Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

Summary of Sixth Meeting
Oct. 20-21, 2005
Washington, DC

The Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children was convened for its sixth meeting on Thursday, Oct. 20, 2005, in the Rotunda Ballroom at the Ronald Reagan Building and International Trade Center in Washington, D.C. The meeting was adjourned. on Friday, Oct. 21, 2005. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments from 1 p.m. to 2:00 p.m. on Friday, Oct. 21, 2005.

Committee Members Present:

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I. WELCOME, OPENING REMARKS

Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children
Professor, Department of Pediatrics
Leonard M. Miller School of Medicine
University of Miami

Dr. Howell welcomed participants to the sixth meeting of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children.

Dr. Howell informed Committee members that Dr. Jennifer Howse, president of the March of Dimes, had completed her term on the Committee on September 30th and that he had written her a letter thanking her for her outstanding service. He noted that Dr. Howse would be missed but said that she would continue to be actively involved in the Committee's work.

Dr. Howell also welcomed several new organizational representatives to the Committee: Dr. Norman Kahn, serving as the representative from the American Academy of Family Practice (AAFP); Dr. E. Stephen Edwards, serving as the representative from the American Academy of Pediatrics (AAP); Dr. Nancy Green, representing the March of Dimes; and Dr. Tony Gregg, representing the American College of Obstetrics and Gynecology (ACOG) (not present). He said that the Association of State and Territorial Health Officials (ASTHO) had not yet appointed a permanent representative to the Committee but that Ms. Lauren Raskin-Ramos was representing ASTHO at this meeting.

Dr. Howell added that the Committee would be discussing the possibility of additional organizational representatives to the Committee—specifically, from the U.S. Department of Defense (DoD), which has quite a bit of involvement in newborn screening, and from the U.S. Food and Drug Administration (FDA), which is involved in many issues related to the Committee's work, including therapies for rare diseases.

Dr. Howell then outlined the agenda for the 2-day meeting:

- **Presentation on the Advisory Committee on Immunization Practices (ACIP).** Dr. Larry Pickering, Executive Secretary, ACIP, would discuss the ACIP's committee structure and decision-making practices with a view toward considering their applicability to the Committee's own work.
- **Presentation on the role of evidence and other factors in decision-making.** As a follow-up to the Committee's earlier discussions about the role of evidence and other factors in decision-making, Dr. David Atkins, from the Agency for Healthcare Research and Quality (AHRQ), would talk about decision-making and examining evidence in the context of screening newborns and children for heritable disorders.
- **Nomination process for conditions, tests, and technologies for evaluation by the Committee.** Dr. Rinaldo and Dr. Becker would discuss a proposed nomination process to be used by the Committee.
- **Update on the status of the States with respect to newborn screening.** Dr. Bradford Therrell, Director of the National Newborn Screening and Genetic Resource Center (NNSGRC) would report on where the States were in terms of their newborn screening programs.

- **Subcommittee meetings and reports.** On Friday, Oct. 21, 2005, the Education & Training Subcommittee, the Follow-up & Treatment Subcommittee, and the Laboratory Standards & Procedures Subcommittee would meet and give reports to the full Committee about what they hoped to accomplish.
- **Public comments**. Members of the public would be given an opportunity to make statements to the Committee during a public comment session on Friday, Oct. 21, 2005.

Finally, Dr. Howell noted that Committee members Dr. Duane Alexander and Mr. Derek Robertson had sent word that they unfortunately would not be able to attend this meeting.

II. COMMITTEE BUSINESS

Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children
Professor, Department of Pediatrics
Leonard M. Miller School of Medicine
University of Miami

Approval of Minutes. The first item of business, Dr. Howell said, was the approval of the minutes from the previous meeting of the ACHDGDNC held July 21-22, 2005. Committee members reported that they had not yet seen the minutes, so the approval of the minutes was deferred until later in the day. The meeting adjourned on Oct. 21, 2005, without a vote on the minutes, so Dr. Lloyd-Puryear polled Committee members by e-mail following the meeting. Dr. Boyle indicated that her title and address should be changed to the following:

Director
Division of Birth Defects and Developmental Disabilities
National Center on Birth Defects and Developmental Disabilities
1600 Clifton Rd., Mailstop E86

Drs. Becker, Boyle, Bower, Coggins, Dougherty, Hawkins, Howell, Rinaldo and van Dyck indicated their approval of the minutes. Dr. Alexander and Mr. Robertson were not polled because they were not present at the meeting.

Letter to the HHS Secretary. The Committee's letter related to public comments on the ACMG report on newborn screening, Dr. Howell said, was sent to the Secretary of Health and Human Services (HHS) Michael Leavitt in late September 2005. (A copy of the letter was included in the briefing book provided to Committee members, Tab 5.) HHS Secretary Leavitt has read the letter and is currently drafting a response to it.

As the Committee moves beyond its heavy focus on the ACMG report, Dr. Howell suggested, it ought to keep several things in mind: (1) the need for further discussions about how the Committee examines evidence related to decisions about adding conditions and what constitutes evidence; (2) the importance of addressing issues related to long-term follow-up and the Regional Genetic Services and Newborn Screening Collaboratives funded by HRSA; and (3) the need to provide the Secretary advice on grant programs and advice on technology development.

III. COMMITTEE DECISION-MAKING

Rodney Howell, M.D.
Chair, ACHDGDNC
Professor, Department of Pediatrics
Leonard M. Miller School of Medicine
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The topic of decision-making by the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children was continued from previous meetings. At this meeting, the Committee invited two people to give presentations related to the topic: Dr. Larry Pickering, Executive Secretary, ACIP at Centers for Disease Control and Prevention (CDC) gave a presentation of the policies and procedures used by the ACIP; and Dr. David Atkins, from AHRQ discussed the role of evidence and other factors in decision-making related to screening children and newborns for heritable disorders.

A. Examining the Advisory Committee on Immunization Practices (ACIP): ACIP Committee Structure and Decision-making

Larry K. Pickering, M.D., M.P.H.
Executive Secretary
ACIP
Centers for Disease Control and Prevention (CDC)

Dr. Pickering opened his presentation on the ACIP by noting that there is quite a bit of overlap between the ACIP and the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. The objectives of his presentation, he said, were (1) to review the vaccine approval process that the ACIP undertakes; (2) to discuss the responsibilities, structure, and function of the ACIP; (3) to review the interaction of the ACIP with public and private organizations and societies; and (4) to summarize some issues facing the ACIP.

ACIP's Vaccine Approval Process. The ACIP becomes involved in the development of pediatric vaccine recommendations very early—at the time when the vaccine manufacturer submits a biologics license application to FDA for the licensing of the vaccine. FDA's review generally takes about 10 months.

Immediately after a vaccine is licensed, the ACIP meets to make its recommendations about the vaccine. At the same time, the AAP Committee on Infectious Diseases meets and makes recommendations. In the past, there were discrepancies between the two groups' recommendations. Now, however, members from each committee serve on the other committee to harmonize the two groups' recommendations.

The ACIP's recommendations are not official until approved by CDC Director Dr. Julie Gerberding and HHS Secretary Michael Leavitt and published in *Morbidity and Mortality Weekly*

Report. This process takes several months. The uptake in State laws and financing comes in only after the ACIP recommendations are official.

ACIP's Responsibilities. Since 1964, the ACIP has provided advice and guidance to the HHS Secretary and director of CDC on the most effective means to prevent vaccine-preventable diseases in pediatric and adult populations (i.e., the application of antigens and related agents and the use of vaccines). In addition, since 1993, the ACIP has had responsibility for determining the vaccines, number of doses, schedule, and contraindications for vaccines in the Vaccines for Children (VFC) program—a $1.5 billion annual entitlement program established by the Omnibus Budget Reconciliation Act of 1993.

ACIP's Structure. The ACIP has 15 voting members, 8 ex officio members, and 22 organizational representatives:

- ***15 voting members, including the chair, who serve 4-year terms:*** CDC nominates these members, usually by sending two names for each position with a description of what the position entails and why someone in the particular category is needed and why the individuals nominated are being nominated. Subsequently, the HHS Secretary's office selects them, and they are installed as members. The chair is selected from current members.
- ***8 ex officio members representing Federal agencies***: FDA, the DoD, HRSA, the National Vaccine Program Office, the Centers for Medicare & Medicaid Services (CMS), NIH, the Indian Health Service, and the Department of Veterans Affairs. These members generally do not vote, but may be designated to vote in specific circumstances by the ACIP executive secretary.
- ***22 liaisons representing professional societies and organizations*** responsible for vaccine development and immunization programs. Liaison representatives are nonvoting representatives who are expected to represent the position and views of their sponsoring organization. They help to harmonize what the ACIP does and their organizations' policies and may also serve as consultants to working groups to provide expertise and represent their sponsoring organization's views and positions. Currently, organizations with ACIP liaison members are the AAFP, AAP, America's Health Insurance Plans, American College Health Association, ACOG, American College of Physicians, American Medical Association, American Pharmacists Association, Association of Teachers of Preventive Medicine, Biotechnology Industry Organization, Canadian National Advisory Committee on Immunization, Healthcare Infection Control Practices Advisory Committee, Infectious Diseases Society of America, London Department of Health, National Association of County and City Health Officials, National Coalition for Adult Immunization, National Foundation for Infectious Diseases, National Immunization Council & Child Health Program, National Medical Association, National Vaccine Advisory Committee, Pharmaceutical Research & Manufacturers of America, Society for Adolescent Medicine. More organizations want to send liaison members to the ACIP than can be accommodated.

ACIP's Functioning. The ACIP holds three meetings annually (February, June, and October). The formulation of agenda items is critical. Agenda items are solicited from ACIP members, liaison, CDC staff, and others using a standard form, then finalized by the ACIP chair, executive secretary, and CDC steering committee. This follows Federal Advisory Committee Act (FACA) rules and procedures. The ACIP's recommendations are published in final form in *Morbidity and Mortality Weekly Report.*

The ACIP requires people with various types of expertise: infectious diseases, immunology, pediatrics, internal medicine, public health, vaccine research and policy, and consumer concerns. The ACIP relies on working groups to develop draft policies/options for review/vote by the full ACIP. As of October 2005, the ACIP had 14 active working groups, including four permanent and 10 task-oriented working groups. Each working group includes at least two ACIP members, one of whom chairs the working group. In addition, each group includes CDC staff; may include ex officio representatives; and has at least two liaison members. These groups work by teleconference and before/during ACIP meetings. Working group meetings are closed so manufacturers can provide information that they would not provide in an open meeting.

The ACIP is guided by several key documents: (1) the ACIP Charter, as amended in October 2004; (2) ACIP Policies and Procedures, published in October 2002 (currently being updated); (3) Guidelines for Working Groups, which discusses what working groups can do, how they should be formed, and how they function (currently being updated); and (4) a new member orientation booklet that is used in combination with a mentoring program for new members.

The ACIP is managed by CDC. Working with the ACIP Chair Dr. Jon Abramson, the ACIP Executive Secretary Dr. Pickering leads CDC's management of the ACIP, ensures that meetings follow guidelines, prepares meeting agendas, and guides the development/revision of documents. Dr. Pickering also prepares briefing documents of meetings for the CDC director.

The ACIP is currently situated in the National Immunization Program, which provides critical management and support services. There are two full-time equivalent positions: an assistant to the director for immunization policy; the ACIP program analyst; and ACIP's Executive Secretary Dr. Pickering.

CDC's ACIP Steering Committee, which is convened by the ACIP's Executive Secretary Dr. Pickering with the ACIP Chair Dr. Jon Abramson, coordinates the ACIP's activities across CDC's Coordinating Center for Infectious Diseases. Soon there will be four centers in CDC's coordinating center, and one person from each center will be on the steering committee. The CDC Federal Advisory Committee Management provides information to the ACIP about rules and guidelines under the Federal Advisory Committee Act (FACA) when needed. CDC's Office of General Counsel is helpful in addressing legal issues that the ACIP encounters, particularly those involving conflicts of interest. CDC also provides funding for the ACIP's operations.

CDC's ACIP Steering Committee consists of the director of the National Immunization Program, representatives from the Coordinating Center for Infectious Diseases, the assistant director for immunization policy, the ACIP program analysts, and FDA ex officio member. The committee develops the agenda for ACIP meetings (beginning 2 months in advance of each meeting); develops a nomination slate to replace departing members and chair; and develops consensus CDC positions on ACIP issues, policies, and procedures (e.g., the need for new liaison organization, the structure/function and activities of working groups). Many of the steering committee's meetings are held via teleconference.

The U.S. immunization system includes a broad range of participants, including the government (Federal, State, and local government), private industry, academic institutions, private providers, and insurers. Three major entities make recommendations regarding childhood vaccine policies: CDC's ACIP, the AAP Committee on Infectious Diseases, and the AAFP. Unless their recommendations are harmonized, the situation becomes very confusing. Since 1994, the ACIP, AAP, and AAFP have produced a harmonized childhood and adolescent immunization schedule. The ACIP and AAFP produce a harmonized adult immunization schedule.

The evidence considered in the ACIP's vaccine policy development is evidence related to the following: (1) preventable burden of disease; (2) efficacy and effectiveness of the vaccine in various age groups and populations; (3) safety of the vaccine; (4) interactions with other vaccines; and (5) economic analysis.

The ACIP makes two general types of recommendations:

- Universal use recommendation (age-based recommendation—e.g., rotavirus vaccination at 2, 4, 6 months; zoster vaccination for individuals over age 60). This type of recommendation is the least confusing and easiest to implement; the vaccine must benefit all.
- Risk-based recommendation (i.e., based on medical, occupational, behavioral risk). It is difficult for providers to identify individuals who should be vaccinated, and this type of recommendation is much less well implemented than a universal use recommendation.

Financing the Purchase of ACIP Recommended Vaccines. The cost of vaccines to parents is a significant barrier to vaccination. Thus, adequate financing of vaccines is critical to successful implementation. Ensuring the purchase of ACIP recommended vaccines is a shared responsibility of the public sector and private sectors. In fiscal year 2004, funding for childhood vaccines came from the following sources:

- **Private sector funding (45 percent).** Private health insurance usually includes an immunization benefit. Some children (only about 2 percent) have insurance that does not cover vaccines, so their parents must pay for vaccines.
- **Federal Vaccines for Children (VFC) program (40 percent).** The VFC program is an entitlement program in all States under which vaccines specified for inclusion in the program by the ACIP are provided to disadvantaged children without cost to the provider or parent. About 45 percent of young children are eligible for the program. The VFC program has 45,000 provider sites (75 percent are private provider sites and 25 percent are public sector sites). Collectively, VFC providers vaccinate 90 percent of children.
- **Federal Section 317 grant program (8 percent).** The 317 grant program provides discretionary grants to federal grants to State, local and territorial public health agencies. There are no restrictions on vaccines or populations in this program.
- **State programs (7 percent).** The State role in purchasing vaccines varies substantially by State, although most States do contribute some funding. Some States guarantee purchase of all vaccines. States also regulate most insurance companies and can mandate inclusion of vaccines into their insurance packages.

The number of vaccines in the routine childhood immunization schedule has increased from 7 in 1985 to 13 in 2005. Federal contract prices for vaccines in 1985 were $45 per child; by 2005, the price was $570 per child, with a large portion of the increase due to the inclusion of pneumococcal conjugate vaccine.

In conclusion, Dr. Pickering made several points. First, the ACIP feels that routine immunizations provide a tremendous benefit to infants, children, adolescents, adults, and to society. Second, immunizations are a shared public/private responsibility. Third, the ACIP is a well-functioning, well-respected FACA committee. Fourth, there are many challenges facing the ACIP, including vaccine financing, vaccine supply and vaccine acceptance issues, that will have to be addressed to ensure a very successful program.

Questions & Comments

Following Dr. Pickering's presentation on the ACIP, Committee members posed a number of questions. Dr. Brower, noting that the vaccine manufacturer's FDA submission appears to trigger the ACIP's involvement, asked how the ACIP finds out what is going on prior to that point. Dr. Pickering explained that the ACIP generally learns about things from manufacturers and the research community, because FDA is very constrained by rules and regulations.

Dr. Brower then asked how the ACIP decides which vaccines to look at in a formal working group and sets priorities about what is presented and when. Dr. Pickering explained that if a vaccine is going to be submitted to FDA, the ACIP must consider it, so it will form a new working group or try to it fold in. CDC's ACIP Steering Committee sets priorities. People are never happy with the amount of time they have, but they are happy to be on the agenda.

Dr. Edwards asked Dr. Pickering to comment further on the logistics of involving 50 or more people—15 voting members, 8 government ex officio members, 22 liaison members, staff, etc.—in ACIP meetings. In all, Dr. Pickering said, there are usually about 300 to 400 people present at each ACIP meeting. The 15 voting members plus the 8 ex officio members (who can be asked to vote if there is not a quorum of ACIP members) sit at an inner table, and the 22 liaison members sit at an outer table. These are the people who speak during the meeting. In addition, there are usually about 200 or so people representing the public and the press, and they can speak during the public comment period.

Dr. Kahn said the harmonization of the immunization schedule has been an important public service over the last decade and asked Dr. Pickering to comment on why one of the liaison organizations has not participated in that harmonization. Dr. Pickering explained that the American College of Physicians (CAP) has not participated because CAP is a very evidence-based organization and believes that the ACIP's recommendations are not sufficiently evidence based. To address this issue, ACIP recently established an Evidence-Based Working Group. This working group is examining the mechanics of how the ACIP looks at evidence to develop recommendations to help to ensure that the same evidence-based approach is used for each ACIP recommendation. The working group's recommendations may be discussed at the next ACIP meeting and will probably be officially implemented soon thereafter.

Dr. Rinaldo asked why there was no formal representative from the American Society of Microbiology as liaison member on the ACIP. Dr. Pickering said that that organization deals more with the development of vaccines than with vaccine policy and has not applied to be a liaison organization. Following up, Dr. Rinaldo commented that the ACMG expert group had to table consideration of infectious diseases as part of a screening panel, because we were unable to engage infectious disease organizations. Dr. Pickering replied that two groups on infections diseases do give good input: (1) the Infectious Diseases Society of America (clinicians that do infectious diseases, including many who also belong to the American Society of Microbiology); and (2) the National Foundation for Infectious Diseases.

Ms. Raskin-Ramos from ASTHO asked Dr. Pickering to comment on the fact that some States are still having trouble buying vaccines for all children; she also asked him to comment on the role that congressional appropriations play in financing vaccines. Dr. Pickering explained that vaccines for children in the United States are financed through several programs as mentioned earlier. The VFC program is an entitlement program, and once a vaccine is recommended by the ACIP and voted on for the VFC program, all children get it. The Section 317 grant program covers vaccines for poor children; the program must be approved yearly by Congress, however, and the funding has not quite kept up with the need, so when a new vaccine is licensed and

approved, States must decide whether to continue immunizing children with the vaccines already in use or whether to add the new vaccine. State funds can be used to supplement Section 317 grant funds, but financing remains difficult. In addition, insurance companies cover certain individuals, but a delay often occurs between the approval of a vaccine and the time when insurance companies cover the vaccine. This funding of vaccines for children in the United States is a major issue, Dr. Pickering said, and he hopes that Congress will recognize this.

Dr. Green, returning to the issue of adequate evidence, asked Dr. Pickering whether the ACIP used a flowchart of a strict paradigm, or more generic consideration. She also asked him to share any specific criteria used by the ACIP with Committee members. Dr. Pickering replied that the ACIP started out with generic discussions of adequate evidence but is now developing specific figures and tables. He agreed to share the figures and tables with the Committee when they are available and indicated that he would work with Dr. Lloyd-Puryear on this.

Dr. Boyle, noting that the question of financing and barriers keeps coming to ACHDGDNC, asked what influence the VFC program has had in terms of making the ACIP's advice with respect to childhood immunizations a reality. Dr. Pickering said the VFC program is a wonderful program that has made a huge difference in giving disadvantaged children an opportunity to become immunized. He would like to see similar programs for other preventive services for children.

Dr. Edwards asked Dr. Pickering to comment on whether he believed the ACIP model was an appropriate model for ACHDGDNC to consider applying to newborn screening tests. Dr. Pickering replied that he had discussed this with Dr. Howell and does think the ACIP model is an appropriate model for newborn screening—it is a parallel track with different issues. What the ACIP benefits from, and what could also benefit newborn screening, Dr. Pickering believes, is gathering experts to provide advice, strong interaction with public/private sector, including government organizations and the liaison organizations; the openness of meetings to get good input from the general public; and a real structure and structured activities. Given the similarities, Dr. Pickering said, he believes that having a committee similar to the ACIP for newborn screening tests would be very beneficial.

Dr. Becker agreed that the ACIP model is a good one, adding that he had written a list of similarities and differences between the ACIP and the ACHDGDNC. The similarities are similar stakeholders; many people making recommendations, working groups, shared public/private responsibilities, and challenges in financing. The differences are that (1) the ACIP has better methods of disseminating recommendations (e.g., via *Morbidity and Mortality Weekly Report,* via its liaison organizations, via States); (2) the ACIP has a many more liaison organizations; (3) the ACIP has a new member orientation process, which seems like a good idea; (4) the ACIP has tried to solve some financing issues with VFC entitlement program, something ACHDGDNC may want to consider given the many uninsured, underinsured, underserved people needing newborn screening; (5) the ACIP puts information on the status of recommendations on Web sites, whereas ACHDGDNC's mode of communication at present is limited to meeting announcements and the minutes of the meetings; and (6) the ACIP is under CDC, and the ACHDGDNC is under HRSA, although both are under the U.S. Department of Health and Human Services (HHS).

Dr. Boyle noted that one additional difference is that the ACIP is dealing with vaccines which are sort of a one-shot deal—the child gets the vaccine and that is it—whereas with newborn screening, there is a continuum of activities (testing, follow-up, and care for a person's lifetime), so it is much more complex. That makes the parallels a little different. Dr. Pickering said that was

a good point but noted on the other hand 4 million children are born each year that have to be immunized, and the ACIP has a very extensive surveillance system for the diseases that have to be monitored.

Dr. Rinaldo noted that a key component of the ACIP is to monitor and detect adverse effects following immunization, so there is a similarity to newborn screening. Dr. Pickering agreed, noting that an Immunization Safety Office in the CDC director's office under the direction of the associate director for science carefully monitors the safety of all vaccines through several well-established mechanisms, so in a sense there is follow-up.

Dr. Rinaldo asked Dr. Pickering how the ACIP handles the strong opposition to vaccination among some people. Dr. Pickering replied, "with a lot of patience," continuing to educate parents, patients (if they are old enough), and professionals about the benefits of vaccines.

Dr. Howell asked how the ACIP obtained input from families. Dr. Pickering said that obtaining input from the general public is an issue the ACIP has grappled with. The ACIP does have a single community representative among the 15 voting members. That person serves on working groups where there may be contentious issues. The ACIP also has open comments at the public meetings. The ACIP takes the comments of parents who are for or against vaccines into consideration.

Dr. Howell asked how the development of vaccines is funded, noting that he had heard that vaccine manufacturers have difficulty making money. Dr. Pickering said he believes that the vaccine manufacturers bear much of the cost of vaccine development, but Federal funding of vaccine development is important as well. It is very, very expensive to develop a vaccine, and some vaccines never make it to the market, and some vaccines (e.g., rotavirus) are recalled for safety reasons.

Dr. Howell also asked when the ACIP started. Dr. Pickering said he believes that the ACIP was established in 1960s. Unlike the ACHDGDNC, therefore, the ACIP is a mature committee that has had a fair amount of time for evolution.

Dr. Hawkins asked how educational materials related to vaccines are developed, who provides the funding for such materials, and how such materials are disseminated. Dr. Pickering replied that many States develop excellent educational materials related to vaccines; CDC has excellent communications people who develop materials about vaccines (e.g., questions and answers about vaccines that go on the Web, posters, CDs, etc.); and private sector organizations such as the American Academy of Pediatrics and American Academy of Family Physicians develop educational materials for their members and the public. Dr. Hawkins asked who guarantees uniformity of this. Dr. Pickering replied that CDC develops a lot of the information and makes it available for general utilization, working closely with the States. In the case of influenza, for example, CDC has established a Web site www.cdc.gov/flu, where all of the information on influenza from CDC is placed, and that are then available for use by people in the public and private sectors.

Dr. Howell returned to the issue of the evidence base for ACIP's recommendations. He said his understanding is that the ACIP does not plan to gather new evidence but basically is going to categorize the material it has on hand. Dr. Pickering said that Dr. Howell's understanding was correct; there will be no real change in how data are gathered or evaluated, just in the ranking of the recommendations.

Dr. Boyle asked for more specifics on how the ACIP's working groups gather data and function, saying that the information might be useful to the subcommittees of the Secretary's Advisory Committee. D r. Pickering used the ACIP Hepatitis Working Group as an example. When the ACIP Hepatitis Working Group was formed, a senior person from the CDC's Hepatitis Branch took the lead. That individual selected other appropriate CDC staff not only from the hepatitis branch but from other areas of CDC so that all people were represented. Then as the working group is formed, two or more ACIP members were selected by the ACIP chair to serve on the working group. The ACIP's Hepatitis Working Group has seven ACIP members on it. In addition, it includes liaisons with experience or needs in this area, along with individuals from universities and manufacturers to provide information. The person who keeps things going, however, is the lead CDC staff person.

Dr. Howell observed that in comparison to the ACIP, the ACHDGDNC is very young and has a very modest budget. Dr. Boyle noted that according to the amendment to the ACIP charter, the estimated annual cost of operating the committee, including compensation and travel expenses for members but excluding CDC staff support, is $109,067; the estimate of annual person-years of staff support required is 2.1 at an estimated annual cost of $290,086. Dr. Lloyd-Puryear noted that these figures do not include all the CDC staff time or the commissioning of papers and research. Dr. Pickering concurred, noting that the figures include the hotel, the meeting site, transcriptions, stenographers, and the travel of voting ACIP members.

B. The Role of Explicit and Evidence-Based Process for Making Recommendations Regarding Newborn Screening

David Atkins, M.D., M.P.H.
Chief Medical Officer, Center for Outcomes and Evidence
AHRQ

Following Dr. Pickering's discussion of the ACIP, Dr. Atkins discussed how ACHDGDNC might use more explicit, evidence-based processes for making recommendations regarding newborn screening.

The reasons for using a more explicit and more evidence-based process, he noted, are to enhance credibility; to enhance transparency, so people can understand what you did; to facilitate reproducibility and limit bias, so that different people will arrive at the same result; to identify gaps in evidence; and to reduce the chance of getting a recommendation wrong.

Having an explicit, evidence-based process for making recommendations, he said, means providing a more explicit description of what was done, and how it was done, and how it got you to your recommendations. It requires the following:

- Specifying questions to be answered
- A consistent process for reviewing evidence
- Procedures to reduce bias and conflict of interest
- Rules of evidence vs. other factors in recommendations
- Indicating which recommendations are based on evidence of improved outcomes vs. other considerations (e.g., prevailing standards)

Organizations learn as they go about how to make their evidence-based process both functional and clear, so it is not surprising that the ACIP is discussing being a little more explicit and transparent in what it requires and how it gets to conclusions.

The U.S. Preventive Services Task Force (USPSTF) uses an evidence-based process to develop recommendations for clinical preventive services. The USPSTF is an independent panel of experts in primary care and prevention sponsored by AHRQ that is supported by evidence-based practice centers that conduct systematic reviews of the evidence on specific topics in clinical prevention that serve as the scientific basis for USPSTF recommendations.

In developing recommendations related to newborn screening, the ACHDGDNC might find it useful to distinguish, as the USPSTF does, between the following:

- The process for sifting through evidence about a particular questions related to newborn screening in a systematic and well-described way and for producing a synthesis of the review without conclusions
- The process used to judge whether all the evidence has been adequately considered and, then considering that evidence, to make a judgment about what recommendation to make

In this framework, a body other than the ACHDGDNC would review the evidence. The body tasked with reviewing the evidence would (1) perform a systematic search for relevant information; (2) develop an objective synthesis of the evidence (using predetermined criteria and avoiding conflicts of interest); (3) combine expertise in research methodology and in content areas; and (4) address criticisms from peer review. The ACHDGDNC, on the other hand, would (1) represent all key stakeholders; (2) develop criteria for recommendations; (3) identify key questions to be addressed; (4) review a summary of the evidence; (5) weigh other considerations; and (6) make recommendations.

Dr. Atkins identified seven major components of an explicit, evidence-based approach to making recommendations, and then discussed these in the context of the ACHDGDNC's work related to newborn screening.

1. Identify target population and audience—what is goal and to whom do the recommendations apply?

- Population: infants born in the United States
- Audiences: State screening programs, clinicians (generalists and experts); parents, public health practitioners, policymakers

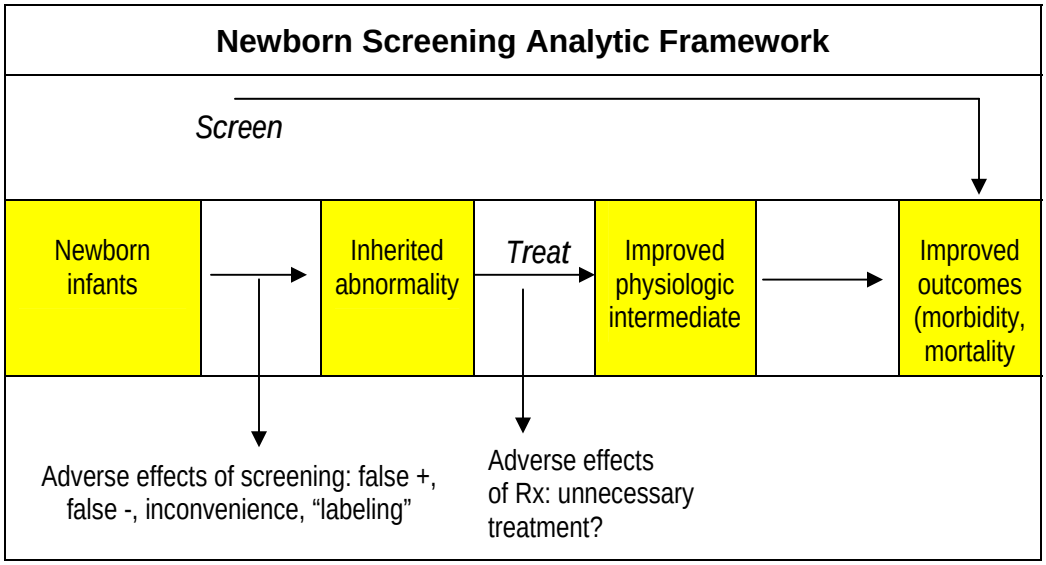
2. Identify topics for consideration

- Specify criteria that would justify review (e.g., available test, burden of disease)
- Solicit nominations of candidate topics (e.g., from experts, public programs, industry) and request background information with nomination [the ACIP has an open nomination process. The challenge is to sift through nominations in a way that makes people feel they have a fair hearing]
- Assess each topic against criteria. [This is a resource-intensive process. The USPSTF uses Lewin to do this.]
- Panel votes on priorities for review

3. Specify outcomes of interest (including unanticipated and potentially harmful outcomes)

- Reducing morbidity and mortality in infants with inherited disorders
- Reducing impact of inherited disorders on family and society
- Minimizing harms to healthy infants and their families
- Ensuring efficient use of resources of newborns screening programs (depending on scope of the Advisory Committee)

Dr. Atkins presented the following illustrative analytic framework for specifying outcomes of interest in the case of newborn screening.



4. Define what evidence is relevant (role for this Committee to give marching instructions to people)

- Issue: evidence is limited for many rare newborn conditions
- Need to expand review beyond most rigorous study designs (randomized clinical trials) without including invalid findings
- Role of the panel: *define* general standards against which to judge evidence
- Evidence review: *evaluate* evidence against those standards

5. Judge the quality of the evidence

- What do we mean by quality?

  —"Extent to which a study's design, conduct, and analysis has minimized selection, measurement, and confounding biases." (Lohr & Carey, *J. Clin.Q. Improvement,* 1999)

  —"Extent to which one can be confident that an estimate of effect is correct." (Grade, *Br. Med. J.,* 2004)

- The USPSTF relies heavily on randomized clinical trials (RCTs) as evidence, which give the highest internal validity. RCTs are obviously not feasible in newborn screening or in many other fields. It is important to recognize that an explicit, evidence-based process

does not require evidence from RCTs, exclude the consideration of expert opinion, exclude input from other stakeholders; or prohibit making recommendations in the face of poor evidence. There are many frameworks for judging the quality of evidence, and those with RCTs at the top will not work ideally for the ACHDGDNC. In the case of judging the quality of evidence for newborn screening, the Committee's role is to set the bar. The USPSTF sets the bar fairly high for adult screening tests. If the bar is set too high, it will wait too long to recommend something that is helpful; if the bar is set too low, it will waste resources.

A. Assessing the quality of individual studies—should I trust this result?

- *Goal:* identify those studies least likely to be biases (*internal validity*).
- Quality is function of study design (e.g., randomized clinical trial or controlled cohort vs. case series); study execution (e.g., loss to follow-up).
- Critical elements vary by topic.

  —In diagnostic studies, for example, is the patient population representative of newborns who will get this result? Are results generalizable to typical practice in State screening programs? Have tests been confirmed with accepted gold-standard test? How good is the gold standard for identifying infants who would be affected clinically? Can sensitivity/specificity/positive predictive value be calculated?

  —In treatment studies, for example, can I be sure the effects are due to treatment? Are we sure of what the clinical course would have been without treatment? Is the population comparable to those who would be detected by screening?

B. Assessing the quality of a body of evidence—can I answer the question at hand from the available evidence?

- *Internal validity*—are studies designed to minimize bias?
- *External validity*—are populations and interventions applicable, in general, to the typical practice?
- *Consistency*—are results of different studies consistent?
- Quantity—are the number and size of studies adequate?
- "Directness"—do studies directly address the intervention and outcome of interest?

C. Balance of benefits and harms—can I be sure this intervention will do more good than harm?

- Considering harms of screening—all screening tests have harms; they may not be important (e.g. false positive for cholesterol), but they need to be considered. If there are harms, they could offset small benefits.
- False positive results from technical limitations of the test, errors in lab processes, etc.
- Harms include psychological harms to parents; downstream testing; treating kids unnecessarily; economic costs without benefit.

6. Link recommendations to strength of evidence (make different grades of recommendations based on strength of evidence)

- Strength of the recommendation—"the extent to which one can be confident that a recommendation will do more good than harm."

  —quality of the evidence (for benefits and harms)

  —tradeoffs (the relative value attached to the expected benefits, harms, and costs)

  —ability to translate evidence into practice in a specific setting

- To link recommendations to the strength of the evidence, the USPSTF makes the following distinctions and also gives a paragraph rationale with its recommendations:

  —A. *Strongly recommend* (good evidence, benefits substantially outweigh harms)

  —B. *Recommend* (at least fair evidence, benefits outweigh harms)

  —C. *Insufficient evidence* (uncertain balance of benefits and harms—lack of evidence on clinical outcomes, poor quality of existing studies or conflicting results; may make recommendation based on other grounds)

7. What other considerations—separate from question of whether a screening test will work—are relevant to recommendations?

- It is important to be clear what the basis for recommendations is and to separate out the relative contribution of scientific evidence and factors such as the following when making recommendations.

  —Equity

  —Prevailing practice

  —Parent/society preferences

  —Feasibility

  —Costs

  —Resources

In the current environment, Dr. Atkins noted, it is difficult to ignore costs, although costs are rarely used explicitly in recommendations. In the case of screening, there are the initial costs of screening as well as the downstream costs of testing, including follow-up, testing, referral, and treatment. Many cost-effectiveness analyses are not done rigorously. If costs are introduced as a basis for recommendations, they should be introduced in a rigorous and credible way.

Obtaining input from families and public is important, but it is also important to balance interests from affected children with the people who represent the interests of all children. The Secretary's Advisory Committee should try to find articulate people to give it a sense of how important something is to the children who are affected, as well as to find articulate people who are thinking more globally about the best ways to protect the interests of all children.

When the evidence about something is insufficient to answer a particular question, Dr. Atkins said, the ACHDGDNC has various options. One option is to turn to experts for help. When relying on expert opinion, it is important to get a balanced group of experts to reduce the possibility of bias. It is also important not to rely only on experts who feel strongly for or against something, because their judgment might not be representative. Content experts may be better at assessing components (e.g., is a test accurate?) than in integrating tradeoffs (e.g., is screening worthwhile?).

There are also other options for making recommendations in the face of poor evidence. The ACHDGDNC might extrapolate from other data and say although we don't really have the data we want, we think this other condition is comparable enough. If there are studies of treatment that have not really followed kids out to morbidity but have followed them to an intermediate metabolic endpoint that the Committee is confident is a measure of effectiveness, the Committee might extrapolate from this intermediate endpoint. The Committee might say a particular problem is so big or so important that it does not want to wait for perfect evidence and is going to make a recommendation based on that fact. Or the Committee might say that it is not sure of the benefits through evidence but it knows the test is safe and is going to guess that the benefits are likely to outweigh harms or that it is going to consider clinical tradition.

The USPSTF, which has the luxury of having reasonably good quality data, says it is not going to recommend anything for routine use unless there is evidence that the intervention actually does what is expected—relying on the principle *primum non nocere* (first do no harm) when making recommendations. Another approach that the ACHDGDNC might use would be to say that when we need to make policy recommendations without the evidence we would like to consider factors such as expert opinion, potential benefits, patient/family preference, etc.

Dr. Atkins said another option for the ACHDGDNC would be to consider different levels of recommendations for newborn screening rather than just "recommend/do not recommend." Among the possibilities, for example, are the following:

- **Recommend.** Use this when there is adequate evidence on specified parameters (e.g., accuracy of test, clinical implications of positive test, and effectiveness and safety of intervention).
- **Evaluate in a pilot program**. Use this as a middle option when there is some evidence about an intervention but some uncertainty about a component or about putting it all together, yet there is sufficient promise that deferring a decision does not seem like the best option.
- **Defer decision, identify research needs**. Use this when there is insufficient evidence.

Dr. Atkins advised paying attention to perceived conflicts of interest as well as real ones. A conflict of interest is something that makes it hard for a person to step back and look at the data objectively. It is not necessary to exclude any person with a potential conflict of interest, but it is important to recognize and deal with potential conflicts of interest by disclosure, by balancing conflicts, or by recusal if needed.

Summing up, Dr. Atkins said, he recommends that when ACHDGDNC makes recommendations, it do the following:

- Clarify standards for evidence and recommendations.
- Separate process for evidence review from the process for recommendations.
- Enlist a designated center to support evidence reviews.
- Ensure representation of all stakeholders.
- Formalize the process for outside review.

Questions & Comments

Committee members posed a number of questions to Dr. Atkins following his presentation. Dr. Kahn, referring to Dr. Pickering's presentation said although the ACIP uses an evidence-based process, some groups think it is not evidence-based enough. Does the USPSTF have that problem? Dr. Atkins replied that the USPSTF has the opposite problem—people think they set the bar too high. But, Dr. Atkins added, *the issue is less where you set the bar than that you set the bar*. It may be that the objections to the ACIP's process may stem from the fact that the ACIP has not codified the process clearly enough. The important thing is to *codify the process* to make it transparent and ensure that important issues are not overlooked.

Dr. Rinaldo asked Dr. Atkins if he could give the ACHDGDNC guidance for handling situations when, for example, in the case of screening by tandem mass spectrometry, there is the possibility of detecting a secondary condition with only 5 or 10 cases in the world, for which we are not close to having a reasonable level of evidence, should that be a deterrent to screen for a condition for which the evidence is strong? The fundamental concept of the screening by a multiplex platform (e.g., mass spectrometry) is that all these things are interconnected and cannot be taken apart. Dr. Atkins replied that similar issues arise in the case of prostate-specific antigen (PSA) screening for prostate cancer. It is important to acknowledge unanticipated downstream consequences associated with screening in such cases. That there is no simple answer about how to handle such cases. One option might be to make a recommendation to minimize the downstream consequences; another option might be to give guidance for different populations.

Dr. Boyle noted that Dr. Atkins suggested having a body separate from the ACHDGDNC to sift through the evidence and make those separate activities. She explained that the Committee had planned to try to do everything by itself and asked: Do you think we can do that? Dr. Atkins said he did not want to overemphasize the separation of the evidence review body and the Committee; however, he does think that there is a value in working with an external group that does evidence reviews. There are time constraints, as well as a learning curve in doing evidence reviews, and you get efficiencies with a group doing it over and over again. Dr. Howell noted that the Committee had thought about having an external group to help with the review and he thought that the Committee would have to look at that further.

The discussion then turned to the issue of conflicts of interest. It was noted that most of the people involved in developing recommendations related to newborn screening are people who have been interested in newborn screening or relatives of affected individuals, so one criticism is that these people are biased—they all have conflicts of interests. Dr. Atkins replied that the essential thing is to make sure that potential conflicts of interest are disclosed and that there is a process to decide when the conflict of interest rises to the level that a person should be asked to recuse himself or herself (e.g., you might want to ask parent representatives to recuse themselves when making recommendations related to the disorder that their child has). Dr. Atkins also said that it is important to try to balance potential leanings by recognizing that certain individuals bring one perspective to the table (e.g., people concerned with the welfare of children), and then asking what other perspectives might be (e.g., administrators concerned with costs and feasibility).

Dr. Brower asked Dr. Atkins to comment on the timing of screening newborns for disorders, noting that with newborn screening, there is often only one capture point, unlike adult screening, where you may have subsequent screens. Dr. Atkins said that this is an important point, but it does not change the fact that the decision point is either to screen all newborns or not, and you need to think about other consequences of that decision and how many things one ought to screen for. Dr. Rinaldo observed that the situation is complicated because some conditions (e.g., Wilson disease) cannot be detected in the immediate newborn period.

Dr. Becker observed that one is likely to see criticism or questioning of the evidence at every stage of the implementation of a recommendation and asked Dr. Atkins to comment on how a separate evidence review group would have to interact with the Committee to make sure that all the appropriate information is considered. Dr. Atkins said the question he heard being asked was about the evidence-based recommendations and then real-world implementation questions and that he thought that both of these ought to be captured in the original evidence review, because the Committee needs to think about whether something is going to work in the real world. That question may not be answerable at the time the Committee makes a recommendation, but it at least should be put on the table. In some cases, the Committee may want to identify issues that it needs to come back to, because it realizes that there is going to be new information as people get experience that may change its recommendation. Dr. van Dyck said he saw the process as (1) the evidence review group does a job and turns it over to the Committee; (2) the Committee makes its recommendation; (3) subsequently, any new evidence or criticism is brought to the full Committee, which then has to decide whether to take it back to the evidence review group.

Dr. Atkins noted the Committee needs to consider just how much it wants to get into implementation issues—is it the Committee's job just to say "go" or "don't go," or is it to go beyond that and say how to maximize benefits and limit harms, make it more efficient, etc.

Dr. Green, following up Dr. Boyle's earlier comment about the single testing point in newborn screening, pointed out that there are different levels of implementation of newborn screening, so the Committee should not feel pressured into thinking that it is all or none. There can be anonymous incidence studies done and also pilot studies, as was done in Massachusetts, with various phases of re-evaluation. Dr. Atkins replied that now that the Committee is in existence and has higher visibility, he thinks more States will increasingly look to the Committee for guidance, so it will be difficult to learn from individual variation in the States. For that reason, as discussed earlier, the Committee might want to consider different levels of recommendations for newborn screening rather than just "recommend/do not recommend"; it might want a process to encourage people to do a pilot.

C. Nomination Process for Conditions, Tests, and Technologies for Evaluation by ACHDGDNC

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Dr. Rinaldo and Dr. Becker outlined their thoughts on the process that might be required by proponents to nominate new conditions for inclusion in the uniform newborn screening panel recommended in the ACMG newborn screening report. The discussion centered on a 7-page handout Dr. Rinaldo and Dr. Becker had prepared with the following components:

- **A 1-page flowchart of the overall process** for nominating a condition, evaluating the evidence, and then having the full Committee make a recommendation about whether to

include the condition in the uniform newborn screening panel recommended by the ACMG report.

- **6-pages of nomination forms** for proponents to nominate conditions to be added to the ACMG uniform newborn screening panel, including

  — a 4-page "Nomination of Condition—Score Card," including a list of criteria and scores used to evaluate conditions in the ACMG newborn screening report and a worksheet listing reference conditions in the ACMG uniform panel

  —a 2-page "Nomination of Condition—Fact Sheet" (black and white pages)

Overall process. Dr. Rinaldo explained that the 1-page flowchart of the overall process for getting conditions added to the uniform panel flowchart has a clearer beginning and end than the flowchart that he and others had initially proposed for the Laboratory Standards & Procedures Subcommittee in April 2005. The new flowchart reflects the following assumptions: (1) there should be a relatively simple nomination process; (2) the assessment should have similarity to the one used by the expert group to establish the ACMG uniform newborn panel for the sake of fairness and consistency (reliance on established criteria in the ACMG report, other criteria and utilization of similar tools based on the experience learned during that process); (3) the approval should go through progressive steps involving HRSA, the ACHDGDNC, the three subcommittees of the Committee, and an ad hoc working group with representation of each subcommittee, with final recommendation for inclusion/deferral of the condition in the uniform panel resting with the full Committee.

The **1-page flowchart of the overall process** for getting conditions added to the ACMG uniform newborn screening panel included the following steps:

- ***Step #1: Nomination of a condition.*** The proponent of adding a condition to the uniform panel submits a nomination form to HRSA. The nomination process would be very open. Any proponent of adding a condition—a provider of newborn screening services, a representative of a professional organization, a representative of a patient support group, a clinician, a scientist, a for-profit organization, a patient himself or herself, a family member or advocate, or whoever—could submit a nomination to HRSA using the appropriate nomination form.

- ***Step #2: HRSA administrative approval for the nomination to be reviewed by the full Committee.*** HRSA administratively reviews the nomination form submitted by the proponent of adding a condition and decides either (a) to approve the nomination form or send it on to the full Committee for consideration; or (b) to decline the nomination form.

- ***Step #3: Evaluation by various bodies***

  —The full Committee receives a nomination approved by HRSA and either (a) declines to forward the nomination to its subcommittees; or (b) approves the forwarding of the nomination to its subcommittees.

  —The subcommittees of the Committee recommend either (a) that the full Committee form an ad hoc working group to review the evidence; or (b) not to form an ad hoc working group.

  —The full Committee either (a) forms an ad hoc working group, inclusive of liaisons from the three subcommittees, to review the evidence and make a report to the full Committee; or (b) declines the nomination.

- ***Step #4: Report to the full Committee by the ad hoc working group*.** The ad hoc working group, with liaisons from the three subcommittees of the Committee, deliberates and makes a written report and oral presentation to the full Committee.
- ***Step #5: Recommendation by the full Committee.*** The Committee makes a recommendation either (a) to include the condition in the uniform panel; or (b) not to include the condition in the uniform panel.

According to Dr. Rinaldo several questions remain to be determined about the overall process for modifying the ACMG uniform panel, including (1) how to get the word out about the process (call for proposals, liaisons); (2) what decision-making process should be used for the full Committee and its subcommittees (e.g., how to resolve disagreements); (3) details about the ad hoc working groups (e.g., selection process, size, timeline, selection of subcommittee liaisons); and (4) HRSA's process for implementing the Committee's recommendations to modify the conditions in the uniform panel.

Nomination forms. Dr. Rinaldo explained the proposed nomination forms for proponents to nominate conditions to be added to the uniform panel would include the following components: (1) a cover letter, giving latitude to the proponent to explain why the condition should be added to the uniform panel; (2) a 4-page "Nomination of Condition—Score Card," including a list of criteria and scores used to evaluate conditions in the ACMG newborn screening report and a worksheet listing reference conditions in the ACMG uniform panel (green pages); and (3) a 2-page "Nomination of Condition—Fact Sheet" for listing and scoring the condition(s) being proposed for inclusion in the uniform panel.

Dr. Becker concluded the presentation by noting that a strength of the proposed nomination process is that it would apply the same metrics to candidate conditions that were used in the ACMG report. Thus, it would retain the consistency of the evaluation process, something which Dr. Pickering had emphasized the importance of consistency during his presentation on the practices used by the ACIP.

D. Discussion of Committee Decision-making

Following the presentation by Dr. Rinaldo and Dr. Becker, Committee members spent considerable time discussing both (1) the process of getting conditions nominated for consideration by the Committee for inclusion included in the ACMG uniform newborn screening panel; and (2) the overall process and criteria that the Committee will use to modify the conditions included in the uniform panel. At the conclusion of the discussion of those topics, Dr. Boyle raised a new, unrelated topic—the need to harmonize the work of the full Committee and its subcommittees.

1. Proposed Form for Nominating New Conditions for the ACMG Uniform Newborn Screening Panel

Several Committee members raised concerns that the proposed nomination forms—the 4-page Score Card and the 2-page Fact Sheet—would be overwhelming to people. Dr. Boyle, Dr. Kahn, and Dr. Hawkins agreed that the form should be much simpler.

Dr. Boyle noted that the nomination form should be transparent and explicit, and she suggested using the 2-page Fact Sheet as the nomination form. Dr. Rinaldo said he had no particular attachment to the forms, although he thought that proponents should have to provide at least some

minimal evidence in support of the nomination so that the Committee was not swamped by nominations without merit.

Dr. Kahn commented that the proponents of adding a condition to the uniform panel would not be objective enough to answer the types of questions that were posed in the forms (e.g., whether the burden of disease was profound, severe, moderate, mild, or minimal) and that such questions ought to be addressed by a more objective group. Dr. Hawkins said the nomination process should be simpler and suggested that perhaps when an ad hoc working group was formed to review and report back on the evidence to the full Committee, that working group could fill out the 4-page Score Card.

Dr. Green noted that the Committee seemed to be coming to a consensus that the 2-page Fact Sheet was more along the lines of what the nomination form should look like in terms of ease of submission for proponents of adding new conditions. She suggested that the Committee use the 2-page Fact Sheet for the nomination form and ask a small group to tweak it and then present it for approval at the Committee's next meeting. Dr. Howell agreed there seemed to be a general consensus among Committee members that the scoring system should not be used in the nomination form and that something along the lines of the 2-page Fact Sheet should be used as the nomination form.

Dr. van Dyck agreed that the nomination form should be simple but emphasized that it should match the criteria that will be used to evaluate the nomination. The nomination form also should enable HRSA to ascertain whether the nomination is of a high enough priority to accept. Dr. Dougherty and Dr. Boyle agreed with Dr. van Dyck, emphasizing that the criteria used for the nomination forms should parallel the criteria used by the Committee in evaluating whether conditions should be added to the uniform newborn screening panel. They noted that the same criteria should be used at every level of review, although the depth of review would vary.

Dr. Rinaldo suggested that the Committee as a whole go over the criteria for the nomination form. Dr. Howell suggested the Committee might begin looking at the criteria in the remaining time for the day. Dr. van Dyck said he thought it was unfair to try to determine the criteria in such a short time and recommended that the Committee spend its remaining time at this meeting working through changes in the flowchart for modifying the uniform panel and figuring out where in the process criteria would be needed. Then it could ask a subgroup of the Committee to work on developing those criteria in the next couple of months. Dr. van Dyck's suggestion was accepted.

2. Proposed Flowchart of the Overall Process and Criteria for Modifying the ACMG Uniform Newborn Screening Panel

Dr. Howell asked Committee members to comment on the flowchart of the proposed process for the Committee to use to consider adding new conditions to the ACMG uniform newborn screening panel.

Dr. Coggins asked whether the proposed process outlined in the flowchart would allow for the consideration of new technologies, new analytes, or new markers that might allow for improved screening for conditions included in the uniform panel. Dr. Rinaldo replied that the proposed process did not allow for the nomination and consideration of new platforms but indicated that the process might be modified to allow for this.

Dr. Becker suggested a change to the flowchart, noting that if HRSA had a nomination that was properly presented, it might be good to allow HRSA to bypass the Committee and send things

directly to the ad hoc working group that is evaluating the evidence. The ACIP does this in its process, and USPSTF does something similar. The ad hoc working group could then make a report to the full Committee on the evidence so that the Committee could make a recommendation.

Other Committee members agreed with Dr. Becker's suggestion. Dr. Kahn said he liked the idea of bypassing the full Committee and having HRSA send things directly to the ad hoc working group. Dr. Green noting that the pace of the development of vaccines is fairly slow, but there is no shortage of disorders that one could potentially screen newborns for, agreed that it might be good to get some questions directly to the ad hoc working group that is evaluating the evidence.

Dr. Dougherty indicated that she was pleased that the Committee seemed to be moving closer to a systematized process for evaluating new conditions for inclusion in the uniform newborn screening panel. Setting the stage for much of the Committee's subsequent discussion of the flowchart, she also asked a few questions:

- Who will evaluate the evidence? What role, if any, will the Committee's three subcommittees play in the evaluation process?
- What criteria are to be used in the evaluation?

Who Will Evaluate the Evidence? Questioning the wisdom of using ad hoc working groups to evaluate evidence in light of Dr. Atkins' report that the USPSTF has found over time that using an external group to evaluate evidence for each condition, Dr. Dougherty asked Dr. Rinaldo to clarify the nature of the ad hoc working groups proposed in the flowchart.

Dr. Rinaldo said that the details of the ad hoc working groups remained to be worked out. He said he would not be surprised if there were 10 legitimate nominations for additions to the newborn screening panel at once and asked: Would the Committee have to set up one ad hoc working group at a time, or could it set up several at once? He asked HRSA to comment on resources and logistics for the ad hoc working groups.

Dr. Dougherty noted that there are many mechanisms in the Federal Government that could be used to cope with the workload (e.g., evidence-based practice centers and task order contracts) and emphasized that her concern was that the evidence reviewers in ad hoc working groups with liaisons from each of the Committee's three subcommittees would not be sufficiently independent of the Committee.

Dr. van Dyck reported that HRSA had been considering what mechanisms the Committee should adopt to evaluate evidence and having discussions with various people about this.

- One model for evaluating the evidence is the ACIP model discussed by Dr. Pickering: the ACIP tends to form ad hoc working groups around specific areas that that are led by a CDC staff member and include members from the committee, liaison members, and outside experts.
- Another model for evaluating the evidence is the USPSTF model discussed by Dr. Atkins: USPSTF tends to rely on an external, independent, outside-contracted, evidence-based review group that does reviews on a regular basis.

For the ACHDGDNC , Dr. van Dyck said, HRSA is leaning more toward the USPSTF model of contracting with an independent, external group to review the evidence. Such a group, which would be separate from the Committee, would do evidence-based reviews on a regular basis and

make verbal and written presentations about the evidence to the Committee, with an opportunity for questions in a public forum. An external evidence review group will probably be more expensive than an internal evidence review group, Dr. van Dyck said, but the benefits such a group brings may be worth the extra cost. It might be necessary to do one or two evidence reviews to get an idea of what the time and resource requirements would be.

Dr. Kahn, representing AAFP, which participates in both the USPSTF and the ACIP, said he would be very supportive of having the Committee use the USPSTF model. Dr. Boyle was also supportive of the idea of having the Committee follow the USPSTF model of contracting with an independent, external group to review the evidence.

Dr. Boyle and Dr. Dougherty asked for clarification about what the Committee subcommittees' roles would be in evaluating new conditions for inclusion in the uniform panel. Dr. Rinaldo replied that if HRSA asked an independent, evidence-based review group, along the lines of that used by the USPSTF to do evidence reviews, the subcommittees would not have any particular role in the evaluation process. Dr. Rinaldo said he thought there was a consensus at the Committee's April 2005 meeting to have each subcommittee deliberate on each condition, but he added that it was fine with him to streamline the process. Dr. Boyle explained that she was just rethinking the process and how the subcommittees would function in the process.

Dr. van Dyck said he could speak for or against the subcommittees' involvement in the process. In the event that the Committee receives a large number of nominations, the subcommittees might set priorities among them; then the process could loop back to full Committee to make a choice. If the Committee does not receive a large number of nominations, the process could skip the subcommittees and go straight to the ad hoc working group. In addition, Dr. van Dyck said, if the USPSTF model of reviewing the evidence is used, the boxes on the flowchart referring to "ad hoc working group" should be changed to something like "independent evidence review group"; this change would not preclude the involvement of the subcommittees in the evaluation process.

Dr. Becker said his preference would be to have the full Committee retain the option, with deliberations, of sending something either (a) to a structured ad hoc working group or an independent evidence review group; or (b) through the Committee's existing subcommittees. Dr. Kahn agreed that the full Committee might want to retain the option to go to its three subcommittees —and might exercise that option at some point—but he noted that if the external, evidence review group is truly independent and truly does a good job in its review, the subcommittees would seldom need to be involved in the evaluation. Dr. Rinaldo, reminding Committee members that one reason for adding members to the subcommittees was the expectation that there would be a role for these members on the ad hoc working groups, asked: Is the Committee changing its mind about the role of the subcommittees?

Dr. Edwards said he believed that there should be a couple of representatives from the Committee on the ad hoc group evaluating the evidence related to newborn screening. A representative from the Committee would be helpful in explaining the decisions of the group evaluating the evidence to the Committee as a whole. Dr. Kahn agreed with Dr. Edwards that having a liaison from the Committee for the purposes of communication and clarification would be useful, but said that otherwise the involvement of Committee members on the evidence review group should be minimal. Dr. Becker said that having representatives from the full Committee available to provide support to the ad hoc working group, but not to vote, was probably appropriate.

Dr. Becker asked Dr. Kahn to comment on what he thought the nature of the evidence review group's report back to the Committee should be. Dr. Kahn said he supports the USPSTF model

with the independent evidence-based practice centers, noting that the people who do the evidence reviews do them over and over using the same criteria. The reports to the full USPSTF are presented in a standard format and always use the same criteria and same weighting scheme. These reports allow the USPSTF to deliberate on the tough questions, the subjectivity, the rating, the ranking, the prioritization, etc., and make a decision.

To illustrate how the USPSTF evidence review process feeds into the recommendations, Dr. Dougherty referred to one of Dr. Atkins slides. The USPSTF, giving as its rationale that there was insufficient evidence to determine whether the harms of routine screening for prostate cancer using prostate-specific antigen (PSA) outweighed the harms, gave routine screening for prostate cancer using PSA testing an "I" recommendation, which means leave it up to the clinician to decide. The review of the evidence in this case indicated how well the PSA screening test performs, what the benefits of screening with that test might be in terms of outcomes from treatment, and what harms might occur because of the screening test or the treatment or the diagnostic procedures. Dr. Kahn noted that the one paragraph that Dr. Dougherty cited was a very concise summary of what would be the report from the evidence review group.

Dr. Howell asked for further comments on whether the Committee should be represented on the evidence review group, as suggested by Dr. Edwards. Dr. van Dyck said that he had no problem with having a liaison to the evidence review group; although he did not think it would be necessary. When asked for clarification of what the role of the person being discussed would be, Dr. Edwards said that what he had in mind was a couple of people serving as liaisons from the Committee to the evidence review group.

Dr. Boyle reported that her experience participating in the data gathering as part of some of the USPSTF topic areas led her to think that there could be some Committee members who would help oversee the evidence review process. The guidance was on global issues and on more specific issues. Dr. Howell asked for further comments, and both Dr. Brower and Dr. Hawkins indicated that they agreed with Dr. Boyle. Dr. Howell concluded by saying that there was 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.

Dr. Rinaldo indicated that he would change the flowchart to say "Committee approval to form or empanel an evidence review group" and to reflect other changes that had been agreed upon during the discussions. Dr. Becker, noting that the original flowchart had the subcommittee recommending not to send a proposal for an evidence review with a dashed red line back to the start, proposed eliminating the dashed red line back to the start and making the full Committee (not the subcommittee) body to recommend for or against forming an evidence review group. No one objected to this change.

Dr. Becker made the following motion, and it passed unanimously with no further discussion.

> ***MOTION: The Committee accepts the flowchart [of the process for adding conditions to the uniform panel] with the changes discussed as its process for nominations of conditions for newborn screening.***

What Criteria Are To Be Used in the Process of Considering Whether To Add New Conditions to the Uniform Panel? The Committee engaged in an extended discussion of what criteria the Committee should use to evaluate whether conditions should be added to the ACMG uniform newborn screening panel.

Dr. Boyle, following up on a point made earlier by Dr. van Dyck, emphasized that the criteria the Committee presents to the public as the criteria by which a nomination will be evaluated should be the same criteria used throughout the evaluation process. Thus, whatever the criteria are specified in the nomination form should be the Committee's criteria overall. Dr. Howell concurred that proponents of adding conditions to the uniform screening panel would need to know at the time the submitted their nomination what criteria will be utilized in the evaluation.

Dr. van Dyck said that he would hope that the following three sets of criteria would be developed and be similar:

1. Criteria for the nomination form
2. Criteria for HRSA's acceptance or rejection of the nomination form
3. Criteria for evaluation of the condition by evidence-based workgroup

Dr. Becker said that he would not expect HRSA to make a decision to decline a nomination unless it just did not meet the nomination criteria or the form was not correctly filled out. Dr. Howell said he would interpret that step the same way—as a purely administrative rejection. Dr. Rinaldo said that there probably would be nominations that probably don't have much scientific or medical merit and he thought those would be fairly easy to weed out. Dr. Hawkins suggested that one criterion that HRSA could use for deciding whether to send the nomination forward if the simpler nomination form were used would be the existence of a test for the condition. If there is no test, the nomination of the condition probably should not go forward for a recommendation by the full Committee. Dr. Kahn concurred and suggested that there might be additional criteria that HRSA should consider in the first step.

Dr. Dougherty asked: Where do we set up the criteria to give to the evidence reviewers? The forms distributed by Dr. Rinaldo were just a start, she said, because Dr. Atkins had said that it was necessary to separate costs from effectiveness, not just have one overall score. She said she thought it was clear, even when the Committee agreed to send the letter to the HHS Secretary, that the Committee needed to reexamine the criteria. Dr. Atkins had said the domains were the right domains, but if the criteria within those domains are not the right criteria, it was all folly.

Dr. Rinaldo took issue with the suggestion that the criteria used in the ACMG newborn screening report were faulty. He said he believes the criteria are sensitive, complete, and cover all the aspects that need to be addressed. Furthermore, he thinks that no one had made a cogent, credible argument about the fallacy of the criteria. He would like to have discussion of each criterion and where the problems lie. Dr. Dougherty said she agreed with Dr. Rinaldo that the Committee ought to discuss the criteria and the scoring one by one, because that is the starting point. The letter to the HHS Secretary from the Committee said the process and criteria used in the ACMG report was the best available at the time, but that the Committee recognizes that the process needs to evolve.

Dr. Howell asked Dr. Dougherty to elaborate on the difference between criteria and domains. In response, Dr. Dougherty explained that a "domain" would be, say, the incidence of a condition or the burden of disease. Dr. Howell said that is also listed on the sheet as a criterion. Dr. Dougherty replied that the "criteria" really are for inclusion of the scores that are given based on these breakouts. Dr. van Dyck interjected that Committee members did not all seem to be thinking of the same thing when they talked about a process or a criteria or a domain. He emphasized that the Committee needs to make clear what it calls criteria and what it calls a process. He thinks of "criteria" as 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. He said his recollection was that there not much controversy about the domains, but there was controversy about the scoring process.

Given the sensitivity about the scoring that green sheets bring up, Dr. van Dyck said, it might be a good idea for the Committee to start with Dr. Atkins's suggestions about what he called criteria and domains and then see how the ACMG criteria fit into those. Probably most of the criteria would fit and the difficulties would center on the scoring—whether something should be score 100 or 50, or even scored at all.

Dr. Dougherty said that she completely agreed with Dr. van Dyck's suggestion. Her concern was that the Committee was proceeding with a process where the underlying feature were these criteria and scoring approach, which is what she thought she heard Dr. Rinaldo say. She agreed that the scoring was a problem, noting that evidence-based practice centers do not use scores. Dr. Rinaldo said if the problem is with the relative weight of the criteria and the way they were scored rather than the criteria themselves, he would have no objection to revisiting the scoring process.

Dr. Dougherty explained that she would like the Committee go to the kinds of big categories suggested by Dr. Atkins, then agree on which are the most important domains that this Committee wants to look at, and then look at the criteria within those domains. She would like the Committee to decide and vote on whether to come up with new criteria. Dr. Rinaldo said he had listened very carefully to Dr. Atkins and there would be nothing different.

Dr. van Dyck noted that although the Committee might end up with about the same number of very similar criteria—and thus end up affirming the quality of what had been done in the ACMG report—having the Committee go through the process suggested by Dr. Dougherty would give the Committee more ownership and buy-in to the criteria, and the process would be more transparent to the public. Dr. Rinaldo said that although he saw no evidence for blanket criticisms of the criteria, he recognized there was always room for improvement and would be happy to participate in the process of improving the criteria.

Following up on Dr. van Dyck's earlier suggestion, Dr. Boyle suggested that a smaller workgroup of the Committee meet to discuss the criteria and come back and present a revised group of criteria/scores at the Committee's next meeting. At Dr. Howell's request, five Committee members—Dr. Boyle, Dr. Dougherty, Dr. Rinaldo, Dr. Green, and Dr. Coggins—agreed to meet and present a revised group of criteria to the full Committee at its February 2006 meeting. Dr. Brower suggested that the Criteria Workgroup ask one of the parents to review the nomination form to make sure that it was not too burdensome. Dr. Brower also asked that the workgroup distribute something for the full Committee to review before the next meeting, so that Committee members could come ready to have an active discussion. Dr. Howell agreed that this would be helpful. He said the Criteria Workgroup could convene by whatever mechanism it chose so that it could prepare something for distribution prior to the February 2006 meeting. Dr. Lloyd-Puryear said that HRSA would assign staff to help with the effort.

3. Harmonizing the Work of Committees and Subcommittees

Finally, Dr. Boyle raised a new topic related to the Committee's decision-making processes—the need to harmonize the work of the full Committee and its three subcommittees. Dr. Boyle indicated that the work of the Follow-up & Treatment Subcommittee that she chairs is a bit overwhelming with all of the issues involved. She noted that the work of the subcommittees and

the full Committee seems to be very different, and she is not quite sure how to align the two. She said she hopes that the Committee will address this topic at some point.

Dr. Howell asked the chairs of the other subcommittees to comment. Dr. Brower, who chairs the Laboratory Standards & Procedures Subcommittee, pointed out that the subcommittees were just getting started—they just got their charters approved—and the full Committee had been focusing quite heavily on the ACMG report. She thinks that in the future, the work of the Committee and its subcommittees will become more closely related.

Dr. Becker acknowledged the disconnect between work of the full Committee and its subcommittees but agreed with Dr. Brower that the process would work out over time. He indicated that it might be helpful for the full Committee to help with setting priorities for the subcommittees to keep them from being overwhelmed with issues.

Dr. Dougherty raised a question about what the outcome of the work of the subcommittees is supposed to be. As a member of the Follow-up & Treatment Subcommittee, she said, she had gone back to see what reports had been written on barriers to follow-up and treatment. There are many reports on this, and if the subcommittee just comes out and lists them and identifies options for overcoming them—something that the AAP has already done—what good will that do? And what if no one acts on the recommendations made by the Laboratory Standards & Procedures Subcommittee? Dr. Becker noted that the Committee's recommendations are advisory, but the Committee also advises on grant programs. He is very excited about the Regional Genetic Services and Newborn Screening Collaboratives funded by HRSA and thinks that the Committee should make recommendations related to them. Dr. Howell indicated that the Committee would continue to discuss these topics.

IV. STATUS OF THE STATES—UPDATE ON NEWBORN SCREENING PROGRAMS

Bradford Therrell, Ph.D.
University of Texas Health Science Center at San Antonio
National Newborn Screening and Genetics Resource Center (NNSGRC)

Changes in Newborn Screening in the States Since 2000. At the outset of his presentation, Dr. Therrell presented a series of U.S. maps of showing changes in the number of disorders mandated for newborn screening by the States beginning October 2000, then in May 2001, March 2003, May 2004, and October 2005. Although these maps count hemoglobulinopathies as one disorder and the recently completed ACMG newborn screening report counts them as three, he noted, the maps do reveal what has happened with respect to newborn screening in recent years. This was something that Committee members had indicated at a previous meeting they would like to see.

In October 2000, Dr. Therrell said, everyone was talking about 8 disorders, not the 29 disorders included in the recently completed ACMG report. In October 2000 and May 2001, only 8 States were mandating newborn screening for more than 8 disorders. By March of 2003, things were really beginning to crank up a little bit, with 16 States mandating screening for more than eight disorders. By May 2004, when the ACMG report was being discussed, the States clearly began reacting to the discussion: 28 States were mandating screening for more than 8 disorders. As of October 2005, 36 States mandate newborn screening for more than 8 disorders; no States mandate screening for only three disorders. About 36 or 37 States are currently using tandem mass spectrometry (MS/MS) in newborn screening.

In response to Dr. Therrell's request for questions, Dr. Dougherty asked how the NNSGRC is tracking newborn screening for the 24 secondary conditions in the ACMG report. Dr. Therrell responded the NNSGRC is tracking screening for these conditions and putting the information on its Web site. The Web site (http://genes-r-us.uthscsa.edu/) lists the 29 core conditions recommended in the ACMG report and indicates whether States are mandated to screen for each condition 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. NNSGRC has an indicator for every State for every one of the 29 core conditions and every one of the 24 secondary conditions. The Web site also lists 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. Committee members can download all this information from the NNSGRC Web site, or if Committee members want, NNSGRC could distribute the information as a three-page handout at each meeting.

Dr. Edwards said he would have thought that the States that screened newborns for the 29 core conditions in the ACMG uniform panel would also be screening for the secondary conditions because they had to evaluate for the secondary conditions in order to completely eliminate the core conditions. Dr. Therrell said there is no consensus among the States about listing all the conditions. Dr. Rinaldo thanked Dr. Edwards for his comment and emphasized that with the exception of two conditions, everything included in the secondary grouping is part of a differential diagnosis of one of the primary conditions.

Changes in Newborn Screening in the States in the Last 90 Days. Dr. Therrell next discussed responses to a request from NNSGRC to State newborn screening programs' laboratory and follow-up components asking them to report any significant activity in the last 90 days that they would like to have reported to the Committee:

- Alaska, which began screening for carnitine palmitoyltransferase I (CPT-I) deficiency in October 2003, has now confirmed 22 cases of CPT-I, all Native Alaskans—an incidence of 1 in 225 Native Alaskan births. Alaska's Newborn Screening Advisory Committee has created a cystic fibrosis (CF) task force to consider issues related to CF screening. (Dr. Rinaldo explained that CPT-I is the main step in fatty acid regulation, and the manifestations of CPT-I deficiency include severe liver disease, hypoglycemia, maternal complications of pregnancy, and sudden death. One ethnic group in Alaska has this disorder, but the disorder is quite rare everywhere else.)
- Colorado has completed its NNSGRC program review and is planning implementation in the spring of 2006.
- Florida began biotinidase screening throughout the State on Oct. 1, 2005.
- Iowa began CF screening in July 2005, and after Hurricane Katrina began receiving Louisiana's newborn screening specimens. Iowa has temporary staff in place to maintain testing for several months. It is participating in a national public service project to retest Louisiana babies whose tests are uncertain.
- Maine's Newborn Screening Advisory Committee recommended that the 19 optional tests currently offered as part of the required screening panel be offered as part of the required screening panel on January 1, 2006.
- Mississippi, though devastated by Hurricane Katrina at the end of August 2005, had no significant problems in newborn screening as a result of the hurricane. The specimens

from newborn screening were tested out of State by Pediatrix Inc, and a courier was used to transport them.

- New Jersey's Newborn Screening Annual Review Committee made recommendations to the commissioner for a computer system upgrade, training of current lab personnel, and hiring better trained lab personnel. The State is also reviewing parent and professional literature in light of the ACMG report.
- Pennsylvania Senate Bill 901 (introduced Oct. 5, 2005) further defined disease in their law by adding "testing for severe combined immunodeficiency" (SCID). It is the first State to talk about SCID.
- Rhode Island is preparing for regulatory hearings to expand its newborn screening program to encompass the 29 conditions in the ACMG uniform panel in July 2006. Currently, the State screens only for medium chain acyl-CoA dehydrogenase deficiency (MCAD) and amino acids.
- South Carolina is expanding its data reporting system so that in the next few months it will have the ability to give primary care providers Internet access. It also is hoping to expand that to newborn screening.
- Texas is under a legislative mandate to reexamine its newborn program and make decisions so it can expand by 2006. The State has been meeting with partners for obtaining bids to outsource the program. The bidder would have to be 10 percent lower than the State to get the bid.
- Washington's Board of Health, in October 2005, gave approval to file a rule to add CF to its newborn screening panel and to begin a process of evaluating 16 conditions for inclusion ins it screening panel (the reminder of 29 core condition in the ACMG report).

Update on Screening Newborns for the 29 Core Conditions in the ACMG Report. Dr. Therrell showed an October 2005 U.S. map showing the status of newborn screening in the States in terms of the 29 disorders in the ACMG uniform panel. Seven States require or universally offer newborn screening for fewer than 10 disorders; 11 States, for 10 to 19 disorders; 2 States, for 23 to 25 disorders, 4 States, for 26 disorders; 5 States, for 27 disorders; 13 States, for 28 disorders; and 9 States, for all 29 disorders in the ACMG report's core panel. States that require or universally offer newborn screening for 28 disorders generally do not include hearing screening.

Hurricane Katrina Action. Finally, Dr. Therrell talked a little bit about hurricane disaster action in the wake of Hurricane Katrina, which hit New Orleans on Aug. 29, 2005, and devastated Mississippi. Louisiana's newborn screening laboratory, is located in downtown New Orleans in a building near the Superdome, and had 5 ft. of water in basement and no electricity or water after the hurricane.

On Aug. 31, 2005, the people in the Louisiana newborn screening program were able to start 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 at no charge. On Sept. 1st, they contacted the Emergency Management Assistance Compact (EMAC), a mutual aid agreement and partnership that offers a quick and easy way for States to send personnel and equipment to help disaster relief efforts in other States and jurisdictions, and submitted an "Interstate Mutual Aid Request." This was brokered by the Association of Public Health Laboratories. Iowa was given the newborn screening mission after the Labor Day weekend and began receiving samples on September 8th. What happened to specimens between August 29th and Sept. 6th and specimens sitting around when the hurricane hit is not known, but the question is currently being pursued.

Dr. Therrell reported that the people he has talked to in Louisiana and Iowa and at the Association of Public Health Laboratories has been complimentary about the process and about the Federal Emergency Management Agency (FEMA). The issues that arose were of three types: operational, implementation, and other:

- *Operational issues.* These issues included merging State systems (test menu, specimen timing, data collection, data reporting, follow-up); and increased capacity at the Iowa laboratory for testing and data entry.
- *Implementation issues.* The Association of Public Health Laboratories facilitated linking activities. Louisiana received multiple offers of assistance, including offers from private companies such as Pediatrix. EMAC was used for public health emergency response. The major issues had to do with the screening panel and how to report the results back. For confirmatory testing, help came from labs at the University of Miami, Maryland, and the District of Columbia. After a month of screening (9/8 to 10/7), results on 4,983 newborns were obtained; out of 35 presumptive positives (most of which were hemoglobinopathies), there was one confirmed case of phenylketonuria (PKU).
- *Other issues.* Payment for screening activities not yet resolved; the assumption is that EMAC will assist. The pharmacy for distribution of metabolic formula relocated from New Orleans to another city, and payment issues remain. Louisiana's follow-up staff had evacuated and had to be relocated. Hospitals have been slow reopening; and some screening specimens have been found holding at hospitals; also some specimens have been found mistakenly sent to different areas. About 700 samples are unaccounted for, and there is an ongoing effort by the Centers for Disease Control and Prevention (CDC), Iowa, and others to locate the unscreened infants.

Questions & Comments

Following Dr. Therrell's presentation, Dr. Howell asked what percentage of newborns are getting an expanded panel of newborn screening tests—that is, 25 or more tests. Dr. Rinaldo replied 58 percent, and Dr. Therrell said that the percentage had not changed since the last meeting.

Dr. Howell also asked about what was going on in Florida, which has a mandated expanded panel but is still not on the radar screen. Dr. Therrell explained that Florida was expanding slowly from Jacksonville out, building capacity as it goes. Dr. Rinaldo said he had been working with Florida and understood that they were really trying to expedite the expansion to cover the entire State, but right now the coverage is primarily in the north. He expects that the mandate will be implemented in the entire State within the next year. Dr. Therrell observed that Florida is not the only State that has mandated screening but that is not yet doing it.

Noting that Dr. Howell had indicated that the Committee would be discussing the possibility of additional liaison members to the Committee—specifically, from the DoD and the FDA, Dr. Green suggested to the Committee that some additional organizations be considered for liaison status:

- Infectious disease organizations
- Pediatric neurology organizations (because many children diagnosed by newborn screening are taken care of by pediatric neurologists)
- The American Medical Association (which has a "smoldering" interest in newborn screening that might be useful)

Dr. Boyle recommended that the U.S. Department of Education, which has an early intervention program, also be considered for liaison status.

Dr. Howell asked Dr. van Dyck and Dr. Lloyd-Puryear to clarify how the Committee decides upon liaison representatives. Dr. van Dyck explained that the process depends on the Committee's recommendations and ability to accommodate liaison representatives, but suggested that the Committee collect ideas formally and set priorities. Dr. Howell asked Committee members with suggestions for liaison organizations to write him a letter recommending them, so that the Committee could discuss them further at its next meeting. Dr. Rinaldo said he thought that the Committee should wait for organizations that want to send a liaison representatives to initiate a request to do so. Dr. Howell explained that DOD, FDA, and the pediatric neurologists had already initiated a request to send liaisons to the Committee.

V. COMMITTEE BUSINESS—SUBCOMMITTEE MEETINGS & REPORTS

The Education & Training Subcommittee, the Follow-up & Treatment Subcommittee, and the Laboratory Standards & Procedures Subcommittee of the Advisory Committee held meetings that were open to the public from 8:30 a.m. to 11 a.m. on Friday, Oct. 21, 2005. Subsequently, the chairs of each subcommittee reported to the full Committee.

A. Follow-up & Treatment Subcommittee Report

Chair:
Colleen Boyle, Ph.D., M.S.
Associate Director, Science and Public Health Team
National Center of Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention (CDC)

Dr. Boyle reported that Dr. Tim Hoff, from the State University of New York (SUNY)–Albany, was an invited guest at the Follow-up & Treatment Subcommittee's meeting and gave a presentation that was very helpful in terms of trying to identify some of the challenges with long-term follow-up. Dr. Hoff has been involved with Dr. Brad Therrell on a project to assess long-term follow-up from State newborn screening programs. The subcommittee had a very lively discussion about some of the policy implications from his work in the areas of defining the responsibilities for short-term and long-term follow-up and the impediments that State health departments face. And these are to try to identify and reconcile contradictions that appear to exist between the theory of long-term follow-up and what is actually happening in reality. Dr. Hoff's work is evolving, and the subcommittee will continue to involve him in its deliberations.

The Follow-up & Treatment Subcommittee has established four workgroups around the issues the subcommittee has been charged with addressing. The Follow-up & Treatment Subcommittee's charge is to engage in a multi-step process that:

- Identifies barriers to short and long-term follow-up and treatment of newborn screening results specific to the challenges in integration of health care systems, financing of services, and information systems;
- Develops recommendations for overcoming identified barriers in order to improve short and long-term follow-up results; and

- Recommends mechanisms for establishing accountability for newborn screening follow-up guidelines.

At Dr. Boyle's request, a representatives of each workgroup—integration of health care systems, financing for follow-up, impact on families and caregivers, and information systems—reported to the full Committee.

1. Workgroup on Integration of Health Care Systems—Dr. Dougherty. Dr. Dougherty reported that the workgroup on the integration of health care systems had discussed a draft partial preliminary report that she prepared. The draft document put newborn screening follow-up issues in the context of the rest of the health care system and its challenges in integration; then in the context of children with special health care needs and their challenges in getting integrated services. The document also discussed the elements of the short- and long-term follow-up for newborn screening and barriers to achieving the goals of short-term and long-term follow-up. People thought the draft document was a fairly good start. They had some wonderful suggestions about how to improve it and also volunteered to look at the electronic version and fill in more of the elements of short- and long-term follow-up and some of the barriers to achieving those goals. It was agreed that it would be good to have someone look at the report from the State newborn screening program perspective, because there is nobody with that perspective on their group. People are to give their comments and suggestions on the document to Dr. Dougherty by mid-November. The workgroup will have a conference call in early January 2006 to finalize the document or at least have another discussion about the document on barriers. Eventually, the workgroup hopes to develop recommendations to overcome the barriers. Dr. Boyle added that eventually she would like to have something tangible that could be related to policy that might help with achieving measurable milestones for short- and long-term follow-up.

2. Workgroup on Financing for Follow-up—Dr. Therrell. Dr. Therrell reported that the workgroup on financing for newborn screening follow-up began by asking for some guidance about where it should go: Is the question about financing follow-up in treatment or bigger financing issues? Financing permeates everything. There are questions about fee structures and so many different policies around the country related to financing that the workgroup thought that perhaps one of the best things that might happen would be to have a national meeting of State representatives to discuss financing issues and to have people who have successful parts of financing strategies talk about how they achieved their successes and whether their models might be applicable in other States.

3. Workgroup on Impact on Families and Caregivers—Ms. Jill Levy-Fisch. Ms. Levy-Fisch, the National Director of Education and Awareness, Save Babies Through Screening Foundation, said she had contacted six or seven advocacy groups to ask about the needs of families and caregivers for follow-up and treatment and then prepared a written report on her findings. As summarized in her written report, Ms. Levy-Fisch found that families have a number of needs. Parents have to constantly battle insurance companies for formula coverage and are not always successful. Some families are not receiving positive screening results in a timely manner, so their babies die or suffer a crisis. After diagnosis, many pediatricians do not have the information that parents need. Clinical staff and physicians, as well as parents, need to be educated about the purpose, results, and importance of newborn screening tests. Many families have had issues with their early intervention programs. Coordinators do not seem to have enough knowledge to solve problems as they arise, such as feeding and oral motor issues. Families expressed a great desire for a medical home. Many families are trying to coordinate services and specialists for their children, and they feel extremely burdened and overwhelmed. Many families are managing care on a daily basis they are feeling overwhelmed, exhausted and isolated. They desperately need

respite care. There is a severe lack of specialists to care for these children. Many insurance plans do not pay for specialists out of State. Medicaid reimbursement for home nursing care is very poor and getting quality care is an issue. Most metabolic specialists are pediatric specialists, and older patients do not feel comfortable visiting pediatric clinics for treatment. The issues older patients face are much different from those faced by infants. Ms. Levy-Fisch said that she would send her full report to the full Committee and update it as she gets additional responses.

4. Workgroup on Information Systems. Dr. Boyle reported that she had contacted Dr. Alan Hinman to address some of the information technology integration issues in terms of major issues and hope to use him as a consultant to arrive at some recommendations in this area.

B. Education & Training Subcommittee Report

Chair
William J. Becker, D.O., M.P.H.
Medical Director
Bureau of Public Health Laboratories
Ohio Department of Public Health

Dr. Becker begin his presentation by reminding Committee members that the Education and Training Subcommittee's approved charges are as follows:

- Review existing educational and training resources for health professionals, parents, screening program staff, hospital/birthing facility staff, and the public.
- Identify deficiencies and make recommendations for action regarding the five groups.

The Education & Training Subcommittee has recently undergone several changes in its membership. The former chair of the Education & Training Subcommittee Dr. Jennifer Howse completed her term on the Committee on Sept. 30, 2005, and she asked Dr. Becker to serve as the new subcommittee chair. Dr. Hawkins remains a member of the subcommittee.

In addition, the subcommittee now has three members who represent organizations: Dr. Edwards from AAP; Dr. Tony Gregg from ACOG; and Dr. Norman Kahn from AAFP. Other positions on the subcommittee to be filled in the not too distant future include a representative of parents, a representative of a newborn screening program, a representative of a screening birth facility, and a representative of nurses/midwives.

In the first part of the subcommittee meeting, organizational representatives from AAFP and AAP updated the subcommittee on their educational and training activities. Dr. Kahn noted that AAFP, as had been reported previously, has a program called Annual Clinical Focus (ACF), which focuses on educating its members about a single topic for an entire year. The 2005 ACF program is on Genomics, developed with 19 partner organizations. One of the modules in the ACF Genomics program is newborn screening. The newborn screening module, which is up on the AAFP's Web site at www.aafp.org, was designed for physicians, but it is likely that it could be used with newborn screening program staff as well as birthing center staff, and the subcommittee is going to look at that. Dr. Becker has given subcommittee members an assignment to review the AAFP newborn screening module and make comments on it about its utility, especially for other groups, in the near future.

Ms. Anne Gramiak from AAP reported that the newborn screening parent and provider materials that AAP and other professional organization have been working on with HRSA's Maternal Child

Health Bureau (MCHB) and Dr. Terry Davis and her colleagues at Louisiana State University will be released in early November 2005. At Dr. Edwards' request, AAP has devised an evaluation process for these materials in the form of a survey, as was requested at the subcommittee's previous meeting. AAP is also working on the development of a policy statement in the form of what they call a clinical report on newborn screening and the medical home.

Although Dr. Tony Gregg from ACOG was not present at the subcommittee meeting, Dr. Becker said that he had heard of several activities that ACOG has been involved in. As reported at the last subcommittee meeting, ACOG entered into a subcontract with HRSA/MCHB to work on the final development and dissemination for field-testing of the newborn screening educational materials for parents and providers developed by HRSA and Dr. Terry Davis and her colleagues.

In addition, Dr. Becker noted that he had heard from Ms. Gilian Engelson from NIH, who had given a presentation in July 2005 about a consortium of Federal agencies that are developing information about their activities in newborn screening education. Ms. Engelson e-mailed to say that she did not have anything to report at this meeting, but they are putting together a matrix of gaps identified that they expect to be ready to share with subcommittee members by the time of the next meeting of the Committee in February 2006.

The Education & Training Subcommittee discussed broadening its consideration of how to distribute printed resources on newborn screening to the general public. It also discussed the need to consider how to offer education about newborn screening to people who are illiterate, deaf or blind. One novel idea that proposed was to ask Google to make its search engine work so that when a person types "newborn screening," it leads the person to generic resources or resources that are appropriate.

The Education & Training Committee also would like to put out for consideration by the full Committee the concept of a public service announcement (PSA) to parents and providers when the HHS Secretary takes action on the ACMG newborn screening report. The subcommittee felt that the message to parents ought to be about the general importance of newborn screening; the message to providers should be about the importance of emerging national recommendations for newborn screening. It also thought that the PSAs might be taken through the association partners perhaps and/or the March of Dimes.

The Education & Training Subcommittee has been focusing a considerable amount of attention to educational issues but will also begin considering training—from State programs, laboratorians, providers, residents, health care workers, etc. It recognizes that there will be overlap with other subcommittees' work in this area.

Finally, the subcommittee suggested that the Committee consider finding a national spokesperson for newborn screening. There clearly are people who would have high visibility, and Dr. Becker said he could think of a couple of people who might be interested and/or willing.

Finally, Dr. Becker indicated that the Education & Training Subcommittee would like to establish more regular conference calls so that members can stay in contact. It also would like to invite Ms. Donna Williams from the NNSGRC to return to the subcommittee's next meeting in February 2006. as a consultant to give her presentation on the survey of States about their policies and procedures for public and professional education related to newborn screening. Many of the current subcommittee members were not present when she gave her presentation to the full Committee.

C. Laboratory Standards & Procedures Subcommittee Report

Amy Brower, Ph.D.
Executive Director
Medical Informatics and Genetics
Third Wave Molecular Diagnostics

Dr. Brower, the chair of the Laboratory Standards & Procedures Subcommittee, reported that the subcommittee had decided to defer work on mechanisms related to assessing the conditions the uniform newborn screening panel to the full Committee and to focus on the subcommittee's two charges related to laboratory procedures and infrastructure services:

- Define and implement mechanisms for the periodic review and assessment of infrastructure services needed for effective and efficient screening of the conditions included in the uniform newborn screening panel
- Define and implement mechanisms for the periodic review and assessment of laboratory procedures utilized for effective and efficient testing of the conditions included in the uniform panel

As its first priority, the Laboratory Standards & Procedures Subcommittee wants to focus on the harmonization of operational lab procedures. Its 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 the subcommittee will be doing is defining better cutoffs by looking at disease range instead of the normal general population. It will be working to compile the experience of multiple laboratories and working with APHL. The goal of the subcommittee's efforts is to be able to develop guidelines or techniques to offset cutoffs, and the subcommittee will present its 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 the subcommittee especially wants to capitalize on all the great efforts that are going on in the regional collaboratives.

One of the Laboratory Standards & Procedures Subcommittee's first priorities for the short term is to design a study to assess the utility of the routine second spot. The subcommittee has formed a working group to address the design of that study, and that group will be working to define the indicators and the criteria for that study

VI. PUBLIC COMMENT SESSION

The following individuals made public statements on the afternoon of Friday, Oct. 21, 2005. The written text of their statements appears in Appendix A.

1. John Adams
Parent & Treasurer
Canadian Organization for Rare Disorders (CORD)

Mr. Adams, a PKU dad from Toronto, Canada, and the brand new Treasurer of the Canadian Organization of Rare Disorders, or CORD, said CORD has adopted a policy on newborn screening that CORD 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.

CORD is the first organization at the national level or the provincial level in Canada to take a position on newborn screening. Canada has no national strategy, activities, or funding for newborn screening. The word "screening" does not appear in any fashion in the Canada Health Act, and Canada has no office of rare disorders at the Canadian equivalent of the NIH; no policy on orphan drugs at the Canadian equivalent of the FDA; and no definition what is a rare disorder at the Federal or the provincial levels.

Using Dr. Bradford Therrell's map showing how many American College of Medical Genetics newborn screening conditions are "required or universally offered" in each State in October 2005 for comparative purposes, Mr. Adams noted that most of the Provinces in Canada currently fall well within the bottom category of screening newborns for fewer than 10 conditions. Some progress is being made, but Mr. Adams looks to best practices in other jurisdictions, including the United States for some guidance. He personally thanked the Committee, the Health Resources and Services Administration (HRSA), and some of the particular participants for being resources and being sources of information and inspiration. He said he hoped they would continue to do their hard work and to keep an eye in terms of the role model that you are serving as an open advisory process for others.

2. Jana Monaco
Parent & Board Member
Organic Acidemia Association

Ms. Monaco, the parent of two children with isovaleric acidemia, thanked the Committee for the continuous opportunity to offer her comments in support of the process of expanding newborn. She urged Committee members not to get too caught up with "evidence base" and to keep in mind facts that are not measured in quantitative means. She also took exception to the suggestion in Dr. Atkins' presentation that parents could be too biased when it comes to the evaluation process of adding disorders to the list. She believes that parents should be viewed as experts and stakeholders.

Ms. Monaco agreed with Dr. Nancy Green that neurologists, if they express an interest, would be useful as liaison representatives to the Committee because of their role in caring for children with organic acidemia and other disorders with neurological issues. In addition, Ms Monaco suggested the possibility of having other specialists involved in managing genetic and heritable disorders—gastroenterologists and metabolic specialists—send liaison representatives to the Committee.

Finally, Ms. Monaco emphasized the importance of staying linked with the network of Regional Genetics and Newborn Screening Collaboratives funded by HRSA and to maintain a methodology of tracking newly diagnosed cases and track the management and care of current cases. She suggested that this should be a key objective in the Advisory Committee's Followup & Treatment Subcommittee.

3. Kelly R. Leight, Executive Director
CARES Foundation, Inc.
Congenital Adrenal Hyperplasia Research, Education, and Support
(statement presented by Mickie Gartzke, Hunters' Hope Foundation)

Ms. Leight raised concerns related to the monopolistic control of certain types of supplies and equipment for newborn screening and asked the Committee to address them. Where these manufacturers of technology, assays or other materials and equipment have quality control problems, shortages, or the like, the States are left in a difficult situation with no where else to turn. The problems that result, she noted, can overwhelm State newborn screening programs that run on limited resources. They also can harm to families and children through false positives/negatives and delays in diagnosis. False positives, in particular can be very damaging as they lead easily to skepticism on the part of the health care community.

4. Cynthia Joyce
Executive Director
Spinal Muscular Atrophy Foundation

Ms. Joyce urged the Committee to review spinal muscular atrophy (SMA) for inclusion in the uniform newborn screening panel as a primary target for newborn screening. SMA, she noted, is one of the most common autosomal recessive diseases and is SMA is caused by a loss function mutation in the SMN gene that results in motor neuron death, muscle atrophy and severe-to-catastrophic loss of function.

The SMA Foundation believes that SMA falls well within the criteria established by the Committee for the development of the uniform newborn screening panel. The mutation causing SMA is detectable by blood sample testing immediately on birth, when symptoms are not apparent; the test for SMA is sensitive, specific, and definitive in more than 94 percent of cases; early detection will ensure that children suffering from SMA will receive the benefits of effective management, including respiratory care, preventive physical therapies and nutritional support; and early detection of SMA will enable clinical trials of agents that may save motor neurons and preserve function for these children.

5. Barbara Trainor
Board Member
Families of Spinal Muscular Atrophy

Ms. Trainor, a board member of Families of Spinal Muscular Atrophy and the founder of the Chesapeake Chapter, one of 25 chapters throughout the country, explained that she is the mother of three children, including her daughter Erin Marie, who lost her life at only 5½ months of age almost 13 years ago to SMA.

At the time of Erin's diagnosis, parents with children diagnosed with SMA had no hope. Today, though, the technology exists to begin screening for SMA immediately, which would allow us to identify SMA children soon after birth. The test is cost-effective and results are available in a timely fashion with a very high rate of accuracy. Although a specific treatment for SMA does not

exist currently, it is true that care plans and supportive care make an important difference for families affected by SMA. Furthermore, Phase II clinical trials are underway around the world. The development of a cure depends heavily on screening newborns in order to identify SMA afflicted children who might participate in clinical trials. Universal newborn screening for SMA is an integral component in the development of a cure.

6. Carol Greene, M.D.
Chair
Society for Inherited Metabolic Disorders (SIMD)

Dr. Green said that SIMD greatly appreciates the ongoing activities of this Committee and is eager to work with the Committee. SIMD continues to emphasize the need for the Committee to address long-term issues related to newborn screening. 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. SIMD also hopes that the Committee will address the need for data collection on outcomes to improve the system as a whole.

SIMD also urges continued efforts to improve the quality of testing in newborn screening. In some States and for some tests, the level of false-positive screens is very high. The newborn screening system succeeds or fails beginning with the quality of the initial screening test, and it is important to seek 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.

7. Andrea Gropman M.D., FAAP
Pediatric Neurologist
Child Neurology Society

Dr. Gropman, noting that there are 1,000 child neurologists in the United States, said that child neurologists struggle with the management of individuals with complex health care needs and wholeheartedly support the Advisory Committee's efforts related to newborn screening and followup. She asked the Committee to consider child neurologists, along with other subspecialists (e.g., endocrinologists, hematologists, and infectious disease specialists), as potential consultants or liaisons, especially in when considering the integration of health services for affected individuals.

8. Claudine Tiffault
Project Evaluator
National Coordinating and Evaluation Center
Sickle Cell Disease Association of America (SCDAA)

Ms. Tiffault made a very brief statement, thanking the Committee for its wonderful work in behalf of sickle-cell disease and urging it to continue this work. She said the SCDAA was very glad to be involved, even at the table with Dr. Telfair, and just to be witness to what is going on.

VII. COMMITTEE BUSINESS

Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children
Professor, Department of Pediatrics
Leonard M. Miller School of Medicine
University of Miami

At the close of the day, Dr. Howell addressed several housekeeping issues before turning to Committee business.

Dates of Future Committee Meetings. The first item was dates for future meetings of the Committee. The dates that will *not* work in February, June, and October 2006 are highlighted on the future meetings calendars in Committee members' briefing books (Tab 13). Dr. Howell indicated that Dr. Lloyd-Puryear would re-circulate queries to Committee members about what dates they were available so that dates for the Committee's 2006 meetings could be set.

Dr. Rinaldo asked whether the Thursday-Friday meeting schedule had to be maintained; if possible, he would prefer having Monday-Tuesday meetings so as not to lose a working day in travel. Dr. Brower indicated that she would prefer days in the middle of the week. Dr. Telfair observed that it is more stable to keep the meetings the way they have been. Dr. Becker said he would like Monday-Tuesday meetings; however, he thinks the most important thing is that the Committee be consistent, because scheduling is easier for Committee members if the meetings are always on the same days of the week.

Consideration of New Liaison Members at the Next Meeting. Dr. Howell suggested that the Committee discuss adding liaison members representing professional societies and organizations to the Committee at its next meeting—specifically, the U.S. Department of Defense (DOD) and the U.S. Food and Drug Administration (FDA) at the next meeting. Dr. Telfair and other Committee members endorsed the consideration of DOD and FDA at the next meeting, and Dr. Howell indicated that they would be invited to appear. Dr. Howell also asked anyone suggesting additional organizations for liaison status to write him a letter to that effect, so that they could be considered at an appropriate time in the future.

New Liaison Representative from the Association of State and Territorial Health Officials' (ASTHO). Ms. Raskin-Ramos announced that Dr. Chris Kus, the pediatric director from the New York Department of Health, has agreed to represent ASTHO on the Committee.

Agenda Items for the Next Committee Meeting. In response to a request from Dr. Lloyd-Puryear, several Committee members suggested topics for the February 2006 meeting:

- Dr. Dougherty suggested that the Committee—and especially its Followup & Treatment Subcommittee—could benefit from hearing a presentation by the Regional Genetics and Newborn Screening Collaboratives. Dr. Becker and Dr. Howell agreed, adding that perhaps the National Coordinating Center at the American College of Medical Genetics (ACMG) could be invited to give a presentation, too.
- Dr. Telfair recommended the liaison representatives be asked to give a brief update on their work as it related to the Committee, adding that this would improve the engagement between the liaisons and the Committee. Dr. Howell said he liked that idea and that the

- Dr. Howell said he would like to invite Dr. Stephen Groft and his people at the National Institutes of Health (NIH) Office of Rare Diseases to come in to discuss their centers of excellence in rare diseases. Committee members agreed that that was a good idea.

- Dr. Rinaldo raised the possibility of inviting the people who have made strong claims that significant harm is caused by the unintended consequences of newborn screening in *Nature* and the *New England Journal of Medicine* and other journals to present their evidence of harm to the Committee. Dr. Howell reminded Committee members that an expert pediatric historian is doing a project on adverse effects recognized and reported on newborn screening, but Dr. Rinaldo said he wanted more than that—he wanted the newborn screening critics to come defend their positions. Dr. Howell said that if there is information to bring to the Committee, he would be in favor of that and that the Committee would see about the possibility of getting someone to come. Dr. Rinaldo said to leave sufficient time for questions following the presentation.

- Dr. Lloyd-Puryear reminded Committee members that the workgroup recommended by Dr. Boyle the previous day to examine the criteria for including conditions in the uniform newborn screening panel was going to report at the Committee's February meeting, too. She said that her notes indicate that the criteria workgroup is supposed to be figuring out three sets of criteria: (1) criteria for the nomination form; (2) criteria for the Health Resources and Services Administration (HRSA) to accept or reject the nomination form; and (3) criteria for the evaluation of evidence-based workgroups. Dr. Dougherty reported that the five people on the criteria workgroup, including Dr. Boyle, had met the previous night and developed a list of buckets of criteria that they are now circulating to Committee members. They would like to have help from Dr. Lloyd-Puryear in setting up a conference call to discuss these prior to the next Committee meeting.

- Dr. Becker noted that one important group for the Committee to consider in its deliberations is policymakers. The Education & Training Subcommittee did not include policymakers in its charges but has realized that educating policymakers will be critical. Noting that the Committee now has a liaison representative from ASTHO, Dr. Becker suggested that the Committee might benefit from hearing a presentation from the National Conference of State Legislators (NCSL) at the February meeting. Dr. Lloyd-Puryear indicated that she would get in touch with NCSL to discuss this possibility.

- Dr. Boyle reminded everyone that the full Committee needs move along in the process of nominating and evaluating and reevaluating candidate conditions on the uniform newborn panel recommended in the American College of Medical Genetics (ACMG) report. Dr. Howell noted that the criteria workgroup is one key underpinning of that. Dr. Boyle said she was assuming that HRSA would make some decisions prior to the next Committee meeting about how the expert review group that reviews the scientific and other literature will be managed. Nevertheless, she thought that the presentations by the Advisory Committee on Immunization Practices (ACIP) and Dr. David Atkins the previous day suggested that the Committee ought to give thought to the framework for the overall process. The Committee has the skeleton of a process but needs to put flesh on the bones. Dr. Lloyd-Puryear asked whether it would be helpful for Dr. Rinaldo to redo the flow diagram and send it out again. Dr. Boyle said yes, and then prior to the next meeting, maybe the Committee can think about what needs to be done in a deliberative way. Dr. Lloyd-Puryear said that she thought the presentation at the next meeting by the criteria work group would feed into this.

- Dr. Howell concluded by saying that once the Committee comes up with the evaluative forms, and once HRSA has considered how the evidence-based review will work, the Committee will want to have a trial run of the proposed process for modifying the ACMG newborn screening panel using the suggested criteria to see how the process works and what changes might be needed. Dr. Boyle asked whether the Committee should look at a new condition or at a condition already on the ACMG uniform panel. Dr. Rinaldo said he would like the Committee to do a trial run of a new condition—spinal muscular atrophy (SMA). The uniform panel is a young panel, he said, so he recommends just adding criteria and letting the Committee turn to new conditions. Dr. Howell suggested that the Committee look at Dr. Rinaldo's diagram again, and then look at the criteria from the workgroup. He said that he also would like to do a trial run using a new condition but that a trial run of a condition already on the panel might be useful, as well.

On behalf of the Committee, Dr. Telfair and Dr. Howell thanked the people who helped support the subcommittees, noting that the subcommittees were very productive at this meeting. Dr. Howell concluded the meeting at 2:08 p.m.

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We certify that, to the best of our knowledge, the foregoing meeting minutes of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children are accurate and correct.

/s/ _____

R. Rodney Howell, M.D., Ph.D.
ACHDGDNC, Chair

/s/_____

Michele A. Lloyd-Puryear, M.D., Ph.D.
ACHDGDNC, Executive Secretary

These minutes will be formally considered by the Committee at its next meeting, and any corrections or notations will be incorporated in the minutes of that meeting.

APPENDIX A: WRITTEN PUBLIC COMMENTS

1. John Adams, Parent & Treasurer, Canadian Organization for Rare Disorders (CORD)

2. Jana Monaco, Parent & Board Member, Organic Acidemia Association

3. Kelly R. Leight, Parent & Executive Director, CARES Foundation, Inc., Congenital Adrenal Hyperplasia Research, Education and Support (statement presented by Mickie Gartzke, Hunters' Hope Foundation)

4. Cynthia Joyce, Executive Director, Spinal Muscular Atrophy Foundation

5. Barbara Trainor, Parent & Board Member, Families of Spinal Muscular Atrophy

6. Carol Greene, M.D., Chair, Society for Inherited Metabolic Disorders (SIMD)

7. Andrea Gropman, M.D., Pediatric Neurologist, Child Neurology Society

8. Claudine Tiffault, Project Evaluator, National Coordinating and Evaluation Center, Sickle Cell Disease Association of America (SCDAA)

1. John Adams
Parent & Treasurer, Canadian Organization for Rare Disorders (CORD)
Statement to the HHS Advisory Committee
on Heritable Disorders and Genetic Diseases in Newborns and Children[*]
Oct. 21, 2005

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 from 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 CORD 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 interior 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 [*Dr. Bradford Therrell's map showing how many American College of Medical Genetics newborn screening conditions are "required or universally offered" in each State in October 2005]* for a second to do a quick visualization of the comparison of 13 different

[*] From transcripts.

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 advocacy 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 free. W e 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 sickle 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 to speed up the pace of implementation of change.

So with that, and the other thing I will bring, the Ontario ombudsman, they 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 talk 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.

2. Jana Monaco
Parent & Board Member
Organic Acidemia Association
Statement to the HHS Advisory Committee
on Heritable Disorders and Genetic Diseases in Newborns and Children[*]
Oct. 21, 2005

Good afternoon! I thank you for the continuous opportunity to offer my comment to you in support of the process of expanding newborn screening and I commend you for your efforts to move the process along. I am on the Board of Directors of the Organic Acidemia Association and the parent of two children with Isovaleric Acidemia and can attest to all that Jill Fisch mentioned earlier in her report. As I sat and monitored my son's seizure last night, I thought about how Stephen 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, Stephen meets the criteria but is a result of not being screened at birth. A test was available, but he didn't get it. Treatment was available but came a little too late. As for the burden of the disease, we don't have time to completely review the result of severe brain damage to a child and the family. 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. We would all like to see more outcomes like hers. I ask you to be cautious and not get too caught up with "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 interest? 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 in Dave Atkins' presentation that parents could be too biased when it comes to the evaluation process of adding disorders to the list or that anyone could be somewhat biased. 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 "score card" and list of criteria. He and his staff are "trained experts", that were originally chosen to complete the task and can provide valuable insight and answer many questions that people may have regarding the score card and criteria for adding 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 will certainly be able to 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. 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 Stephen 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 neurological concerns but no diagnosis yet. Gastroenterology is another specialty that could be considered. We have a large number of children dependent on G Tubes or NG tubes or even TPN lines at times for implementing their nutritional needs recommended by the metabolic specialists. I would be remiss, if I did not include the metabolic physicians. There clearly is not enough representation of these specialists involved in the process of creating a Uniform Newborn Screening Program. They are the key players of the team when it comes to managing these disorders and making decisions regarding those individuals born with these

[*] From transcripts.

conditions. No health care decision can be made without their input. It only makes sense to utilize people who have direct involvement and knowledge of these disorders and are interested in contributing their expertise to the committee.

As we move along in the process of expanded newborn screening much emphasis is shifted to the subcommittees work and their charges, I think it is imperative to stay linked with the regional collaboratives and what they are focusing on. We have discussed the idea of data bases before, though it has been 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 in the list. I see this as a vital piece to help in the process of adding conditions to the Uniform Panel. This should be a key objective in the Followup 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 that there are a lot of misconceptions out there regarding HIPPA that impede on good thorough documentation of information. Each of the family organizations has their own rudimentary data base and this is an example of OAA's. In OAA, we have recently celebrated the birth of a baby of one of our adults with IVA. She had a very safe and healthy pregnancy, labor and delivery thanks to the careful collaboration between her metabolic team and OB/GYN. Her delivery was via cesarean due to the size of the baby, but there were no complications otherwise. This pregnancy needs to be and should be documented in a manner that others can refer to it and learn from it. That knowledge is going to be imperative for the future IVA girls like my own daughter. So I ask you," what is going to be done to develop that type of information tracking system?"

I conclude by thanking you for your continued efforts to develop the Uniform Newborn Screening 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 the area of expanding newborn screening, but we must continue to help get it to that Uniform Status across America.

Thank you!

3. Kelly R. Leight
Parent & Executive Director, CARES Foundation, Inc.
Congenital Adrenal Hyperplasia Research, Education, and Support
Statement to the HHS Advisory Committee
on Heritable Disorders and Genetic Diseases in Newborns and Children
Oct. 21, 2005
(presented by Mickie Gartzke, Hunters' Hope Foundation)

October 18, 2005

Dear Michele [Lloyd-Puryear],

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 & Genetics later this week. We are concerned about a problem that has arisen lately with newborn screening. We have seen that some suppliers of newborn screening equipment and supplies have apparent monopolies on the provision of certain types of supplies and equipment. Where these manufacturers of technology, assays or other materials and equipment have quality control problems, shortages or the like, the States are left in a difficult situation with no where else to turn. They may be required to re-evaluate and re-set cut-offs 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 anyway. In addition, it 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 lead easily to skepticism on the part of the healthcare 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 parents or ordering follow-up tests and appropriate treatment.

We hope that the committee will consider this issue and perhaps come up with ways to alleviate these kinds of problems."

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4. Cynthia Joyce
Executive Director, Spinal Muscular Atrophy Foundation (SMA)
Statement to the HHS Advisory Committee
on Heritable Disorders and Genetic Diseases in Newborns and Children
Oct. 21, 2005

Good afternoon, Dr. Howell and members of the Committee. Thank you for giving me the opportunity to speak to you today. My name is Cynthia Joyce and I am the Executive Director of the Spinal Muscular Atrophy Foundation, which is a non profit organization dedicated to accelerating a treatment for Spinal Muscular Atrophy (SMA). I am here today along with Barbara Trainor from Families of Spinal Muscular Atrophy, an international organization dedicated to eradicating SMA, helping affected families cope, and educating the public and professional community.

I am here today to request the addition of SMA to the list of primary targets for uniform newborn screening efforts. The biology of SMA is compelling. It is one of the most common autosomal recessive diseases, with a birth rate of 1/6000–10,000 and a carrier frequency of 1/35–1/50. SMA is caused by a loss function mutation in the SMN gene that results in motor neuron death, muscle atrophy and severe-to-catastrophic loss of function. At least 60% of the children born every year with SMA present with the most catastrophic phenotype of the disease. Specific and sensitive diagnostic genetic testing has been available for many years, but is often implemented only as a last resort. Consequently, infants and children are subjected 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 SMA to the uniform newborn 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 of emerging treatment paradigms. We believe that SMA meets the Principles and Criteria established by the Committee and strongly encourage with the Committee to review this disease state for inclusion in the panel as a primary target for newborn screening.

Key points include:

- First, the mutation causing SMA is detectable by blood sample testing immediately on birth, when symptoms are not apparent.
- Secondly, the test for SMA is sensitive, specific and definitive in >94% of cases. The differential diagnosis of SMA can be a circular exercise and a painful process for all children, often involving a muscle biopsy and/or extensive neuromuscular testing. Despite the best efforts of specialists in the area, a genetic test is most often performed last instead of first in the diagnostic process. Inappropriate testing adds needless time, stress and expense to the care process. Genetic tests for SMA are not cost prohibitive. Current testing procedures are easy to perform using common PCR-restriction fragment length polymorphism assays to detect the mutation. The community is working to reduce costs further in anticipation of routine newborn screening and is actively working with NICHD to address this issue.
- Thirdly, early detection will ensure that children suffering from this disease will receive the benefits of effective management—including respiratory care, preventive physical therapies and nutritional support. Early diagnosis will enable the family and treating

physician to prepare a treatment plan for the first medical emergency that will reduce stress for infants and ensure the most effective care.

- Lastly, early detection will enable clinical trials of agents that may save motor neurons and preserve function for these children. Evidence from pre-natally identified children indicates that motor neuron loss in SMA occurs after birth, suggesting that a neonatal treatment window is not only possible, but may be essential for this disease.

The SMA professional community is well-organized to provide care and poised to help advance newborn screening efforts in their areas. Primary treatment centers are most often MDA clinics—over 100 are supported nationwide.

Specific treatments for SMA are on the horizon. There are a number of Phase II trials underway throughout the world, including two being conducted in the US using valproate and hydroxyurea, drugs that are already widely available in the market. It is essential that newborn screening be widely available at the time a new treatment option is shown to be effective in order to help as many children as possible at the earliest possible point in time.

In conclusion, by virtually all measures, SMA falls well within the criteria established by the Committee for the development of the uniform newborn screening panel. It is 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. The investment is well-worth the cost.

Thank you for giving me the opportunity to speak to you today and now I would like to introduce, Barbara Trainor.

5. Barbara Trainor
Parent & Board Member, Families of Spinal Muscular Atrophy
Statement to the HHS Advisory Committee
on Heritable Disorders and Genetic Diseases in Newborns and Children
Oct. 21, 2005

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 of Spinal Muscular Atrophy and the founder of the Chesapeake Chapter, one of 25 chapters throughout the country. I am also the mother of three children, including my daughter Erin Marie, who lost her life at only 5 ½ months of age almost 13 years ago to SMA. I am humbled to be here representing the millions of parents who have had children affected by SMA.

All new parents make the assumption 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 through family history that a child might be at risk for SMA. Having already given birth to one healthy daughter, I expected nothing less from 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, in less than four (4) 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 and feeling 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 SMA 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 information immediately and begun planning for the care of my child.

While a specific treatment for SMA does not exist currently, it is true that care plans and supportive care make an important difference for families affected by SMA. Furthermore, as Cynthia mentioned, Phase II 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 newborn 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 towards a 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 their graciousness and willingness to listen to me. I would be happy to answer any questions that you may have.

6. Carol Greene, M.D., Chair, Society for Inherited Metabolic Disorders (SIMD)
Statement to the HHS Advisory Committee
on Heritable Disorders and Genetic Diseases in Newborns and Children*
Oct. 21, 2005

I am Carol Greene, a physician-geneticist and a board member of the Society of Inherited Metabolic Disorders, speaking on behalf of the Society. SIMD 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, SIMD would like to make two points today.

First, in keeping with the membership pool that we have previously presented here, the SIMD 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. SIMD 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. SIMD 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 spectrometry, 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.

* From transcripts.

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 SIMD is ready and eager to work with this committee in any way we can help to achieve our mutual goals.

7. Andrea Gropman, M.D., FAAP, Pediatric Neurologist, Child Neurology Society
Statement to the HHS Advisory Committee
on Heritable Disorders and Genetic Diseases in Newborns and Children*
Oct. 21, 2005

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 1,000 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 followup of 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.

* From transcripts.

Claudine Tiffault, Project Evaluator, National Coordinating and Evaluation Center, Sickle Cell Disease Association of America (SCDAA)
Statement to the HHS Advisory Committee
on Heritable Disorders and Genetic Diseases in Newborns and Children[*]
Oct. 21, 2005

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.

[*] From transcripts.