 90 days that they would like for me to report to this group. So, what you are going to see is those that sent me something, not necessarily everything that is going on because some people didn't send anything. So, if your state is not there and something is going on and I don't have it, it is because they didn't tell me. To start with, here is Alaska. The interesting thing in Alaska is that they currently, as of yesterday evening, have now confirmed 22 cases of CPT-1. They are all in native Alaskans and the significance of this is as yet undetermined. They began screening for this in October, 2003. They have about 10,000 annual births, of which a quarter are native Alaskans. So, if you do the math you come out with--all these were native Alaskans so that is about 5000. So, 22 cases in 5000 is an incidence of about 1:225, which is sort of phenomenal.

DR. RINALDO: Not so phenomenal. DR. THERRELL: Not so phenomenal?

DR. RINALDO: It is actually a well-known effect. There is an ethnic group. It is the same for Alaska; it is the same for CAH, congenital adrenal hyperplasia in Alaska affects one in every 600 so it is well-known.

DR. LLOYD-PURYEAR: Can you explain the significance of the disease?

DR. RINALDO: CPT-1 is actually really the new laboratory step in the fatty acid oxidation pathway so it is a step required to begin the transfer of fatty acids to the mitochondrial membranes. There is actually a tricky biochemical phenotype because you will find a very high level of free carnitine and low level of AC carnitines because, again, that is what enzymes are supposed to do, take fatty AC carnitines and take them through. The manifestations are severe. There is usually severe liver disease, hypoglycemia, sudden death, and in that region there are actually reports of an association with maternal complications of pregnancy similar to other fatty acid oxidation disorders. So, it is definitely a disease with significant morbidity and mortality and it is quite rare obviously everywhere else.

DR. THERRELL: Also in Alaska the advisory committee has now created a CF test to consider issues related to adding CF to their panel.

Colorado has just completed a review and they are planning implementation of an expanded panel by spring of 2006. So, they are having debates about how best to do that right now.

Florida began biotinidase screening statewide and that is really the only thing that has changed on that map, which you can see at the end, since the last meeting. At the last meeting they were targeting and they have expanded to the whole group.

Iowa began CF screening in July, just before your last meeting. They moved to a new building so as the hurricane hit that became an important aspect of things but on September 8 they began receiving the Louisiana newborn screening specimens. They had to have temporary staff to do that. That staff is in place right now and is expected to be maintained for several months. They are currently participating with Louisiana in a project to try to locate those babies that might have been missed because of the hurricane. Either the specimens were lost, or they weren't screened, or they relocated, or whatever and I am going to talk more about that in just a minute.

Maine--in September their advisory committee recommended that they include the 19 tests that were optional in their state as part of the mass spec as mandates. So, that will be required as of January 1, 2006. So, their required tests will go from 9 to 28.

Mississippi, as the result of hurricane Katrina, had really no significant problems. The specimens there were tested out-of-state by Pediatrix and they used a courier, and that became important because, as I will show you in a minute, with the U.S. mail in the Louisiana situation a lot of specimens are missing. But with the courier service those were able to be tacked from the time they were taken to the hospital to the time they got to the laboratory. The contractor and the state had been working hand-in-glove to make sure that no babies were missed in Mississippi and that has not been a major problem.

New Jersey--their September newborn screening annual review committee made some recommendations to their commissioner. One was for a new computer system upgrade. The others had to do with better training of personnel. What they realized is that they have a lot of personnel who have been there a long time who might not necessarily have the knowledge that they need with the new technologies coming on board. So, they are getting a recommendation from their advisory committee to the commissioner to upgrade the staff basically. They are reviewing all the parent and professional literature as an outfall of looking through the ACMG report and saying you need to do that.

Pennsylvania--this is interesting, in your book I think you will find a copy of this law that was introduced on October 5, 2005. Senate Bill 901 was introduced in Pennsylvania which further defined "disease" in their law by adding to the definition "and testing for severe combined immunodeficiency." That has gone to committee and we will see what happens but that is the first state to talk about SCID which is not on any of the lists.

DR. RINALDO: Do you have any other information--

DR. THERRELL: That is all I have. I have asked people from Pennsylvania and nobody really could tell me why that was introduced and what is happening.

Rhode Island--they are preparing for regulatory hearings to expand the program, and they expect to expand by July of 2006. They currently only do MCAD and amino acids.

South Carolina is expanding their data reporting system so that in the next few months they will have the ability to have Internet access by primary care providers and they are hoping to expand that to newborn screening.

Texas, as I mentioned last time, is under a legislative mandate to re-look at the program and make some decisions so that they can expand by October of 2006. So, for the past three or four weeks they have had a partner meeting every week with "partners" to discuss the possibility of a process for obtaining bids for outsourcing parts of the program. The requirement that they have come up with is an RFP process that will be limited to laboratories. they have not defined the scope of that laboratory contract but they have defined that whoever the bidder is from outside would have to be ten percent lower than the state in order to get the bid. They also must respond to a review that our center did and perform a cost analysis in March 2006.

The State of Washington just met earlier this week and they gave approval to the final rule to add CF and to begin the process of evaluating 16 additional conditions for inclusion in their panel. In Washington they actually require an accounting review and cost effectiveness analysis as part of their process for adding new disorders so they will begin that process now. They project that by the time they get through with all the things that have to go on, bureaucratically it will be February, 2006 before CF is approved finally to be added to the panel.

Here is the map, Coleen. This is a map that shows across the country, in terms of the ACMG panel, where those are available to the whole population at no additional cost. So, whether they are mandated or whether they are made optionally available, they are listed here. If you look, there are seven states that mandate or have available less than ten disorders, and those are the ones in green. There are 11 that have 10-19. Those are the ones in yellow. There are two that have 23-25, and those are the ones in

orange. There are four that have 26 disorders and those are the ones in light green. There are five that have 27. Those are the ones in red. There are 13, in light purple, that have 28 disorders and there are nine that actually have the 29 available. That doesn't mean they have them mandated. There are nine that have them available for the entire population.

DR. RINALDO: It seems to me that the last four colors really--or even more--should be just one because, again, we are talking about really tiny differences.

DR. THERRELL: There are lots of ways to do the maps. I did it this way but I will take it under advisement.

DR. RINALDO: I don't know, but I think really there is no difference between 26 and 29. I think it is just about semantics or recognizing one of the secondary targets. So, I really think that they belong to the same.

DR. THERRELL: Well, these actually don't have the secondary targets. This is the core. Okay? This is the 29 core.

DR. RINALDO: Okay.

DR. THERRELL: The reason that most are 28 and not 29 is because of hearing screening not being available. Remember, in the deliberations hearing screening is one of those things, and there are other types of screening, not just biochemical screening that we are talking about here.

Now let me switch just for a minute to what happened with hurricane Katrina. This is the map on the Internet that shows you the track that the hurricane took. New Orleans is right here, and it continued on up. This is Mississippi. I don't know if you can see that or not, but Mississippi is right in here. So, the only part of Louisiana that got hit is just really the southeastern tip and the storm went through Mississippi and wiped out the bottom part of Mississippi much worse than it did New Orleans, although New Orleans got the after effects much worse than Mississippi did.

For instance, in Biloxi, Mississippi this is my nephew's house. He and his wife had been married six months and this is what they came back to--steps, and this is the front lawn.

This is the house in New Orleans of Charlie Myers, who is the follow-up coordinator who runs the New Orleans program. He described it as a petri dish. He came back and said there was mold everywhere. He had been gone for three weeks and couldn't get back in. When he got back this is what his living room looked like. You can't tell but these paintings around here were all done by his father, who is now dead.

This is downtown New Orleans where the laboratory is. The state newborn screening laboratory is located in New Orleans, not Baton Rouge. They sent me this picture that shows a 2 ft. high water mark on the buildings. This is very close to the Super Dome. While there was just a 2 ft. mark on the outside, the basement was full and it took two weeks to pump the water out of the basement. Now, the laboratory turns out to be on the fifth floor but they couldn't get into the laboratory and they didn't have electricity and water so there were some immediate problems when the hurricane hit. Just to sort of orient you, this is a picture everybody saw on TV I think, and this is where the laboratory is, in this area, right here, about two or three blocks from the Super Dome. So, this area was flooded with about 2 ft. of water.

The timeline after the hurricane hit of what happened with the newborn screening program--well, on August 29 the hurricane hit.

On the 31st in Louisiana the people in the program were finally able to do something and they started looking for help. They were getting offers of help, by the way, from a lot of different states and private companies who were offering to take the samples in--no charge; whatever help you need.

On September 1 they made contact with EMAC, and I will tell you a little more about that in a minute, which is Interstate Mutual Aid Request, part of FEMA and that group. That was brokered actually by the Association of Public Health Laboratories.

On September 2 the Iowa software was demonstrated on the web and EMAC offered forms from Iowa to sign so that they could help out Louisiana. The reason they chose to go to Iowa was predominantly because Iowa guarantied that they could run the same panel of tests that they did in Louisiana and they had an Internet-based reporting system so that they could get the results back in Louisiana quicker. Then the Labor Day weekend hit and Iowa began on September 6. What happens between August 29 and September 6?

What happened with those specimens that were hanging around when the hurricane hit? What happened to the mail? That is a big issue. That is being pursued right now so you have probably been seeing some type of service announcement from time to time asking mothers of babies who were born in New Orleans at the time who don't know their newborn screening results to check with their physician, and if they don't have the results to get those screens done.

The first samples came in actually on September 8. So, CDC has been working with Louisiana and the Louisiana Health Department is working themselves on the issues right now.

This is EMAC. This is Emergency Management Assistance Compact, a congressionally ratified organization that provides form and structure to interstate mutual aid. So, this is what you get if you go to that web site. Through EMAC, a disaster impacted state can request and receive assistance from other member states quickly and efficiently, resolving two key issues up front, liability and reimbursement. And, it is administered by the National Emergency Management Association. So, EMAC is administered by NEMA which is a part of FEMA, which is part of Homeland Security.

Everybody that I have talked to has been very complimentary about this process actually. You heard a lot negative about FEMA but everybody in Louisiana and Iowa and AHPL has been very complimentary about FEMA. However, people in Louisiana tell me and people in Iowa tell me that there have been a lot of problems and nobody is quite sure who is paying the bill. They are going ahead and doing the screening. Louisiana is not sure what they are going to have to pay and what FEMA is going to pay, and all this sort of thing. So, that is sort of the next step.

There are some operational issues. They had emergency state systems. They had to look at the test menu. They had to look at the timing of the specimens, could they get them to the place quickly. What about the data? How could you get it into the computer systems? What about reporting back and what about follow-up? So, these were all considerations that were going into the process when they selected to send their samples to Iowa.

Some of the operational issues--and these slides, by the way, came to me from Iowa. Some of these will be presented next week in Portland. In terms of the tests, Iowa laboratory was new and had adequate space. They had only been occupying it for three months. They had the ability to hire additional staff. They are part of the university there so the hiring process was pretty simple. There were two additional MS devices available and they are punch devices, provided by Perkin Elmer Company. Reagents have also been provided free of charge for a certain period of time.

In terms of data entry, they are able to scan collection cards into their information system and enter the data side-by-side, and I will show you a picture of that in a minute. They had so much work going on that the director had to come in and do some entry.

Here she is doing entry. She sent me the slides and said be sure to show this slide! This shows the state laboratory director actually pitching in and helping with this program. You can see on her screen--maybe--that they are scanning the forms. So the Louisiana form with the blood specimen is over here and this is their data entry screen so they can just sit there and type it in and it is pretty simple.

In terms of implementation issues, APHL is instrumental in facilitating the linking activities. Again, they had multiple offers for assistance, including private companies. Pediatrix had offered to do some testing. In fact, in Louisiana the State provides testing for most of the State but Pediatrix does have four or five hospitals in the Shreveport area and Baton Rouge, one of the hospitals there, provides their own testing. So, that is also an issue, making sure all those data get together. They used EMAC for public health emergency response. The major issues have to do with screening panel and how to report the results back.

In terms of confirmatory laboratory testing, they also had some issues because they provide confirmatory laboratory testing in New Orleans so they were able to get help from University of Miami for Gal and in Maryland they are doing the PKU confirmatory testing and in the District of Columbia they are looking at other metabolics. So, all those labs called up and said we will help you with confirmatory samples.

They screened for one month and in that month they reported 4,923 newborns that had 35 presumptive positives, most of which were hemoglobulinopathies and they did have one confirmed PKU.

Other issues--again, payment has not yet quite been resolved. They had an issue with a pharmacy that would give out the medical foods and medical formulas. So, they found another pharmacy and that pharmacy for a certain number of days was willing to operate for no money but after that they wanted some money. So, Charlie told me, he said, just bill me. Bill the health department and we will take care of it. But now he says he is worried because their procurement officer is going to ask him why didn't you go through a bid process? So, there are things behind the scenes.

Immediately after the hurricane the follow-up staff were in different areas of the country. They had evacuated so the follow-up person for sickle cell was in Jackson, Mississippi so the Mississippi Department of Health has that person and gave them an office and gave them a computer. There have been some specimens found holding at hospitals.

There have been some specimens found mis-sent to different areas. Last I heard, there were at least 700 or so samples that were unaccounted for. They are looking for those patients to get re-screened. Like I said, there is an ongoing effort to locate the unscreened infants.
CDC is involved; Louisiana is involved; Iowa is involved and the rest of the country is involved to some extent because there are Louisiana residents all over the country. That is it.

[Applause]

DR. HOWELL: Thank you very much, Brad. Are there questions of Brad? I have a question, that is, obviously some of the big states have no people in them but another question is what percentage of the newborns today in the United States are getting what we would call an expanded screening panel, and I would include those that are 26, 25, 26 or above?

DR. THERRELL: Yes, I didn't bring that slide because I presented it last time and it hasn't changed since the last meeting that we had. Do you know, Piero?

DR. RINALDO: Fifty-eight percent.

DR. HOWELL: Okay.

DR. THERRELL: It is in your last handout material. The same slide holds now.

DR. HOWELL: And can you bring us up to
date on what is happening with Florida that has a mandate expanded panel and is still not on the radar?

DR. THERRELL: Yes, what they are doing in Florida is expanding slowly from Jacksonville out. So, they start with a few samples and then they get a few more samples, and they are building their capacity as they go. That is why they just finally made it statewide on biotinidase.

DR. RINALDO: I am sort of working with them and I understand they are really trying to expedite the expansion to cover the entire state. Now it is really the north. Recently they added Orlando. So, they are moving southward. So, probably within the next year Florida should have the entire state covered.

DR. HOWELL: And with luck, they will soon be where the people live.

DR. THERRELL: there are several states, you know, have mandated tests and it takes them a while to get going. So, if you look in our table you will find out that there are a number of places where it says A, which means they have been mandated but they are not yet doing it. Florida is not the only one.

DR. HOWELL: Any further questions or comments? There are a few business items that I have here. The committee is having dinner, many of the committee, tonight, at Chef Jeff's, 13th Street and E Street. There are still some spots available. Dinner is at 6:30.

DR. LLOYD-PURYEAR: There are only three spots available.

DR. HOWELL: There are only three spots so you had better hurry, quick. Any other announcements, or anything? I think we should leave early tonight.

DR. GREEN: May I just ask a question? DR. HOWELL: Yes, Nancy?

DR. GREEN: I am sorry, I don't want to be the only one responsible for holding us up, but I would like to suggest to the committee or to HRSA that some additional organizations be considered for liaison status. I am not sure exactly of the process but I would like to mention a couple, and there may be some more that I don't know if others want to suggest as well for consideration. In particular, certainly the issue of infectious disease input has been raised and I am not sure what organization that would be. I have a couple I want to mention. Also, the possibility of pediatric neurology organizations since many of the children diagnosed by newborn screening are taken care by those experts. Then, perhaps the AMA as well. They have sort of a smoldering interest in newborn screening that might be useful. There may be some additional organizations as well that should be considered for liaison status.

DR. HOWELL: Early in the day I discussed two groups that we have previously discussed that we want to seriously consider. One is the military, which is the Department of Defense, and the FDA, for obvious inter-relationships. DR. BOYLE: Another group that has come up, another federal agency is the Department of Education because of their early intervention
program. That has come up in our work group.

DR. HOWELL: I don't know how we decide on the addition of liaison. Peter, can you or Michelle add to the wisdom here?

DR. VAN DYCK: I think it depends on the recommendations from the committee and some reasonable expectation that we can accommodate them. I think it is important not to try to piecemeal it and every time we have a meeting add another two or three. I mean, there should be some point where we collect

formally ideas from the committee and then set some priorities and try to do it, and then just pick up those that we miss if it comes up.

DR. HOWELL: Can I make a suggestion, Nancy, that you write me a letter recommending the people that you see fit and, Coleen, would you do the same?

DR. LLOYD-PURYEAR: Organizations.

DR. HOWELL: Organizations, and we will put those together and then we will have a discussion by the committee the next time about all
the people that are on the deck. It would be a little more systematic.

DR. RINALDO: Rod, can I make a comment about that? This morning I asked Dr. Pickering about why the microbiologists were not part of the ASM. And, the answer was because they never asked. So, I think we should really start with a formal request on the part of these organizations. If they really care to be part of it, it seems they should take an initiative, and then start physically a process of evaluating rather than us sort of sitting here and thinking, well, who else can we ask? True, it is probably a very valuable point--the Department of Education, but I really think if they really care the first step should be theirs.

DR. HOWELL: For the two people that I mentioned, that request actually came to us. That is how I came up with the Department of Defense and the FDA. Child neurologists also formally asked about that. But that is a worthwhile comment. Any further comments or wisdom?
[No response] So, we will try to collect those together and think about.

DR. EDWARDS: i would like there to be the option for any of us at the table who have other organizations that we think should belong to make recommendations to you. DR. HOWELL: I would strongly encourage you to do that. There are other groups that are extremely involved in this area that really should have serious consideration. We will see you in the morning. At what time do we start in the morning?

DR. LLOYD-PURYEAR: At 8:30. DR. HOWELL: I might point out that apparently the subcommittee list has not been distributed. I have a copy of the subcommittee list. The laboratory standards and procedures committee will be in Continental Room A on the concourse level. Education and training committee is in Meridian B on the concourse, and the follow-up and treatment group is in the Rotunda Room which is on the lower level here. Those
meetings will start at 8:30. Breakfast will be before that on the concourse level.

DR. BOYLE: Is there a place where we will rendezvous to walk to the restaurant for dinner?

DR. HOWELL: I think probably the group is at the Hotel Washington. It is on the corner. It is on 13th Street between E and F. So, it is nearby. It is at 6:30 at Chef Jeff. I think if we leave the hotel at 6:15 that should be about adequate time. Why don't those who are interested collect in the lobby at 6:15? Thank you, all. [Whereupon, at 4:30 p.m., the proceedings were recessed, to reconvene at 8:30 a.m., Friday, October 21, 2005.]

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
HEALTH RESOURCES AND SERVICES ADMINISTRATION
MATERNAL AND CHILD HEALTH BUREAU

ADVISORY COMMITTEE ON HERITABLE DISORDERS AND
GENETIC DISEASES IN NEWBORNS AND CHILDREN
VOLUME II

Printer-friendly Volume II

Friday, October 21, 2005
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Ronald Reagan Building and
International Trade Center
1300 Pennsylvania Avenue, N.W.
Washington, D.C.

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P R O C E E D I N G S

[11:14 a.m.]

DR. HOWELL: Ladies and gentlemen, let's all find a seat and we'll resume the General Committee Meeting today, having had very busy subcommittees earlier today, and we have reports from three subcommittees. The Chair of the first subcommittee seems to be absent at this time--Dr. Becker--but here he comes. And the first report that we're going to have is from Bill, who's going to talk about the meeting of his Education and Subcommittee meeting. Bill?

DR. BECKER: Actually, Rod, they need to change the computer out from my presentation.

DR. HOWELL: Okay.

DR. BECKER: While that's happening, would it be more expedient to go to one of the other subcommittees?

DR. HOWELL: Well, it would be fine with me. Coleen, could you--are you ready to go?

DR. BOYLE: Sure, I'd be happy to.

DR. HOWELL: Okay. Well, we'll switch and ask Dr. Boyle to then do the Follow-up and Treatment while we're modifying the computer system here.

DR. BOYLE: Okay. Follow-up and Treatment

DR. BOYLE: Well, we had invited guests to our subcommittee this morning--Tim Huff, who is in Sunean (ph) Albany, who has been doing--I don't know if he's still in the audience here--oh, there he is, hi, Tim.

He has been involved with Brad Therrell on a project to assess long-term follow-up from state newborn screening programs. I have actually done sort of a two-face project; one was a specific questionnaire to try to highlight some of the issues in terms of barriers to long-term follow-up, and then that was followed up. And in the process of conducting a more of a qualitative-related research project to expand on what he learned from the initial phase, I think what he presented to us was very helpful in terms of trying to identify some of the challenges with long-term follow-up. Some of the, perhaps grayness around the areas of defining what short-term--the responsibilities for short-term follow-up and long-term follow-up, and many of the impediments that state health departments face, I think in terms of we had a very lively discussion following his presentation in terms of perhaps some of the policy implications from his work. And, obviously, his work is evolving and ongoing, and we will continue to involve him in our subcommittee's deliberations. But in terms of some of the policy implications, I thought some of the things that he pointed out as well as others pointed out were very important. I wanted to highlight those. And these are to try to identify and reconcile contradictions that appear to exist between, essentially, the theory of long-term follow-up and what is actually happening in reality. And that is can we ensure access to a medical home be accomplished through long-term follow-up, sort of trying to help prioritize; key areas that we feel, as a committee, might--may be important and to make some kind of recommendations, policy recommendations, in terms of their feasibility, and then also, to try and establish realistic benchmarks for performance for long-term follow-up and to really engage, obviously, the newborn screening programs and other vested parties in terms of trying to understand a little bit more about what would be realistic in terms of benchmarks. And maybe we as a--I guess my preliminary thoughts in thinking through this morning's discussion is that might be something that we as a committee can begin to--at least as a subcommittee--we can come back to you are a recommendation that we think that should be developed and that might be very helpful in terms of assuring quality and equity of care across state programs.

The rest of our morning, actually, was spent on we have broken down as a subcommittee maybe a little too finely, but we have a number of work groups going around the issues that we have been charged with. And I actually was going to ask the leaders of those work groups to just say a few comments about what their work group has been working on and perhaps some of the next steps that they anticipate. I'm going to turn first to my left to Denise, who's been kind of overseeing the work of the work group that's looking at health care systems integration.

DR. DOUGHERTY: Thank you. It's actually health systems integration, since it includes public health and health care delivery, which is very important for newborn screening, but, yeah, those words do get complicated.

What I did for the group was pull together a partial preliminary draft of some issues, putting the newborn screening follow-up issues in a context of, one, the rest of the health care system and its challenges about being integrated and then going to the children with special health care needs and their challenges in being integrated, and then flowing down to the elements of short-term and long-term follow-up that have been identified in pieces of literature such as the ACMG report and the challenges that are faced in trying to, when states can't 100 percent implement those elements, and also pull together out of the literature some models of better care coordination like the chronic care model and the innovative care for chronic illness model, and the EHDI model that was mentioned--everybody wasn't here--on early hearing detection and intervention model for follow-up.

So we still have a lot of work to do, but we agreed to--people thought that this was a fairly good start, and we could work with this document, this draft document. They had some wonderful suggestions about how to improve it, and also volunteer to look at the electronic version and fill in more of the elements of the short and long-term follow-up--because they're not all in this chart that I developed--and also fill in some of the barriers to achieving those goals of short-term and long-term follow-up.

So--and we also agreed that we should have this looked at by somebody from the state newborn screening program perspective, because there's nobody like that on our group, and they would know

more about they the elements and the barriers, so we're going to have that. George and Fan and Julie, we'll ask them to take a look at this, too.

So I think what we agreed to was that we were going to try and complete a document that identified the elements and the barriers or challenges, and that would be an interim document. So people are to follow-ups, or people are to have their comments to me and suggestions and elements and so forth by mid-November, and our subgroup will have a call, a conference call, in early January to finalize the document, or hopefully finalize or at least have another discussion about the document on barriers. And as a next step we would go on to charge two, which is identify some recommendations to overcome those barriers. So, and that's when we really need to pull in the IT, and the financing group, and the parent group and so forth.

So that's where we are. We also talked about adding a couple of consultants to our group, so I had need to talk to our Chair about that. Thank you. Any questions.

DR. HOWELL: Denise, what are you going to do with this document when it's done?

DR. DOUGHERTY: Well, we're not sure, but I mean what we have decided is, like Coleen said, we have broken into these four different subgroups. What we need to do at some point is bring everything together in order to make recommendations. So I think ultimately the decision--I was asking this question yesterday--what do we do after we do all this work? I think we're supposed to give a report to the entire Advisory Committee from the entire subcommittee.

DR. BOYLE: I think what we're trying to do is work towards specific recommendations, and, as I mentioned before, some of those recommendations might be that we've identified the barriers, we've identified potentially some recommendations for overcoming those barriers. There may be something, specifically, that needs to be developed that this larger committee would vote on in terms of perhaps going forward with a white paper on, you know, specific processes and benchmarks to assure short and long-term follow-up related issues. Like I'm just using this as an example, but I guess that's where I'm trying to move the group towards to have something tangible at the end that could be related to sort of policy that might help with achieving measurable milestones for short and long-term follow-up. Brad--where's Brad? Brad was sort of overseeing a work group on thinking about financing-related issues.

DR. THERRELL: We're not quote as well organized in terms of our thought process. This group is Dr. Cunningham, Dr. van Dyck and I, and we sort of asked for some guidance about where we should go with financing. Are we talking about follow-up in treatment, or are we talking about bigger financing issues? And so we sort of took it in a more global context, and we're looking for some guidance on this.

But financing sort of permeates everything, and so, you know, fee structures are there in the states. In most states there are still five places that don't charge a fee, but then they have other financing issues; but those who do charge a fee, we felt like there were a lot of questions about that fee structure: How is it formulated; where does it go; what does it pay for? You know, does it go into a special fund, and are our states allowed to use those funds for treatment and follow-up issues and so on?

So there were so many questions about that and so many different policies around the country related to that that we thought one of the best things that might happen from all this is to have some sort of a national meeting to talk about financing issues and bring forward those people who have successful parts of financing strategies to talk about their successes and how they got there, and how those models might be applied to other state programs. And somebody asked me, "Well, how do we identify those?" And I think the answer to that is when--my experience is--when you ask a state, do you have a good system of such and so, they don't tell you they do unless they're willing to back it up because they know the next question I'm going to ask is: Give me examples of how that works, and can we examine that further?

So I think we could find models, and we could bring people together to discuss these sorts of things if we wanted to go that way. But there are, you know, questions about CPT codes on a national level and how financing is tied to CPT codes, and whether there should be one CPT code that everything, or whether there has to be a variable CPT code because the states are variable in the laboratory services that they offer, questions about who pays for confirmatory and monitoring laboratory testing, and how do we make sure that everybody has access to those kinds of services, questions about how Title 5 and Medicaid are related in terms of relationships within the states that are apparently required by law but may not be in place, and states may not be utilizing that to the best of their ability.

So there are a number of different issues, and I guess what we're looking for right now is sort of should we be limited to looking at in follow-up treatment only, or do you want to look at financing as a bigger issue; do you want to talk about in terms of having sort of a national meeting of state representatives to talk about best models or where do we go from here?

DR. BOYLE: Questions for Brad? Thank you, Brad. Jill, do you want to try and address that, either at the microphone or the table, whichever works for you? And Jill is overseeing a group on the impact on families and caregivers.

MS. LEVY-FISCH: Okay, I prepared a report which I will send to the full committee. I contacted various advocacy groups. There were about six or seven to see what we could do to address the needs of the families and what they view as barriers to their treatment and follow-up for their children. I would just like to say I got a good number of responses. I'm still looking to hear from the sickle cell community; I didn't get one single response, and I know there are needs in that area so I'm hoping that that's something we can address.

One of the main issues that families are facing are issues concerning formula coverage for medical formulas. We need to provide national direction for formula coverage for all the disorders. As things stand now, many of the insurance plans are very disease-specific as to what they cover such as formulas for PKU, but the other disorders that require formulas, if they're not specifically specified, then the families are having extreme difficulty getting coverage.

We also need to address money for low protein foods. These disorders that require a low protein diet, they're available only by mail order, and they're extremely costly and the parents are having a difficult time providing the financial need for that.

Also formula coverage after children age out and are over 18 is an issue that was brought to my attention. Some families have indicated they're not receiving their screening results in a timely manner, which is something that needs to be addressed under short-term follow-up. Many have waited over a week and then received a positive result. And due to these delays some babies have died and others have suffered a crisis, and I've had several reports of hospitals batching their tests, which also delays access to diagnosis.

Many families have also had issues with early intervention programs. They feel it's a great program but extremely difficult for them to put into place. The whole process is not very individualized, and many service coordinators do not get as involved as they should or the parents will bike (ph). In turn, families have been denied crucial services such as feeding therapy because the coordinators did not know the proper way to secure these services for the child. When children are diagnosed at a later age, the families feel they do not have the same access to services as the young child or an infant.

Families expressed a great desire for a medical home. Right now most families are coordinating the wrong services and specialists for their child, and they feel extremely burdened and overwhelmed. Pediatricians are really leaving everything in the hands of the families, and some families stated they're so tired and overwhelmed that it becomes harder to care enough to be more assertive.

Clinical staff and physicians as well as parents need to be educated as to the purpose, results, and importance of newborn screening tests. Some hospitals are forgetting to do the screening prior to the baby being discharged from the hospital. Just to give you one example, one family happened to see a newborn screening brochure on a table as they were being discharged with their new baby, and the screening tests had never been done. The parents asked for their baby to be screened, and this baby turned out to have glycosemia, and this really could have been a disaster.

Families are also desperate for respite care, and that came through loud and clear. They're spending endless days or weeks in the hospital when their children are ill, and then coming home and managing that care on a daily basis they're feeling exhausted, and I hear many times feelings of isolation. There is a severe lack, as we know, of specialists to care for these children. More training is needed for those who are treating children with these disorders. There should be internship programs funded to train doctors and nurses to treat the children who are identified through newborn screening. We really need to figure out a way to draw them in and train them.

When a child is first identified with a newborn screening, the doctor they generally see first is the pediatrician, and the pediatricians do not have enough knowledge of these disorders as to how to treat them and, in turn, do not have the information necessary for families. These families are spending countless hours looking on the internet and making phone calls trying to find information when their time could be certainly better spent.

Many insurance plans do not pay for specialists that families need to see out of state, and, due to the shortage of specialists, many families do travel all over the country to seek proper care for their child. Medicaid reimbursement, it's indicated that the reimbursement for home nursing care is extremely poor and getting quality care is an issue. Many families rely heavily on home nursing care, and when their home care nurses are sick or on vacation, there are many instances where the families are unable to get a replacement.

Families need access to affordable testing to rule out disorders in other family members, and attention must be paid to the older children with disorders sa they transition into adulthood which would fall under long-term follow-up. Most if not all of the metabolic specialists seem to be pediatric specialists. Older patients do not feel comfortable visiting pediatric clinics for treatment. One possibility is maybe to have the pediatric specialists have an adult clinic in an adult setting to see these children as they get older.

The issues the older patients face are much different than the infants. The older children are having a hard time sticking to their special diets when they're with their peers, and certainly those with feeding tubes have issues that need to be addressed. Families would also like access to social workers, not just for their child but for themselves given that the disorders affect the entire family and not just the affected child.

I will update this as I get more responses from families, but this is what I've been able to get right now, and if anyone has any questions?

DR. HOWELL: Thank you very much, Jill.

MS. LEVY-FISCH: Okay.

DR. BOYLE: Thanks, Jill. We also have had a lively discussion on our phone calls as to whether or not there really should be two different committees because, obviously, a lot of the issues that Jill is uncovering through her work really do impact on the issues of health systems integration. So right now we've kept them as separate work groups because I guess feel like it's very important to really highlight the impact on families and caregivers, but maybe through time that we sort of integrate those two groups. And just lastly, our last group is on information systems, and I've done a little bit of work in contacting Alan Hinman trying to address some of the IT integration issues in terms of major barriers and arrive at

some recommendations. And I met with Debby, actually, during our work group time, and she has offered very kindly to help assist me as well as Alan if I continue to use him as a consultant to again arrive at some recommendations in this area.

DR. HOWELL: Questions of Coleen about her committee? It sounds like you had a busy morning. We'll move on. We're running a touch behind time, but apparently Bill is going to address us from the remote side over there. Is that correct?

DR. BECKER: Hello. Yeah, this is a testimony to the incompatibility between Mackintosh and PC. Education and Training

DR. BECKER: I'll try to go fairly quickly. We also are not compatible--oh, it's nice to see the audience. It's also Quicken is not--the Mac equipment is not compatible with the LCD projector, so, unfortunately, I'm unable to project all these. Obviously, we met this morning. There have been some membership changes in the subcommittee. Dr. House's term on the Secretary's Advisory Committee concluded on September 30th, and Dr. House asked me to be the Chair and I agreed. I don't know what I was thinking, but anyway Dr. Hawkins continues to serve on the committee. Dr. Edwards is also a member of the committee--of the subcommittee representing AAP, although he was unable to be here today. And Anne Gramiak stepped in to give a presentation on AAP's activities. Dr. Tony Gregg from ACOG is also a member, but as you all probably know, he's not been able to join us at this meeting. Dr. Norman Kahn from the American Academy of Family Physicians is also a member of the subcommittee, and my point for mentioning all those particular persons is they represent association partners that we feel are essential for the task at hand, education and training. We do have a couple of additional potential positions to be filled from the newborn screening program. I have a nominee from California; also from a newborn screening birth facility from Ohio, and then we still have a couple of open positions that we need to fill in the not too distant future. Subcommittee reviewed the approved charges, and we have no suggestions to make to those at this particular time. Dr. Kahn updated us on AAFP educational activities. They, as had been reported here previously, have a program called Annual Clinical Focus which this year is devoted to genomics. It's a series of eight programs. Newborn screening is one of those programs, and it is up on the web right now, www.AFP.org. There were 19 participating organizations that contributed to this program. It is designed for providers, but it's likely that it could be used with newborn screening program staff as well as birthing centers staff as well, and we're going to take a look at that. In fact, one of my assignments to the subcommittee is that we will review this program and make comments on it about its utility in, particularly, these other groups in the near future. Anne Gramiak from the American Academy of Pediatrics updated us on their work. The newborn screening parent and provider materials that they'd been working on are just infinitely close to being released, anticipated in early November '05. This, as many of you will recall, is the work--it's a combination of association work, Maternal Child Health Bureau, Louisiana state, Dr. Terry Davis, who's spoken before us, as well as the partner associations that I've been mentioning. AAP, at Dr. Edwards' request, has devised an evaluation process for these materials. It will be in the form of a survey, and this was something requested at our last face-to-face meeting back in July. AAP is also working on sort of their policy statement. It's in the form of what they call a clinical report on newborn screening in the medical home, and those policy statements, obviously, will be forthcoming. Other association reports that we received this morning--ACOG, obviously, wasn't able to participate because of Tony's absence--I did hear from Julia Ingleston from NICHD. We had heard from her in July about a consortium, really, of federal agencies that are developing newborn screening materials, and while Julia emailed me prior to this meeting and said she didn't have anything to report new at this time, we do anticipate at least some of their matrix development to be ready for review by the next Secretary's Advisory Committee meeting. Other business, some of the other avenues that we were considering particularly revolved around the concept that perhaps we might need to broaden our consideration of how to distribute printed resources to the general public, and we engaged in a conversation about some ideas of groups where to go. And I can certainly provide you details of that, but I'm going to shorten the conversation down just a bit. Other groups that we particularly mentioned--and I think these are interesting to consider providing newborn screening education for the illiterate, the disabled, deaf or blind persons who might need newborn screening information, those are something that we're going to consider. A very novel idea came up and consider asking Google about the order of information that is

provided when you type into their search engine "newborn screening." In other words, is it possible for us to consider what the order of--you know, I'm going to guess that maybe, you know, most people when they use that particular search engine, they click on the first two or three links that come up. And it may be that we can devise a way to guide them to more generic resources or resources that we think are appropriate. One of the things that I would like to put on the table for committee discussion is--maybe this afternoon after we finish the subcommittee reports--is the concept of a general announcement in the form of perhaps a public service announcement, or PSA, that might come from the Secretary's Advisory Committee for parents and providers. Our subcommittee felt that the message to parents ought to be about the general importance of newborn screening whereas the message to providers would be about the importance of emerging national recommendations for newborn screening that--and this message could perhaps be taken through the association partners or perhaps and/or the March of Dimes. Obviously, this particular suggestion for committee consideration is pending HHS Secretary's approval of our recommendation, but if we feel that that is something that may be imminent, it may be helpful for us to consider a general announcement, you know, to be proactive in forming a PSA or several PSAs in the time that we're waiting for the Secretary to take some action. And then finally, one of the bigger, a couple of ideas, training needs--remember, we're the Education and Training Subcommittee--and this will be an ongoing discussion. Obviously, we could all list, I think, who needs training from state programs, laboratorians, providers, residents, health care workers, et cetera. And there's obviously some overlaps here with the other subcommittees' work. Another novel idea that came out and something we want to put out for the committee's consumption and consideration is consider approaching or establishing, or whatever it needs, a national spokesperson for newborn screening. There clearly are people who would have high visibility, and I can think of a couple people who have even testified to our own committee at some earlier meetings who might be interested and/or willing. And then finally, one of the issues that seems apparent to us is that we're going to need to coordinate the information that's being developed so that there's some uniformity in the messages. Our action steps in most of this I think is basically for Rod and Michele, I think, is we do intend to establish more regular conference calls. I have given them the assignment, as mentioned earlier, to review the AAFP newborn screening program. We will review the HRSA LSU prepared materials when they become available. We would like to invite Donna Williams to the next Secretary's Advisory Committee as a consultant to give her presentation to our subcommittee, most of whom were not present a couple meetings ago and so did not receive, you know, the presentation that she made. So we'd like to bring her back, basically. And that is, in a nutshell, what was a very animated discussion and a very delightful group. Thank you.

DR. HOWELL: Thank you very much, Bill. Are there questions of Dr. Becker?

DR. KAHN: Well, this is not a question, I hope that this is just additive. For those who are interested in going to the web to see this newborn screening program--sometimes websites can be hard to navigate--if you go to AAFP.org right on the home page center column toward the bottom, there are three words: Annual Clinical Focus. Click on that, and when you get to that next page, Pictunomics (ph), and it's in there. And that way, with two clicks you can get to it, and otherwise you'll get lost on the home page. And while I have the microphone, I just want to thank three people without whom this program would not have happened, and that's Michele Puryear and Jim Hanson, and then Jean Johnson from the National Hemogenal Research Institute.

DR. HOWELL: Thank you very much for that comment. Any additional comments of what happens when you click Google on newborn screening? I've never done that. DR. : The National Newborn Screenings and Genetic Resource Center.

DR. HOWELL: Brad's program comes up. We answered that question, okay? Yes, Joe, okay. Joseph?

DR. TELFAIR: Yesterday the question on--I understand, Bill, that materialwise that you're dealing both materialwise in terms of the education side and the training side--what, as a committee, have you considered related to cultural and linguistic competency issues? I know that you have some of the information you mentioned directly through literacy, and I applaud the group for thinking of groups, both low or no literacy, but I'm also wondering about sort of cultural issues as well. Thank you.

DR. BECKER: First of all, the material being developed by the HRSA--the MCHB LSU are both in English and in Spanish, as well in the newborn screening program person that we have invited and tentatively needs to be approved from California, California has one of the largest cadre of multilinguistic newborn screening information that I'm aware of. Brad may be aware of some others, but those are the ones that I'm aware of, and so we feel like we're working towards, you know, including multiple ethnic areas into our conversations.

DR. HOWELL: Other comments for Bill? Thank you very much and so forth. We'll zip along now to the third subcommittee report, and Dr. Amy Brower will talk about the Laboratory Standards and Procedures Subcommittee, which was a very packed agenda this morning.

DR. BROWER: Great. Well, I'll try to keep us on target and get out for lunch on time. Laboratory Standards and Procedures

DR. BROWER: We met today, our Laboratory Subcommittee, and we really focused on our two charges related to the laboratory procedures and infrastructure services. We want to, as our first priority, focus on the harmonization of operational lab procedures. Our ultimate interest is to find all true cases with no false negatives and with the minimum number of false positives. An example of the work that we'll be doing is defining better cutoffs by looking at disease range instead of the normal general population. We'll be working to compile the experience of multiple laboratories and working with the APHL. The outcome of our efforts, our goal, is to be able to develop guidelines or techniques to offset cutoffs, and we'll present our findings to the committee as a whole for consideration. This is going to require our subcommittee working with the APHL, with state laboratories, and with industries, and we also want to especially capitalize on all the great efforts that are going on in the regional collaboratives, and we'll report all that back to the committee. Specifically, we have formed a working group to work on one of our first priorities for the short term, which is really to design a study to assess the utility of the routine second spot, and we'll have a working group that will address the design of that study, and they'll be working to define the indicators and the criteria for that study. And that's it.

DR. HOWELL: Questions or comments about Amy's two key issues that will focus, one of which involves really looking perhaps at a grant type activity that would support the study on the famous second spot? (No response.)

DR. HOWELL: Hearing no comments, you were so brisk we actually finished a bit early but not much, and so we're going to adjourn for lunch, and again the lunch in the Concourse Level is for the committee members and subcommittee and ex-officio members, and we welcome everybody there. We resume promptly at 1 o'clock for the Comments and wind up the Committee Business. Thank you very much. (Whereupon, at 11:55 a.m., the meeting recessed, to reconvene at 1:00 p.m., this same day.)

A F T E R N O O N S E S S I O N [1:00 p.m.]

DR. HOWELL: Ladies and gentlemen, let's find our seats and resume our afternoon session so we can conclude our activities on time. We're pleased to have a distinguished panel of public commentators today, and, as usual, we greatly appreciate and welcome these comments, and they're extremely useful as the committee deliberates directions, et cetera. The first person on my list is John Adams, who's the Treasurer of the Canadian Organization for Rare Diseases. Mr. Adams-- Public Comments MR. ADAMS: Mr. Chairman--

DR. HOWELL: You're ahead of the game, I--

MR. ADAMS: At one point in my presentation, Mr. Chairman, I've got to use who I know, Professor Therrell's slides from yesterday just to make a point. But thank you very much for a fellow named John Adams. It's nice to be back in Washington. This is the third time I've had the opportunity to attend meetings of this, the open sessions of this open advisory committee, which I greatly appreciate. I am, for

those of you who don't know me, I am the PKU Dad for Toronto, Canada, and like almost all parents, my wife and I knew nothing about rare disorders and PK, including PKU, until our son was born 18 years ago and detected. So I'm very, very thankful that many years ago a whole bunch of total strangers set up a universal public health newborn screening, a universal newborn screening system in order to protect my baby and all the other babies as far as it's gone.

I'm brand new as Treasurer of the Canadian Organization of Rare Disorders, or CORD. We have adopted a policy on newborn screening that court urges all Canadian Provinces and Territories to implement as soon as possible comprehensive and inclusive newborn screening within each jurisdiction at the highest prevailing international standards. So keep going at what you're doing. Keep moving those yardsticks, please.

Thank you. I'm sad to report from the Canadian, and adding a little bit of international perspective here today, that no Canadian medical organization has yet seen fit to take a public position on the topic of newborn screening, not the Canadian College of Medical Genetics, not the Canadian Pediatric Society, not the Canadian College of Family Physicians, not the Garad Association (ph), which is the trade association of metabolic professionals and, actually, CORD, I think, is the first organization at the national level or the provincial level to take a position. So we do have a little bit of a gap here.

And just to give you a little perspective, there are some parallels and some differences between the U.S. federal state situation and the Canadian federal provincial one, but I do want to say we have no national strategy, and we have no national process in Canada for addressing the issues of newborn screening. We have no federal activities and no federal funding for newborn screening, not one penny.

All right, the word "screening" does not appear in any fashion in the Canada Health Act, and we have no--for example, we have no office of rare disorders at the Canadian equivalent of the NIH. We have no policy on orphan drugs at the Canadian equivalent of the FDA. We have no definition what is a rare disorder at the federal or the provincial levels. So we have some work to do, and I look to best practices in other jurisdictions, including the United States for some guidance in this respect.

I do say--I'm going to say this twice today in two contexts--but in this respect of rare disorders, Canada operates like a Third World country. I did not invent that phrase, I will attribute it to an independent officer of the anterior government later on. All right. All right, so that's the quick view, and we have some similar issues I wanted to--I just want to use this map for a second to do a quick visualization of the comparison of 13 different jurisdictions across Canada. They range from Saskatchewan screening babies for a total of 29 conditions, and Quebec screening 90 percent of its babies for a total of 28 conditions, to the bottom of the list, my home province of Ontario, which today still screens for a total of three conditions, PKU, CH, and hearing, although we are making some progress. And I want to tell you a little about that, and I want to say to this committee, to HRSA, and to some of the particular participants, I want to say my personal word of thanks for being resources and being sources of information and inspiration in terms of the applicacy that we need so badly in our country to try to pull up our socks.

In a word, there are most of the provinces in Canada would fall well within the bottom category here in Brad's classification of fewer than 10. Matter of fact, today there are only two provinces, all right, and that's what I want to say. We are making progress, though. The Province of Ontario, my home province, is the largest province in terms of population of screening for fee. We have got to the point of an expansion to seven conditions from three. That didn't last too many cycles. We got to the point of 21 conditions, all metabolic; that didn't last the first 24-hour news cycle when it was announced in the first week of September because we still--that expansion still omitted such disorders as the cycle cell diseases, which was completely unacceptable in today's kind of society, and it also missed the endocrine disorders such as congenital adrenal hyperplasia. Last, on September the 28th, the government of Ontario made an announcement they intend to take Ontario from worst to first. We're waiting for a definition and articulation of what is meant by first. The plan is to have tandem mass-based and other expanded screening up by the 1st of March, and, frankly, I'm pushing for as much of the ACMG full panel as endorsed by this advisory committee to your Secretary as possible. I'm also pushing because we are

so far behind, and it will take some time to develop the domestic lab and other capabilities. I am pushing for a quick start that we should swallow our pride as proud Ontarians, and we should buy on a transition basis. We should be prepared to buy the service from outside of Ontario.

So the difference between even the announcement that there are babies being born every week who are at risk of premature death or permanent life-long disability as a result of the gap between three conditions and whatever the Ontario screening panel is going to end up to be. So if you hear me ranting and raving just a little bit about the need for a quick start, I hope to use Ontario as a demonstration project for other jurisdictions who want to do quick starts as a ways and means, as we're not the early adopters, we're late adopters, but perhaps we can apply some of the lessons for to speed up the pace of implementation of change.

So with that, and the other thing I will bring, the Ontario ombudsman, the have an independent officer of the Ontario legislature called the ombudsman, and he wrote a report that was issued in the last week of September. It does have the double helix, and it does have the letters of the helix in the proper order, and it does say--talked about the right to be impatient. And I think that I share that sense of impatience with many other parents and other lay advocates.

So I hope that you will continue to do your hard work, and I hope that you will continue to keep an eye in terms of the role model that you are serving as an open advisory process for others. There was a meeting of the Ontario Advisory Committee on Wednesday afternoon of this week. For the first time they did invite in an endocrinologist and hematologist for the first time there. I look forward to the day when I an report to you on a future occasion that the meetings are open and that they have invited in parent and lay advocates. Thank you very much for your time and attention. (Applause.)

DR. HOWELL: Thank you very much, John. We'll move ahead to Jana Monaco, who is a parent and board member of the Organic Acidemia Association.

MS. MONACO: Okay, good afternoon. I thank you again for the continued opportunity to offer my comment to you in support of the process of expanding newborn screening, and I have to commend you for your efforts to move the process along. Yes, I am on the Board of Directors of the Organic Acidemia Association and speak for all of us, and the parent of two children with isovaleric acidemia. And I have to say that I can attest to all the Jill Fisch said earlier as a parent and my concerns. As I sat and thought about what I wanted to comment, I monitored my son's seizure last night and thought about how Steven will turn eight years old next week, but he will not celebrate in a conventional way like most children his age. That is because if you view him from an evidence-based approach and highlight a few points, Steven meets the criteria but as a result of not being screened at birth. A test was available, but he didn't get it. Treatment was available, but it came a little too late. As for the burden of the disease, we don't have time to completely review the result of the severe brain damage to a child and the family. As for cost-effectiveness, we have that one covered, too. The evidence-based criteria is the same with our daughter Caroline, except the outcome is far different, and we would like to see more cases like hers, so I ask you to be cautious and not get too caught up with the evidence base but keep in mind the facts that are not measured in quantitative means. Does this make me a person with a conflict of interests? I certainly hope not. Rather, I hope that I am viewed as an expert and important stakeholder in this process. I cringed yesterday at the slightest suggestion of David Adkins' presentation that some parents could possibly be too biased when it comes to the evaluation process of adding disorders to the list, or that anyone could be somewhat biased. If this were true and I were only interested in IVA, I would not be here any longer since ours is on the primary target list. When reviewing this process, I would like to think that Dr. Watson would be consulted given the fact that he and the ACMG produced the scorecard and the list of criteria. He and his staff are trained experts that were originally chosen to complete this task and can provide valuable insight and answer many questions that people may have regarding the scorecarding criteria for adding the disorders to the list. This leads me to the addition of new members to the committee. Careful consideration is given when doing so, and the newest representatives on board can certainly contribute to the committee from their area of knowledge and how it relates to newborn screening. Nancy Green recommended a few potential new additions yesterday, and when thinking about

the team of specialists that care for our children with these disorders, it would only make sense to include their involvement if they express an interest. One of her suggestions, neurology is one of those areas of consideration. These disorders, no doubt, can be neurologically involved. There are children like Steven who have a great deal of neurological involvement, hence making that specialty one of the key team players in his overall health care or medical home. In our organization we have several children with neurological issues with their disorders along with others who have these neurological concerns but no diagnosis yet; and yet their neurological status plays a key role in helping to make that diagnosis. Gastroenterology is another specialty that could be considered if they were interested. We have a large number of children dependent on G tubes, or NG tubes, along with various other GI issues. It only makes sense to utilize people who have direct involvement and a certain level of knowledge with managing these disorders. As we move along in the process of expanding newborn screening, much emphasis is shifted to the subcommittee's work and their charges. I think it is imperative to stay linked with the regional collaboratives and what they are focusing on. I will maintain my position in working with the education work group for our region. We have discussed the idea of databases before, though it has quite quiet this time on that topic. I think it is imperative to maintain a methodology of tracking newly diagnosed cases and track the management and care of current cases. It is the most logical way to document vital information to further understand the primary targeted disorders and develop a better understanding about the secondary targeted disorders and those awaiting their place on the list. I see this as a vital piece to help in the process of adding condition to the uniform panel. This should be a key objective in the follow-up subcommittee because medicine builds on itself, and we have to find a way to continue that growth. There have been concerns expressed about privacy issues, yet I have come to learn there are a lot of misconceptions out there regarding HIPA that impede a good, thorough documentation of information. Each of the family organizations has their own rudimentary database, and this is an example of OAA, so with the long list of names of potential people. Recently, we celebrated in OAA with one of our adult cases of the birth of her new baby, and through lots of follow-up and care--I wanted to bring a picture and share the family--everything went well due to good follow-up and collaboration with her metabolic folks and her OB-GYN. So in conclusion, I would like to thank you for your continued efforts developing this uniform panel and newborn screening program and for respecting the role of the parent. As we saw yesterday when looking at the state maps, we are making progress in this area, but we must continue to help get it to that uniform status. Thank you. (Applause.)

DR. HOWELL: Thank you very much, Jana. I failed to ask if there were any key questions after John's talk, but let's see if there are questions of Jana before she leaves.

DR. RINALDO: No.

DR. HOWELL: Still here?

MS. MONACO: Yes, I'm here.

DR. HOWELL: Oh, no, no, for John, I'm sorry. Well, why don't we go ahead and do a question for John, if--he's gone so you're out of luck. Okay, I'm pleased to now recognize Ms. Micki Gartzke, who is presenting on behalf of Kelly Leight, who is Executive Director of the CARES Foundation, Incorporated, which is the Congenital Adrenal Hyperplasia Research, Education and Support. You can sit there right at the head of the table, if you like.

MS. GARTZKE: Yes.

DR. HOWELL: Push the button in any way, Ms. Gartzke.

MS. GARTZKE: Thank you, Dr. Howell. "Dear Michele: "I am writing to you today in the hopes that you will bring up an important issue at the meeting of the Secretary's Committee on Newborn Screening and Genetics later this week. We are concerned about a problem that has arisen lately with newborn screening. "We have seen that some of the suppliers of newborn screening equipment and supplies have

apparent monopolies on the provision of certain types of supplies and equipment. When these manufacturers of technology assays or other materials and equipment have quality control problems, shortages or the likes, the states are left in a difficult situation with nowhere else to turn. They may be required to revaluate and reset cutoffs based upon different lots of assays, or can be left in a bind when technology has quality issues or there are manufacturing shortages. These problems can overwhelm state newborn screening programs that run on limited resources anyways. "In addition, this can lead to harm to families and children through false positives/negatives and delays in diagnosis. False positives in particular can be very damaging as they can lead easily to skepticism on the part of the health care community. Unfortunately, we have seen situations where children have been screened positive, but the primary care providers assume it is a false positive and delay telling the parents or ordering follow-up tests with appropriate treatment. "We hope that the committee will consider this issue and perhaps come up with ways to alleviate these kind of problems. "Kelly Leight, Executive Director of CARES Foundation."

DR. HOWELL: Thank you very much, Micki.

MS. GARTZKE: Thank you.

DR. HOWELL: I think that one of the comments I would make is that at Amy's committee this morning one of the key areas in the Laboratory Subcommittee was focusing on some quality issues, some harmonization issues, and one of the major areas under discussion there was the issue of identifying all children and at the same time minimizing false positives. Amy, would you like to comment about that, because it is specifically relevant to the comment here.

DR. BROWER: I think it was a very important issue and one that the Laboratory Subcommittee is going to tackle right away. We know that through the working group we feel like we can get a good handle on steps to take initially and make some real impact in the near future.

DR. HOWELL: Further questions of Micki? Thank you very much. Micki also represents the Hunters' Hope Foundation, but she's wearing a different hat today and so forth. Next we have two people listed. I think we're going to have a double duo here, but we have Cynthia Joyce, who is Executive Director of the Spinal Muscular Atrophy Foundation, and Barbara Trainor from the Families With Spinal Muscular Atrophy, who are here to present. Ladies?

MS. JOYCE: Thank you, Dr. Howell, and members of the committee for giving us this opportunity to talk. SMA is relatively new to this committee, I think, and as we've learned about it, courtesy of the NICHD and other activities in Washington, we've been really impressed with your progress and we'd like to applaud it. Barbara and I are here today for with a very special request to the committee, and that is that you consider adding Spinal Muscular Atrophy to the uniform panel--or to this panel--for uniform screening efforts. Our point is that the biology of SMA is very compelling. It is one of the most common of the autosomal genetic recessive--autosomal recessive genetic diseases. The birth rate ranges from on in 6,000 to one in 10,000 infants born each year, and the carrier frequency for this disease is quite high with a range of one in 35 to one in 50 adults. SMA is caused by a loss of function mutation in the SMN (ph) gene that results in motor neuron death, muscle atrophy, and severe to catastrophic loss of function. At least 60 percent of children born every year with SMA present with the most catastrophic phenotype of this disease and generally die before reaching two years of age. So, as you can imagine, it's very devastating to families. But special and sensitive diagnostic testing has been available fear many years. It is often implemented only as the last resort in the diagnostic process. Consequently, infants and children are subject to stressful, often painful and inappropriate tests that only delay preventive care. Early diagnosis will enable the development and implementation of treatment plans that can reduce morbidity and save lives. We hope that you will support the addition of SMAS to the Uniform Newborns Screening Panel to help prevent the needless suffering of infants and children, to help the professional and lay community advance standards of care, and to support the use emerging new treatment paradigms. We believe that SMA meets the principles and criterias established by the committee thus far, and strongly encourage the committee to review this disease state for including into the panel as a primary target for the following reasons, specifically: First of all, the mutation causing SMA is detectable by blood sample

testing immediately on birth when symptoms are rarely visible. Secondly, the test is sensitive and definitive in over 95 percent of the cases. Without this test, the differential diagnosis of SMA can be a circular exercise, as I've mentioned already, and can be a painful process and an expensive process for both the families and the health care system. This adds needless time and expense to the care process. The genetic tests for SMA are not cost-prohibitive at this time, but we recognizes that the current testing procedures could be modified and adapted for a more cost-effective manner, and the community is actively working with NICHD to make that happen. Thirdly, the detection, the early detection, will ensure that children suffering from this disease will receive the benefits of effective management, including respiratory care, preventive physical therapy, and nutritional support. These care strategies actually do prevent morbidity and save lives, and they're important to implement early when people are not in any emerging situation. Lastly, early detection will enable clinical trials of agents that may save motor neurons and preserve function for these children. Evidence from prenatally identified children indicates that motor neuron loss in SMA occurs after birth, suggesting that a neonatal treatment window is not only possible but actually may be essential for this disease. We can assure you that the SMA professional community is well organized to provide care and poised to help advance newborn screening efforts in these areas. Primary treatment centers are most often MDA clinics, and there's over 100 of them supported around the country right now, as you probably already know. We hope, in fact, that specific treatments--specific treatments not palliative care treatments--for SMA are on the horizon, and there are a number of clinical trials underway right now throughout the world, two of which are being conduct in the United States right now. It's essential that newborn screening be widely available at the time that any new treatment option is shown to be effective in order to help children as quickly as possible and prevent further disability. In conclusion, by virtually all means and all measures, SMA falls well within the criteria established by the committee for the development of screening panel. It's important to note that early diagnosis will foster disease management to reduce the burden of illness now and will help support the clinical evaluation of emerging new treatment options designed to protect and save motor neurons in the future, and we hope you'll agree with us that this investment is well worth the cost. So I'd like to turn it over to Barbara for a first-hand, a first-person discussion of what this might mean. Thank you.

MS. TRAINOR: Dr. Howell, and members of the committee, thank you for the opportunity to appear before you today. My name is Barbara Trainor, and I am a board member of Families With Spinal Muscular Atrophy and founder of the Chesapeake chapter, one of 25 chapters throughout the country. I am also a mother of three children, including my daughter Erin Marie, who lost her life at only five and a half months of age almost 13 years ago to spinal muscular atrophy. I am humbled to be here representing millions of parents who have had children affected by SMA. All new parents make the assumptions that the healthy baby they bring home from the hospital will be with them forever. Sadly, this is not always the case. Because SMA is a recessive disorder, there is rarely any indication throughout family history that a child might be at risk for SMA. Having already given birth to one healthy daughter, I expected nothing less of our second child, Erin. At Erin's birth, there was not a single indication when we brought her home from the hospital that there was anything wrong. Yet less than four weeks this otherwise alert baby began to show signs of deteriorating movement. Her deterioration was swift and painful. At the time of Erin's diagnosis parents with children diagnosed with SMA had no hope, which makes the devastation, the feelings of helplessness that much more intense. Yet today hope exists in the form of newborn screening. The technology exists to begin screening for SMA immediately, which would allow us to identify children soon after birth. The test is cost-effective and results are available in a timely fashion with a very high rate of accuracy. As a mother, I would have welcomed this important information and begun planning for the care of my child. With a specific treatment for SMA, even though it does not exist currently, it is true that care plans and supportive care make an important difference to families affected by SMA. Furthermore, as Cynthia had mentioned, phase two clinical trials are underway around the world. It is ironic to me that newborn screening for SMA is not indicated because a cure does not exist. Yet the development of a cure depends heavily on screening newborns in order to identify SMA-afflicted children who might participate in clinical trials. Universal screening for SMA is an integral component in the development of a cure. It is my sincere wish that one day children born with SMA will be identified soon after birth and can begin treatment immediately to protect their motor neurons and stave off the degeneration that can lead to death. While the march toward the cure will not bring back Erin, it can prevent other parents from experiencing the excruciating pain of losing a child. My hope today is that in the future we can give new parents of children diagnosed with SMA the hope that newborn screening can provide. I thank the

committee for your graciousness and willingness to listen to me. If you have any questions, I'm more than happy to answer any. (Applause.)

DR. HOWELL: Are there questions of Ms. Joyce or Ms. Trainor? Bill?

DR. BECKER: Yes, thanks. Ms. Joyce, I am generally aware that there is a pilot project. In addition to the clinical trials that you referred to in this country, there's a pilot project that's either been proposed--I think it's maybe with HRSA moneys--to assess the applicability of the newborn screening for sort of high-volume type work, which is something that would be needed for a massive screening project. Are you aware of that, of those grants? Because we were contacted--

MS. JOYCE: Yeah.

DR. BECKER: --we were contacted in Ohio about the possibility, because we have a Pediatric Neurology Center at our Children's Hospital--about the possibility of doing some work with them. We had to turn them down because we're working on Duchenne muscular dystrophy right now, but I know that there's a project out there going on.

DR. HOWELL: Let me comment about that in that it's a public information but NICHD has recently funded a major grant to Dr. Pryor to look at the development and refinement of the test appropriate for the newborn screening. And again, Dr. Pryor is in your state, but it really was predicated on the fact that there are these clinical trials out there, and the newborn screening test had not been at the level that would be required for public use but NICHD has come to the table in a big-time way for that, which is very timely, et cetera.

MS. JOYCE: And thanks for the heads-up about the clinic availability, because we'll make sure that Dr. Pryor knows that there's other clinics interested I participating.

DR. BECKER: Actually, I know Dr. Pryor. He's at Ohio State University, and my other hat--not the state of Ohio--and he's the one that contacted us about development of a multiplex assay, and we have provided him some samples. We just can't do the work ourselves right this second, so we are working with him.

DR. HOWELL: Thank you. Thank you very much, Ms. Joyce, Ms. Trainor, et cetera. Our next person is Dr. Carol Greene from the Society of Inherited Metabolic Disorders. Dr. Greene.

DR. GREENE: Thank you. I am Carol Greene, a physician-geneticist and a board member of the Society of Inherited Metabolic Disorders, speaking on behalf of the Society. SAD appreciates very much the ongoing activities of this committee and looks forward to ongoing improvements in the quality of newborn screening that will result from your input. As you consider next steps in your activities, both in your goals and the strategies to achieve goals, SID would like to make two points today. First, in keeping with the membership pool that we have previously presented here, the SID continues to emphasize the need to address long-term issues in your work. It has been pointed out by various members of the committee yesterday that newborn screening is a system, and newborn screening is not just a test. A critical part of the newborn screening system after screening and diagnosis is long-term care, without which there is no point in screening. The effect of Katrina on interruption of care has been mentioned here. SID points out that as important as it is to develop strategies to protect patients in the phase of the disaster, Katrina just highlights, albeit on a massive scale, what health care providers and patients and families face every day in every state. And here I'll add as an aside, not part of my prepared remarks, that we heard that very eloquently just a little bit ago from Jill Fisch. It is routine to struggle with access to needed health care, either because of lack of specialty providers in an area, or because of funding constraints with access to essential therapies, or to necessary monitoring tests. We hope this committee will address these issues and also address the need for ongoing data collection on outcomes to continually improve the system as a whole. Second--and again as an aside, not part of my prepared remarks--I very much appreciate the work of the subcommittee which I'm privileged to be on which is looking at exactly those issues. Thank

you. Second, we urge continued efforts--and I think we just heard a little bit about this also this morning--on issues of quality in the testing component of the newborn screen. We appreciate the problems of false positive screens. SID members who are part of newborn screen laboratories interact with the primary are providers, who need to send repeat screens on the babies with borderline or gray zone results and to track and match results. And those who, like myself, are clinicians are directly involved with health care providers and families when newborn screening gives an initial critical result or a repeat screen is positive. Some of the current controversies in newborn screening may be at least partly driven by variability and experience at both levels. In some states and for some tests there is a very high level of false positive screens while in others the experience is less burdensome. I have personally experienced some years ago, with a change in state lab galactosemia screening, a level of positive of positive newborn screens for that condition that seriously taxed our care delivery system. Conversely, right now in Maryland, while I cannot speak to the rate of repeat screens required for borderline or gray zone tests, when I receive a call as a clinician for a positive newborn screen from tandem mass specs, since that technique was added in our state, we have at least nine babies with confirmed biochemical abnormalities. Three have classic disease and one has a B-12 deficient mother--of course, that's a quick cure--and that's out of approximately 12 referrals. So we have only three definite false positives. Colleagues in other states are seeing a much higher level of referral for false positives. The newborn screen isn't just a test, but the system succeeds or fails beginning with the quality of the initial test, and we depend on the best possible balance of sensitivity and specificity to avoid both failures in case finding, and on the other end risk of overwhelming families and the system with false positive results that could be avoided by appropriate quality management. And as always, the SID is ready and eager to work with this committee in any way we can help to achieve our mutual goals.

DR. HOWELL: Thank you very much, Carol. Are there comments for Dr. Greene? (Applause.) I'm aware there's a comment area coming out in one of your clinical journals about the importance of false positives soon which will be quite consistent with your discussion here, because that's a critical area, clinically, and can overwhelm the system, et cetera. Thank you very much. Our next person is Dr. Andrea Gropman from the Child Neurology Society. Dr. Gropman?

DR. GROPMAN: Thank you, Dr. Howell, and the committee members. It's been a privilege to participate in the open meeting and also to be able to give my comments here today. I appreciate that. I wear two hats. Yes, I'm a child neurologist and I'm also trained as a clinical geneticist. Today I'm coming on behalf of the Child Neurology Society. There are a thousand child neurologists in the United States, 500 of whom are also members of the Child Neurology Subcommittee of the American Academy of Pediatrics. On behalf of the child neurologists I can say that as a group we wholeheartedly support your efforts in the implementation and follow-up and strategies related to the newborn screening. In that vein we are also accustomed to some of the difficulties that this group is struggling with in terms of management of individuals with complex health care needs as we face some of these similar issues. I cannot emphasize some of the comments that have been raised by the parents because we, also, as sensitive to those issues. The reason I am here today is basically to make a plea on behalf of child neurologists and also the other subspecialists who are not here, but probably should be considered as important partners in this process, especially with regard to the ultimate integration of health services. I speak on behalf of child neurologists, endocrinologists, and also hematologists--one could also extend this to infectious disease specialists-to consider us as potential consultants or liaisons in this process as we try to move forward. I think, particularly for child neurology, this may be a pertinent point to make if disorders such as Duchenne muscular dystrophy for which there are pilot studies looking at the feasibility of including this in the newborn screen, and also other disorders such as SMA are considered to be added to the panel of newborn screening. So to keep the comments brief, in summary, we appreciate the efforts you're doing, and we consider ourselves supporters and hope to be considered as partners in this process, as well as our other colleagues who would also probably feel similarly. Thank you.

DR. HOWELL: Thank you very much, Dr. Gropman. (Applause.) Are there questions? (No response.) Thank you very much. The expertise of your group is obviously greatly appreciated. And our final commentator this afternoon is Claudine Tiffault, who is a project evaluator from the Sickle Cell Disease Association of America. There seems to be considerable surprise on the part of--(Laughter). Maybe you

signed up for dinner last night. (Laughter.) And there was a piece of carbon paper under it, or something. (Laughter.) Having been called upon, would you like to say anything? I mean you've had adequate time to prepare your remarks. (Laughter.)

MS. TIFFAULT: I would have definitely prepared something if I knew I was going to be speaking. But just thank you for the wonderful work you guys are doing in behalf of Sickle Cell Disease. We're glad to be involved, even at the table with Dr. Telfair and just be witness to what's going on. You guys are doing fabulous work and just continue. Thank you.

DR. HOWELL: Thank you very much. (Applause.) Committee Business

DR. HOWELL: That's the end of our public commentators. We are through with that, we are--everybody was succinct with their wisdom this afternoon, and so we come into the final thing on our agenda which is entitled "Committee Business." And let's do a few real housekeeping duties before we get into the discussions, in the event that we have a long discussion. The meetings for the future are under Tab 13, and let's look at those and get those settled. And there are several options that are listed here. And these areas that are highlighted, I am told by Michele, are the dates that have been responded to by those who have responded as being a reasonable time. And so if we look at, more globally, at the event, could I suggest as a talking point that we consider the 23rd and 24th of February for the next meeting? Any comments about that?

DR. TELFAIR: I just--I'm sorry. MS. : We used your calendar, didn't we?

DR. HOWELL: Denise's calendar is in the mix? MS. : Yes.

DR. HOWELL: Your calendar is on the OD (?). Excuse me, Joseph.

DR. TELFAIR: No, it's okay. Thank you very much.

DR. HOWELL: I'm sorry.

DR. TELFAIR: Dr. Howell, I was just wondering, not everyone's here, and I didn't know, or is this adequate to actually get feedback on the dates?

DR. HOWELL: I think so, but let me tell you two things: Number one, everyone has had an email request to please fill in the dates that they found acceptable, and they're all here and so forth, and so that we have some options here, and I think we should go ahead and decide on the thing, because we can't do anything to bring our absent members back. DR. TELFAIR: I'm not in dis--okay, that's an astute obser--no, anyway, I'm not in disagreement with that. I'm just wondering because of a quorum, if you needed a quorum. But, okay.

DR. HOWELL: We do have a quorum. Our core model is just, as I said, is the 23rd--we have two things: One is these are the dates that came back as open on the committee members and so forth, and I'm just suggesting we basically have several options, but I was looking at 23rd and 24th. Does that seem sensible to the gathered group? I see nods up and down. What about the 22nd and 23rd of June, if we kind of go toward the end of the time? And toward the end of October? October 30th and the 31st? Oh, well, we seem to have a crisis in information here. Here comes the person that knows. Kerry is going to tell us, apparently the dates that we are selecting are the dates that were not available. Is that right? We're going to have to take your sage advice because we should have known that you knew what you were talking about, but in view of the fact that the dates we have selected are the dates that nobody's available, that we will have to go back, and we'll depend on Michele to come back and come up with some dates. And we'll just decide this online for the thing. And if you don't respond about the dates, that would be an issue because Kerry has clarified. For those of you that don't know, the person that you get

emails from all the time and so forth is Kerry Diener who just came up and so forth. Okay, you have a question?

DR. RINALDO: Yes. It's Thursday, Friday for the month of, you know, something that has to be that way, or can be--

DR. LLOYD-PURYEAR: Does it have to be, as opposed to Monday, Tuesday? Or Wednesday, Thursday? It can be any--

DR. RINALDO: No, you know, sometime earlier in the week better than the end, but--

DR. HOWELL: Is there any generic comment about is there a time--in general, is there a time of the week that is preferred?

DR. BROWER: Tuesday and Wednesday. Tuesday and Wednesday, or Wednesday, Thursday.

DR. HOWELL: Any comment about Amy's comment. Amy feels it would be better to have days kind of within the week rather than spanning the weekend and so forth. Is there any comment about that? Obviously, you have to be available.

DR. RINALDO: Actually, my inclination was the opposite. I would rather travel on the weekend because, like for me--like this trip really caused a loss of a working day just to get here, and I would prefer to travel on the weekend, but that's just my--

DR. HOWELL: You're talking about, since we end on the-- DR. RINALDO: Coming in on Sunday, ending the meeting Monday and Tuesday.

DR. HOWELL: Which would mean you could leave on Tuesday afternoon and get back, and you basically, you're talking about reducing the time away by a day is what you're saying. If it were earlier in the week, you could travel at the end of the meeting and so forth.

DR. RINALDO: Exactly.

DR. HOWELL: Any comment about that? Amy is, obviously, she's a middle-of-the-week person there. Any other comments? Joe?

DR. TELFAIR: Any--most--a lot of days--and I realize this may be just for myself--but I think some of us who have other responsibilities, it's actually more stable the way it had been to do this other, like teaching, like other group work, like family, you know, et cetera, it's easier, that way of doing that, structurally, was--worked out much better. That's my two cents, but I'm a liaison to the group, so--

DR. HOWELL: Well, we appreciate your two cents.

DR. TELFAIR: Yeah, I understand. Thank you, sir.

DR. HOWELL: Bill?

DR. BECKER: Rod, I agree with Piero's comment. It, doing the meetings on a Monday, Tuesday would alleviate a little bit of a time away concern if you have to make requests for that particular time. On the other hand, I think what's most important and maybe what, part of what, Joseph was mentioning is whatever we do, let's continue to be consistent with it. It's easier to schedule if it's always on Thursday, Friday, or if it's always on Monday and Tuesday, of it it's always on Tuesday and Wednesday.

DR. HOWELL: If it's good with the committee, then we will recirculate this to be certain, because the calendars may have changed, and we'll come up with some days. Can we do that, Michele?

DR. LLOYD-PURYEAR: Um-hmm. I'll do it on Monday.

DR. HOWELL: Outstanding, and so forth. Now, the other thing that I'd like to bring up before we get into what I would call committee business, and that is that we had discussed the fact that we're expecting people will send notes to us about people that they've--or groups that would be appropriate liaison to the committee. And we will develop, as Peter suggested, some systematic way of looking at that about the value and all the other things and so forth. There are two groups that have been before this committee for some time that I would like to bring up again, because we've been discussing them during the past year. One is a person from the military, who has very specific newborn screening issues, and the other that's been under considerable discussion is FDA because of their active involvement in so many things we do. And I'd like to have a discussion of those, and then we will look, then, at a variety of important other groups and people that might need to be added in the future. Can we have a comment about those two groups as far as--these are suggestions for liaison appointments to the committee.

DR. TELFAIR: I can just make a comment because of the other committee that I sit on, and both of those groups, you know, are--or representatives from both of those agencies, the veterans, Department of Veteran Affairs, and the FDA, I sit on those committees, and there's a substantive amount of information and work that's being done on both of those ends related to issues of newborn screening, particularly issues of genetics and newborn screening genomics. So I would really strongly endorse for consideration of those groups, representatives from those groups, working with that and, specifically, their offices within those agencies that focus on these types of issues. So I would strongly encourage that because I think they would bring a lot to this committee.

DR. HOWELL: Would anyone else like to comment about that? The military has been actively involved with the development of the original guidelines that came through and so forth, and they had a lot to say and a lot to add and a lot of specific issues to bring to the table. And certainly I would support that. Peter? Peter's not here. Piero, can you comment?

DR. RINALDO: I'm in support. I believe that the military has jurisdiction over something like 60,000 babies born to active-duty personnel every year, which is larger than probably the average state. So I think they do have a significant stake when it comes to newborn screening issue, and I think they should be involved.

DR. HOWELL: Coleen? It would appear that there's general agreement. We've had some head-noddings and some vocal, but Denise has something to say.

DR. DOUGHERTY: I just want some clarification. When we invite an organization to come as a liaison, do they pay for themselves to come to the meeting? It's all--

DR. HOWELL: Yes.

DR. DOUGHERTY: --it's all on them?

DR. HOWELL: Yes.

DR. DOUGHERTY: Okay, thank you.

DR. HOWELL: That's correct. So that, well, it would seem to me that having heard some specific comments and so forth that we'll proceed, then, to invite the Department of Defense, either the military and the FDA, and then we will proceed as we move along to have other liaisons that will bring certain

expertise and wisdom to this committee. What other things would you like to discuss at this point, ladies and gentlemen, and the area? Lauren?

MS. RASKIN-RAMOS: In a different topic, just an announcement that you can cross out the "To Be Determined" under ASTHO in your member roster now that I'm pleased to announce that Dr. Chris Koss (ph), who is the Pediatric Director from the New York Department of Health, has agreed to represent us still on this committee, and I'm sorry we couldn't get the approvals through for him to be here this week, but we're excited to be more engaged in the future.

DR. HOWELL: Thank you very much. That will be an important addition and so forth, et cetera. Other items of business that someone would like to bring up? Michele, are there some things that we need to bring up?

DR. LLOYD-PURYEAR: The February agenda.

DR. HOWELL: Comments about the February agenda? We will be developing the February agenda over time, but it would be a good time to weigh in on some specific areas of interest that you would have discussed, or people you would like to bring. Denise?

DR. DOUGHERTY: I think it would be good for our committee, especially our subcommittee, to hear from some of the regional collaboratives, probably useful for the rest of the other people, too. Bill whispered in my ear, "Yes."

DR. BECKER: Well, I agree with that, and it may be through the Coordinating Center, through ACMG.

DR. HOWELL: That would certainly be a logical place, I would think. Prior to the meeting here, I had spoken to Michele about the fact that I think that they--what that group is doing has a potential of value in newborn screening, and I think that we would certainly like to have some important input in it about what they're doing.

DR. DOUGHERTY: I think for hearing from the Coordinating Center, and Jill also--Fisch--she has a set of slides--but hearing from some of the collaborators themselves I think would also be helpful to get the kind of front line experience.

DR. HOWELL: Right, it seems to me that there might be some virtue in having a duo or more of some core things and so forth, but every time we discuss this group, there seems to be something else that could be really integrated with their efforts that could be important, et cetera. What other things should we hear about next time? Joseph?

DR. TELFAIR: Yeah, I just have a suggestion for, being someone that's a liaison from a similar committee and in for liaisons, I know it's important because the other committees that I sit on, we do have like a brief update, if any at all of formal liaisons about their work as it relates to this committee. So I think that in the spirit of engagement, you know, to sort of improve the engagement, and maybe if there was maybe like a five-minute, if they have that much information about what they're doing, in relationship that this committee might be interested in, just an update, just a few words or whatever, you know, as a point of engagement I think would be good, if that happened at this committee.

DR. HOWELL: That's an interesting idea, to bring a little bit of commentary on that. For example, for the National Advisory Council's NIH, obviously, have liaisons representing a certain thing, and they do two things. One of the things they do--and you'll be sad you brought this up--is that they prepare a written document for each meeting that describes some of the key things that you've been doing so that it becomes a part of this book. And then you can have an opportunity to comment. And I think those written documents are very valuable and so forth. But I like that idea. Oh, the other area that--excuse me, let me

comment about one thing before I forget it--and the thing is, is that the other group that's doing some important things that we need to hear about, and also perhaps been there, activities to fit in with some of the things we would like to do is the Office of Rare Diseases at the National Institutes of Health, that is funding--they have funded a group of centers of excellence in rare diseases. And I think--this is a personal viewpoint--is that it would be key that, for example, if a person with hyperammonemia is discovered in Montana, that they are able to plug into the Center of Excellence in Urea Cycle Defects that happens to be here in Washington and get plugged into the therapeutic things and what they're doing, and all that sort of thing. But I would hope that we might have an opportunity to have Dr. Groft and his people come in about some of the movements in the Office of Rare Disease. Does that seem--everybody seems to think that's--

DR. RINALDO: This might require some discussion, but, you know, yesterday we had a lot of I think very productive discussions, and one of the things that emerged both in the discussion of the evidence-based process and also in potential revision to the criteria, was a concept of harm caused by newborn screening. At the same time, we all had been hearing or seeing comments made by people who claim significant harm caused by newborn screening. I would like to have them come here and tell us about the harm, and so that we can put all these things at least through the test of evidence and see what is true, what is missing, what is just and true.

DR. HOWELL: One of the things that I'm aware of is that there is a project underway that's just beginning from an expert pediatric historian, a person who's formally trained in history to do analytic things in history, and the specific project is to examine adverse effects that are recognized and reported from newborn screening. And that, I think--

DR. RINALDO: And I would like something more.

DR. HOWELL: Well, this is going to be a fairly detailed report.

DR. RINALDO: Okay.

DR. HOWELL: You would like to have some of the folks talk about adverse effects to come here and defend their position.

DR. RINALDO: Yes.

DR. HOWELL: I don't think they will come.

DR. RINALDO: I really would like to see that happen. And if they don't come, that, I will think, we'll be entitled to infer from their lack of participation what is the evidence behind their claims.

DR. HOWELL: Bill?

DR. BECKER: Another topic.

DR. HOWELL: Let's put that topic to bed, since it may recur. Michele? Peter? I have no problem at all with asking--

DR. LLOYD-PURYEAR: Are you talking about Norm Kahn? I'm just asking--(Laughter.)

DR. RINALDO: Can we start?

DR. HOWELL: You know, I think the thing is about the issue of adverse effects. I think that if--I think some of us have been in newborn screening longer than most people have been alive, and we're aware of

some issues that have come up with treatment. I mean we didn't just get off the boat with people that didn't understand DIAS (ph), and it did what were really not smart things to do. And there were some significant problems that developed occasionally, and a fair number of transient problems. We're fully aware of that. But I think that we're not aware, at least--and I've talked with people like Selma Sniderman, who preceded me, and she's still very much alive. She's the only one that fit that category, and she is unaware of, except for a handful of people, but the thing is that if there are, indeed, significant adverse effects out there, we certainly should know about them. And I mean if there is information to bring to this group that we could benefit for, I'm all for it and so forth. And we can certainly ask.

DR. RINALDO: My point is if you look at the recent scientific and nonscientific articles, we're talking about Nature magazine, New England Journal of Medicine, we're not talking about minor--minor venues, there has been strong claims of, you know, of really the unintended consequences or of the screening. And I think, you know, people may agree or disagree. I just would like to see the evidence used by the people who made those comments to say that, you know, what is the magnitude of the harm caused by screening. That's--now, how to achieve this goal, I'd gladly leave it to you and to--

DR. LLOYD-PURYEAR: Along that line, the criteria work group that was set up, are you--you're supposed to be reporting in February, too, right?

DR. DOUGHERTY: Right. We met, the five of us, last night, and there's a list of just buckets of criteria that are being--we're now circulating so everybody can look at it. And then we'll have a conference call. So we'll need some help with setting that up from you.

DR. HOWELL: Bill, excuse me, you had another comment? The bottom line, we will see about the possibility of getting someone to come, and we know who to get to come.

DR. RINALDO: Make sure to put a lot of time for questions.

DR. BECKER: Rod, one of the groups that our subcommittee did not identify in our charges but probably ends up being an important group across the entire committee are the policymakers. And now we have representation from ASTHO, but there's another group of policymakers that might benefit from interaction with the committee, the full committee, and we might benefit from hearing a presentation from them about their group, and that's the NCSL, National Conference of State Legislators. And I'm aware that there is someone present here at the meeting today, and we don't have to put that person on the spot right this second, but maybe for the February meeting, since that's really what the agenda issue is right now, is to ask for a presentation from NCSL because they are probably a major stakeholder. We thought of this as another group, not necessarily in our charge, but eventually we'll need to consider education for that group of people as we move forward with expanded newborn screening.

DR. HOWELL: Coleen? VOICE: (Off mike.)

DR. HOWELL: We'll ask Michele to be in contact with you at least. Thank you very much. Coleen?

DR. BOYLE: Yeah, I guess for February, I was thinking that as a full committee we needed to move along on the process. And I know that the process of nomination and evaluation of new candidate conditions and, actually, sort of revaluation of existing conditions are on the panel, and I'm not quite sure how to move that process along. I know we're talking about the actual criteria on this small group of five, but I feel like there are other things that we need to be thinking about in terms of flushing that out further. So somehow that process needs to be moved along. I'm not quite sure how to move it along, but I think we need to give some thought to that as well.

DR. HOWELL: Did you have some specific areas you want to focus on? I mean the criteria, certainly, is one key underpinning for that, et cetera.

DR. BOYLE: Well, I'm assuming that perhaps between now and February HRSA will make some decisions in terms of how the expert review group, how that whole concept will be managed in terms of the actual reviews of the scientific and other literature in terms of evaluating tests, new tests or new conditions that are proposed. But again, I feel like there's a whole system in place, as we heard about the example of ACIP yesterday, and we also heard a lot from David Atkins. I feel like there's some--there needs to be some really deliberative thought given to the process that we had that you folks outlined in terms of that, at least the framework for it. I don't know who's going to be thinking about that. I don't feel like it's a done deal. I know we have a skeleton of a process. Now, how do we put the sort of the little flesh on the bones of that process.

DR. LLOYD-PURYEAR: Do you want Piero to redo the flow diagram and send that out again for thinking, for looking at?

DR. BOYLE: Yeah, and maybe between now and February we can think about what needs to be done in a deliberative way.

DR. LLOYD-PURYEAR: Well, the work group, I mean from my notes what I have is that your work group is supposed to be figuring out three sets of criteria. One set would be the nomination form; one set is on what basis for accepts or rejects; and the one set is the evaluation by what we were calling the evidence-based work groups. So that's a key piece that we can't even--we can't--I mean we can--Peter's already told you what we're leaning towards.

DR. BOYLE: No, no, no. I know that. DR. LLOYD-PURYEAR: Your piece is a core part of that, of presenting it to a group.

DR. HOWELL: Piero has something today, but it would be--it would seem to me that once we come up with these valuative forms, shall we call them, for folks to use and so forth, and once the HRSA group has considered the evidence-based thing and so forth, probably one of the first things that is going to happen is to actually have a trial balloon that--a specific recommendation using those criteria and having it go through the system. And probably that'll be the time when we see areas that probably need fine tuning and so forth. Maybe I'm wrong on that.

DR. BOYLE: and I don't know if we want to take a new condition, or we want to take, you know, new conditions that are on the new panel, and maybe one that has considerable evidence and one that doesn't, and see how it works with conditions that are already part of the panel. Something like that.

DR. RINALDO: I don't see that we--well, personally, we prefer to--just look at SMA, you know. That was not even on the radar screen throughout the process, not to the point of being included in 84 conditions. And now we're already talking about really what appears to be immunity implementation. You know, I believe that the uniform plan still are a relatively young product, and I would let it, you know, be for the time being and see how it works, and then look at the evidence. I would work on new conditions, and at the same time my comment would be that, as we discussed yesterday, I think it is quite valuable and to look at those criteria and expand them. I really hope it will--and that could be relatively easy, looking after the least that Denise provided to some of us earlier--if we can look at those and see how those can be incremental criteria. I really hope that--at least I would really think it wouldn't be the best use of our time if we start now going and revisiting the other criteria. So to eliminate talk, let's, if this is a sort of a change of pace and is no longer an issue comparing to the past, let's sought (ph) some criteria quickly. And then, so in February I agree. I think a test drive is really what we all like to see, and I would do it with something that is new and not one of the existing conditions. That would be my preference.

DR. HOWELL: Let's consider these issues and so forth, et cetera. I think that--but I think the key thing is to look again at the diagram. Let's look at the criteria as they are evolving from the committee that you all are actively involved with and so forth and see what we can do. My own personal preference would also be to look at something new, but there may be virtue in looking both ways. My impression is that there are

a handful of conditions that are out there that have considerable evidence underlying them at this point and so forth, and it'll be interesting to look at some of those. I think it would be a good experience and so forth, and again it would also serve the virtue of moving head, which is always good. What other things do we need to discuss before we depart on this Friday afternoon before the rain stops? Anybody have any other comments? Joseph?

DR. TELFAIR: Actually, just that--it's not a comment, it's just a thank you to the persons who came and helped, were supportive to the subcommittees. Their input was very valuable, so I just actually want to thank those persons publicly.

DR. HOWELL: Well, I think I would, on behalf of the committee, would also like to underline that, because the subcommittees were extremely productive this time, and I think of very concrete things are underway. And so we should be able to move this thing ahead, et cetera. Any other comments? (No response.)

DR. HOWELL: Thank you very much. Have a nice weekend and we'll see you in February at a date to be determined, hopefully not on the days that no one can come. (Whereupon, at 2:08 p.m. the meeting concluded.)