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

Summary of Seventh Meeting
Feb. 13-14, 2006
Washington, DC

The Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children was convened for its seventh meeting at 9:00 a.m. on Monday, Feb. 13, 2006, in the Horizon Ballroom at the Ronald Reagan Building and International Trade Center in Washington, D.C. The meeting was adjourned at 2:05 p.m. on Tuesday, Feb. 14, 2006. 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 Tuesday, Feb. 14, 2006.

Committee Members Present:

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I. WELCOME, OPENING REMARKS, APPROVAL OF MINUTES

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 seventh meeting of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children and announced two new members to the Committee: James A Newton, M.D., President, Alabama Neonatal Medical Group; and Mary Jane Owen, M.S.W., Director, Catholics in Action, in Washington, D.C. Dr. Howell then noted that the following individuals had been newly named as organization representatives to the Committee: (1) Christopher A. Kus, M.D., M.P.H., representing the Association of State and Territorial Health Officials (ASTHO); (2) Ethan Hausman, M.D., FAAP, FCAP, representing the U.S. Food and Drug Administration (FDA); (3) Bennett Lavenstein, M.D., representing the Child Neurology Society; and (4) Lt. Col. David S. Louder, III, M.D., representing the U.S. Department of Defense.

Following these introductions, Dr. Howell outlined the agenda for the 2-day meeting:

- **Presentation on the National Coordinating Center (NCC) for HRSA-Funded Regional Genetics and Newborn Screening Collaboratives**. The executive director of the American College of Medical Genetics (ACMG) Michael Watson, Ph.D., who is the project director for the NCC, would give an overview of the NCC and regional collaboratives funded by the Health Resources and Services Administration (HRSA).
- **Reports from three Regional Genetic and Newborn Screening Collaboratives.** Reports on the activities of three of the seven HRSA-funded regional collaboratives would follow: Region 1: New England Regional Genetics Group (by Ann Marie Comeau, Ph.D.); Region 3: Southeastern Regional Genetics Group (by Jess Thoene, M.D.); and Region 4: The Great Lakes Genetics Collaborative (by Dr. Rinaldo).
- **Presentation on Rare Disease Centers of Excellence.** Stephen Groft, Pharm.D., who directs the Office of Rare Diseases (ORD) at the National Institutes of Health (NIH) would report on Rare Disease Centers of Excellence. Dr. Howell said he hoped ORD and the HRSA-funded regional collaboratives would take advantage of opportunities to collaborate.
- **Subcommittee meetings and reports.** A considerable amount of time would be devoted to meetings and reports of the Committee's three subcommittees: the Education & Training Subcommittee, the Followup & Treatment Subcommittee, and the Laboratory Standards & Procedures Subcommittee. Following brief updates on the subcommittees' work, there would be subcommittee meetings open to the public; then there would be additional reports to the full Committee. Dr. Howell said that he wanted the subcommittees to focus on what is achievable. In addition, he would like the subcommittees to focus on advancing the Committee's recommendations to the Secretary of Health and Human Services with respect to advancing the adoption of the uniform newborn screening panel recommended in the ACMG report *Newborn Screening: Toward a Uniform Screening Panel and System.*
- **Nomination process for candidate conditions to the uniform screening panel.** Dr. Green and Dr. Rinaldo would outline a proposed process for the nomination of new conditions to be added to the uniform newborn screening panel recommended in the ACMG report.

- **Presentation on the Lysosomal Storage Diseases Workshop.** There would be a brief presentation on a December 2005 workshop on issues related to presymptomatic diagnosis of lysosomal storage diseases.
- **Presentations from organizations representing state policymakers and legislators.** The National Conference of State Legislatures (NCSL) and the Association of State and Territorial Health Officials (ASTHO) would make presentations about their activities.
- **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.

The minutes from the sixth meeting of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children held Oct. 20–21, 2005, were unanimously approved.

II. COMMITTEE BUSINESS—SUBCOMMITTEE REPORTS

The chairs of the Laboratory Standards & Procedures Subcommittee, the Education & Training Subcommittee, and the Followup & Treatment Subcommittee updated the full Committee on their activities and plans since the previous meeting.

A. Laboratory Standards & Procedures Subcommittee Report

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

Dr. Brower, the chair of the Laboratory Standards & Procedures Subcommittee, said that to advance work related to the subcommittee's charge to better understand and define the steps that would be helpful in harmonizing lab procedures in support of the uniform newborn screening panel recommended in the ACMG's expert panel's report *Newborn Screening: Toward a Uniform Screening Panel and System*, the subcommittee formed a working group related to the need for a routine second newborn screening test. The working group met several times over the last few months and came up with the idea of a targeted data mining effort to identify the parameters that might be useful in a larger study to address the question of the need for a routine second specimen in newborn screening. The workgroup will communicate the outcome of the data mining effort to the subcommittee, which will then seek feedback and advice from the full Advisory Committee about the possibility of a larger study.

B. Education & Training Subcommittee Report

William J. Becker, D.O., M.P.H.
Medical Director
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Dr. Becker reported that members of the Education & Training Subcommittee had held three conference calls in recent months (December, January, and February) to focus on the charges that Dr. Howell gave the subcommittee: (1) to review existing educational and training resources for health professionals; parents; screening program staff; hospital/birthing facility staff; and the public; and (2) to identify deficiencies and make recommendations for action regarding the five groups.

In addition, the Education & Training Subcommittee had added four new members and provided orientation sessions to them. It distributed the Parent Education Newborn Screening Toolkit to members for review. At Dr. Becker's request, subcommittee members reviewed the American Academy of Family Practice's (AAFP) Annual Clinical Focus on newborn screening (www.aafp.org). And the subcommittee has been collaborating with its Federal partners— the National Institute of Child Health and Human Development (NICHD), HRSA, the Human Genome Research Institute, the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC), the National Institutes of Health/Office of Rare Diseases (ORD), and the National Library of Medicine (NLM)—on how to educate stakeholders about newborn screening. A one-stop Web site on newborn screening is under consideration.

In response to Dr. Howell's charge, the Education & Training Subcommittee would like to propose the following goals for the subcommittee:

1. Increase awareness of newborn screening with the general public. (The Education & Training Subcommittee intends to develop a plan for this for the full Committee to consider at the June 2006 meeting.)
2. Increase knowledge of newborn screening among heath care providers. (Associations such as the American Academy of Family Physicians [AAFP], the American College of Obstetricians and Gynecologists [ACOG], and the American Academy of Pediatrics [AAP] are doing good work with their members; the Education & Training Subcommittee would like to begin to focus more on nurses, nurse midwives, and genetic counselor groups.)
3. Increase awareness of newborn screening issues by policymakers (especially, state legislatures, but also state health departments, and newborn screening programs).
4. Increase resources available to families affected by a positive screen. (This will be a longer term goal of the subcommittee.)

In conclusion, Dr. Becker proposed the following action items for full Committee's consideration:

- Discuss/approve the proposed goals for the Education & Training Subcommittee.
- Consider the concept of a national spokesperson for newborn screening.
- Request that the National Newborn Screening and Genetics Resource Center (NNSGRC) maintain updated U.S. maps showing state newborn screening programs (like the ones Dr. Brad Therrell has given the Committee) on its Web site.

Questions & Comments

Dr. Telfair asked how the Education & Training Subcommittee came up with the initial list of groups to target for education and training. Dr. Becker said the subcommittee brainstormed to get a fairly long list of groups and then selected the groups it thought would be most useful, given the resources and composition of the subcommittee. Dr. Telfair recommended that the subcommittee focus on people who deal hands-on with the potential population, including nurse practitioners, certified midwives, pediatric physician assistants, genetic counselors, people who do single gene counseling, etc.

Dr. Howell asked what mechanism the subcommittee would use to contact the groups. Dr. Becker said the subcommittee has various contacts (e.g., newborn screening perinatal coordinator on the subcommittee, a contact for the nurse midwives) and will put a plan together.

Dr. Howell also asked about the one-stop Web site. Dr. Becker explained that that idea came from a consortium of Federal agencies that are developing information about their activities in newborn screening education and that Dr. Jim Hanson and Ms. Gilian Engelson at the National Institute of Child Health and Human Development could elaborate.

Dr. Kus asked how the Education & Training Subcommittee's work would differ from that of other organizations with similar goals. Dr. Becker explained that the subcommittee would bring recommendations to the full Advisory Committee; and the Committee would then make recommendations to HHS Secretary Leavitt. He noted that the Education & Training Subcommittee is charged with creating recommendations that advise the Committee on how to implement the uniform panel.

Dr. Howell said he thought the idea of a national spokesperson for newborn screening was a good idea and asked Dr. van Dyck whether a Committee could have a spokesperson. Dr. van Dyck said he did not know of any other Federal advisory committee that had a spokesperson. Any proposal for a spokesperson would have to be presented as a recommendation to the HHS Secretary.

C. Followup & Treatment Subcommittee Report

Denise Dougherty, Ph.D.
Senior Advisor, Child Health
Agency for Healthcare Research and Quality (AHRQ)

Dr. Dougherty gave a report on the Followup & Treatment Subcommittee for the chair Dr. Boyle, who was delayed by weather conditions. She explained that the Followup & Treatment Subcommittee has developed some broad recommendations for next steps to get closer to an understanding of what needs to happen in financing, information technology, and reducing fragmentation of the system overall to improve followup of children who undergo newborn screening.

The Followup & Treatment Subcommittee's first recommendation is to develop some way to arrive at a consensus about the meaning of long-term followup and treatment. Members of the Followup & Treatment Subcommittee discussed the definition of long-term followup and treatment, but they had differences of opinion and also thought that it was beyond the charge of the subcommittee to determine what the components, length of time, and roles and responsibilities of AAFP, AAP, state health departments, insurers, private sector providers, etc., are in long-term followup. If a consensus about the meaning of long-term followup and treatment is reached, the subcommittee can use that definition as a basis for its efforts to ensure that the financing and other components for long-term followup and treatment are in place.

Questions & Comments

Dr. Howell asked Committee members to comment on what they thought long-term followup means in the context of newborn screening. Dr. Kus said he strongly agreed that there is a need to further define long-term screening and followup and added that the definitions would probably have to be disease specific. He recommended that the effort to define these terms build on existing documents such as the ACMG newborn screening report and a draft document by the Clinical and Laboratory Standards Institute.

Dr. Dougherty explained that the lack of agreement extends not only to what the components of long-term care are but also to what the roles and responsibilities of various parties in ensuring long term-followup should be. Dr. Rinaldo said his impression of what long-term followup is almost intuitive—

lifetime care of a patient with a chronic condition. He thinks the debate is really about where the financial resources for long-term followup are to come from—e.g., should the public health structure be responsible for years and years for people with metabolic disorders?

Dr. Telfair stressed that it would be important to include families—the recipients of and participants in long-term care and followup—in any decisionmaking process.

Dr. Gregg recommended defining what the metrics are: both passive metrics (simply identifying people and tracking them) and active metrics (e.g., things that involve therapeutic interventions) before making any decisions about who is responsible for long-term followup.

Dr. Lavenstein said documents setting forth standards of care for different conditions are needed in order to ascertain what the burden of demand is going to be. Dr. Howell noted that developing standards of care is a big job but said that ideally this should be done for all the conditions in the newborn screening panel.

Dr. Lavenstein added that a second topic he would like to see considered is whether the mandate for followup is at the state level, the regional level, or national level. He said some in pediatrics are worried about this. Dr. Rinaldo said he would like to have a discussion of when the public health sector's responsibility for newborn screening is finished. Expecting the public health sector to do lifetime care seems overly ambitious. At some point, the responsibility for care should pass to the health care system.

Dr. Kus said the responsibility has to be a shared, integrated responsibility. Right now the state health department can report what percentage of children were screened and what percentage were referred for services, but there is little information about what happens to those children. Collecting such information is especially important because we are now dealing with conditions whose natural history we do not know. What are the inherited metabolic disease centers doing? Dr. Rinaldo says the problem is dealing with outcomes where the denominator is 1 or 2; the only feasible solution is to coordinate the gathering of data as in the Regional Genetics and Newborn Screening Collaboratives.

Dr. Howell asked Committee members to make recommendations about how to move forward. Dr. Becker made two suggestions to the Followup & Treatment Subcommittee: (1) Make a recommendation to the full Committee about what type of consensus process might be useful; (2) pick one element of the issues—components of long-term followup, the responsibilities of who does long-term followup, the financing of long-term followup—and try to work though just that one element, recognizing that there are other factors that are going to be involved. Dr. Dougherty replied that the Followup & Treatment Subcommittee might address the first suggestion at its meeting later that afternoon; the consensus development process might be charged with coming up with what long-term followup and treatment components would be in an ideal world as a short-term product, then go back and consider the realities (e.g., of financing, information technology, other resources). Dr. Howell said that it would good to think of what some of the research elements of a followup program would be, as well. Dr. Dougherty commented the best way to figure out the components of long-term followup and treatment would be to first agree upon the goals.

Finally, Dr. Dougherty asked what resources would be available from HRSA for a consensus development conference. Dr. van Dyck and Dr. Lloyd-Puryear explained that there would be very few resources other than people and that all the subcommittees' proposals would have to be examined so that they could be prioritized. Dr. Dougherty said maybe in the subcommittee meeting, they would try to come up with the types of resources they would need. Dr. Howell concluded by noting that there

would be enough to get a small group together to meet, especially if the people lived in the D.C. metropolitan area.

III. THE NATIONAL COORDINATING CENTER (NCC) FOR HRSA-FUNDED REGIONAL GENETIC AND NEWBORN SCREENING COLLABORATIVES

Michael S. Watson, Ph.D., FACMG
Executive Director
American College of Medical Genetics (ACMG)

ACMG, under a cooperative agreement with the Genetic Services Branch, Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA), serves as the National Coordinating Center (NCC) for the seven Regional Genetic and Newborn Screening Collaboratives. In his presentation, the NCC Project Director Dr. Watson explained that the goals of the NCC and regional collaboratives are to do the following:

- Enhance access to genetic services
- Enhance and support the genetic and newborns screening capacity of states (e.g., by addressing the maldistribution of genetic resources, promoting the translation of genetic medicine into public health and health care services, and facilitating the availability of genetic services at local levels).

Although the NCC has been operating for about a year, Dr. Watson noted, it has not done much coordinating yet, because the regional collaboratives' foci to date have primarily been on infrastructure development:

- ***Region 1: New England Regional Genetics Group (NERGG***). Region 1 encompasses Connecticut, Massachusetts, Maine, Rhode Island, Vermont, and New Hampshire. NERGG is working under the direction of Thomas Brewster, M.D., to (1) improve collaboration within their region among states and at local levels; (2) enhance and improve current newborn screening practice models; and (3) improve newborn screening educational opportunities within the region.
- ***Region 2: New York-Mid-Atlantic Consortium (NYMAC) for Genetic and Newborn Screening Services***. Region 2 encompasses the District of Columbia, Maryland, Virginia, West Virginia, Pennsylvania, New York, and New Jersey. NYMAC, co-directed by Kenneth Pass, Ph.D., and Lou Bartoshesky, MD, is developing a regional coordinating plan to improve access to specialty care for children with heritable disorders. In addition, this collaborative is (1) developing local solutions to barriers to access specialty care for congenital abnormalities; (2) addressing the maldistribution of specialists; (3) working with Region 1 New England, Region 3 Southeastern region, and Region 4 (Great Lakes area) to develop an emergency backup system for newborn screening; (4) standardizing newborn screening throughout the region; and (5) educating providers, payers, patients and families in the region about newborn screening; and (6) encouraging collaborative partnerships between primary care providers and specialists for affected children.
- ***Region 3: Southeastern Regional Genetics Group (SERGG)***. Region 3 encompasses Alabama, Mississippi, Georgia, Louisiana, North Carolina, Tennessee, Florida, South Carolina, Puerto Rico, and the Virgin Islands. SERGG, under the direction of David Ledbetter, Ph.D., and Jess Thoene, M.D., is working on a telecommunications project in the

region that connects states' academic and public health representatives. It is also engaged in efforts related to continuing education for nutritionists.

- ***Region 4: The Great Lakes Genetics Collaborative***. Region 4 includes Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio, and Wisconsin. This regional collaborative, headed by Cynthia Cameron, Ph.D., has three ongoing projects: (1) a newborn screening tandem mass spectrometry (MS/MS) project to achieve uniformity of the testing panel within the region and to improve the analytical performance within the region (headed by Dr. Rinaldo); (2) a project to reduce inequities in access to genetic services (headed by Dr. R. Pauli); and (3) a regional public health infrastructure project that is developing a practice model for optimal diagnosis, followup and management for the children that are identified with heritable disorders and birth defects (headed by C. Nash).
- ***Region 5: The Heartland Regional Genetics and Newborn Screening Collaborative.*** Region 5 includes Arkansas, Iowa, Kansas, Missouri, North Dakota, Nebraska, Oklahoma, and South Dakota. This regional collaborative, under the direction of John Mulvihill, M.D., is developing a regional infrastructure to address communication, education and resource needs of the region. In addition, the collaborative is developing what it calls a "Heartland Regional Genetics Strategic Plan." It also has a special smaller regional project that is focusing on identifying gaps in service and education.
- ***Region 6: Mountain States Genetic Foundation. Region 6 includes Arizona, Colorado, Montana, New Mexico, Texas, Utah, and Wyoming.*** This regional collaborative, under the direction of John Johnson, MD is taking steps to establish the Mountain States Genetics Regional Center (MoStGeNe Regional Center) to facilitate coordination, communication and collaboration among the many stakeholders and partners across the region. In addition, it is updating and regionalizing a needs assessment and developing a regional plan for collaborative genetic activities.
- ***Region 7: Western States Genetic Services Collaborative.*** Region 7 encompasses Alaska, California, Hawaii, Idaho, Nevada, Oregon, Washington, and Guam. This regional collaborative, under the direction of Sylvia Au and Kerry Silvey, is moving to implement a regional practice model to improve access to specialty metabolic genetic services and primary care. For the states in the region that had not been a part of the initial planning process, the regional collaborative hopes to conduct a needs assessment to identify activities to increase the capacity for genetic and newborn screening services in those states.

The NCC's advisory committee is chaired by Jonathan Zonana, M.D., and includes broad range of expertise. Representatives of organizations that include the National Society of Genetic Counselors, American Academy of Family Physicians, National Conference of State Legislatures, American Academy of Pediatrics, March of Dimes, Association of Maternal and Child Health Programs, the National Association of Pediatric Nurse Practitioners, National Institutes of Health (, Genetic Alliance, , Centers for Disease Control and Prevention (CDC), and Association of State and Territorial Health Officers are directly involved.

The NCC has the following objectives with respect to the seven Regional Genetics and Newborn Screening Collaboratives: (1) to support the regional collaboratives' efforts to identify issues specific to the utilization of genetic and newborn screening services at all levels; (2) to minimize duplication of efforts, identify "best practices" developed by the regions, further information exchange and professional collaboration; (3) to facilitate the regional collaboratives' focus on maternal and child health and program goals; and (4) to maximize interregional collaboration (e.g., by having language and terminology compatibility across the country; by involving representatives from genetic, public health, state, business, and academia).

Areas of shared need among the seven Regional Genetics and Newborn Screening Collaboratives include the following:

- Communication and information management technologies (e.g., videoconferencing, telemedicine, including Web-based clinical management systems suitable for telemedicine, interstate satellites);
- Establishing provider (genetic service) networks;
- Disease management information;
- Reimbursement in general and when trying to work across state lines or over a long distance (e.g., reimbursement for telephone consultation);
- Evaluation methodologies;
- Expansion of newborn screening and the service infrastructure needed to provide followup services to newborns that test positive;
- Specific regulation and legislation to allow interstate licensing to address liability concerns across state borders;
- Financing for the expansion of newborn screening and service infrastructure for followup services;
- Expanding access to genetic services (e.g., via training geneticists, training primary care providers in the field of genetic medicine; increasing the diversity of trainees; and a mechanism to more systematically address the geographic maldistribution of services); and
- Evaluation.

ACMG has plans for the NCC to do the following: (1) develop networks of centers of genetic services with primary care providers; (2) facilitate data collection, collaborating with the NIH rare disease centers and CDC's genomics centers; and (3) work with organizations such as the American Academy of Pediatrics, and American Academy of Family Physicians to address the development of codes in the Current Procedural Terminology, as well as with organizations such as the Joint Commission on the Accreditation of Healthcare Organizations to bring some uniformity of practice within hospitals for newborn screening programs for taking samples for newborn screening; and (4) encourage information sharing from projects with overlapping interests; and (5) facilitate collaboration and dissemination of best practices.

The NCC'sresource partners, among them National Conference of State Legislatures (NCSL) and the American Academy of Pediatrics (AAP) have identified the following activities:

- NCSL identifies and analyses regulatory issues as needed by program; communicates policy concerns to state legislatures and staff; and addresses areas in which state and Federal legislative and regulatory issues may hinder cooperative activity (e.g., privacy statutes and information sharing; public health data collection activities and joint research projects; political and economic conditions that limit moves to standardization and best practices).
- The AAP has developed several programs related to newborn screening. The National Center of Medical Home Initiatives for Children with Special Needs is a broad program that provides support to physicians, families, and other medical and nonmedical providers who care for children with special needs so that they have access to a medical home (i.e., primary care that is accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective). With support from HRSA, the AAP also has

established a practice-based research network known as Pediatric Research in Office Settings. In addition, the American Academy of Pediatric has done considerable work on developing practice guidelines related to genetic and newborn screening.

The NCC has initiated several projects.

1. ***Building the business case for genetic services***. The NCC has formed a workgroup to use the regional collaboratives to develop the information needed to build the business case for genetic services, and the workgroup expects to hold its first meeting in May 2006.
2. ***Developing a defined network of genetic service providers.*** The NCC has begun considering standards for centers for genetic services; acknowledging qualified providers outside of centers; considering specialty genetic condition clinics and core genetic needs; including primary care providers identified with the AAP's National Center of Medical Home Initiatives for Children with Special Health Care Needs. A workgroup is going to meet once and then complete its work by long-distance communication.
3. ***Newborn screening and clinical genetic management guidelines*.** The NCC is involved in the ongoing development of newborn screening and clinical genetic management guidelines for primary care providers and specialists:
    a. ACTion (ACT) sheets for newborn screening conditions for primary care providers. Dr. Watson explained that NCC has been trying to develop guidelines that are appropriate for providers to use at the point of care. A HRSA-funded workgroup is preparing ACT sheets on specific newborn screening conditions for primary care providers. Each ACT sheet includes a paragraph condition description and information about differential diagnosis; tells a primary care provider what actions to take in the event of a positive screen; identifies national resources for additional information; and includes a space for the insertion of local, state, and regional resources for referral. These ACT sheets are amenable to being directly integrated into electronic medical records and health information systems. Confirmatory algorithms for the purpose of establishing a diagnosis in a screen-positive newborn are also being developed. Currently, the ACT sheets are undergoing pilot testing. The AAP has approached the NCC about integrating the ACT sheets into its national program of getting newborn screening educational materials into every pediatrician's office in the United States.
    b. Management guidelines for adults with pediatric genetic diseases. These will be increasingly needed as states implement broader screening for more disorders and 10,000 people every year are moved into chronic disease management.
    c. Management guidelines for medical geneticists. These are the high-level guidelines that the ACMG pays attention to.
4. *Identifying pilot studies for newborn screening*. NCC will work with the National Newborn Screening and Genetics Resource Center to track and keep a list of pilot newborn screening programs in the states. They will facilitate links between researchers/providers and screening laboratories.
5. *Improving screening laboratory performance.*
6. *Addressing the education needs of the public and providers* (from primary care providers to specialists)**.**

Questions & Comments

Dr. Becker asked whether ACT sheets that provide guidance to pediatric primary care health professionals about how to respond to a positive newborn screen for specific conditions are available online. Dr. Watson replied that six of the ACT sheets are in the final stages of approval and will be publicly available on ACMG's Web site. In addition, the AAP is going to be distributing the ACT sheets to all pediatric practices in the United States. Finally, the sheets are going to be made available as a bound set. The intent is to make the ACT sheets as widely available as possible.

Dr. Becker suggested that the Committee might consider making the ACT sheets available to all state newborn screening programs. Dr. Watson replied that there had been recent discussions about the distribution network and the NCC is drafting letters to send to newborn screening program directors, followup coordinators, lab directors in newborn screening programs, maternal and child health directors in the states, and others about the availability of the ACT sheets. He added that about a dozen states have actively been chasing him.

Dr. Howell asked how the ACT sheets would be maintained and updated. Dr. Watson said that ACMG committees would revisit the ACT sheets periodically, at a minimum of every 3 years, to retire, reaffirm, or revise them. Dr. Hannon suggested the possibility of including a customer comment Web site for the ACT sheets.

Another question was whether ACT sheets would be developed for screen-positive patients who did not require referral to subspecialist. Dr. Watson said the focus of the ACT sheets will probably be on the more comprehensive guideline for the true positive patient. Resources will determine the extent to which they can do the intermediate stages.

Dr. Howell asked whether ACMG is planning on developing ACT sheets for each of the conditions in the newborn screening panel. Dr. Watson said that ACMG would love to do this, but there are 54 conditions, and the cost of doing practice guidelines is prohibitive (e.g., the Pompe's disease guideline cost $62,000 for two meetings of 12-15 people) Dr. Kus asked what Dr. Watson's preferred method of developing clinical guidelines is: expert based, evidence based guidelines, consensus guidelines or what? Dr. Watson said all of the above are useful; it depends on what the condition is and whether you are talking about the diagnosis, the test, the treatment, etc.

Dr. Howell asked where NCC is in its work with the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), noting that many people think that hospitals should have a defined role in newborn screening, which they currently do not. Dr. Watson indicated that working with JCAHO is the NCC's next priority and that effort is being ratcheted up. JCAHO has indicated that its newest standards revolve around the hospital's responsibility in a scenario when a newborn screening test result, that requires action, comes back; JCAHO wants the NCC to demonstrate the downside that has been realized when the system has not worked. Dr. Watson said he would cc Dr. Howell on the letter back to JCAHO.

Dr. Howell asked Dr. Watson to clarify how patent issues are related to the issue of identifying appropriate levels for cutoffs in newborn screening lab results. Dr. Watson replied that there are many patents that come into play for treatments in individual diseases, as well as broader technology patents around tandem mass spectrometry and its use. Some states are wondering whether they may be infringing a patent by providing data to centralized data sources intended to improve knowledge of appropriate cutoffs.

Dr. Becker asked whether the NCC had had any actions with carriers such as Medicare or Medicaid that would be approving reimbursement for long-term followup and treatment for individuals

diagnosed with genetic or metabolic conditions. Dr. Watson replied that there has been little national decision-making on coverage for anything related to genetic medicine. A handful of carriers in the country (Noridian, Trailblazer, and Wisconsin Physician Services) cover about one-third of the states and end up setting the tone. If these carriers buy into something, then you move to what is now being called "an extended local policy," which essentially becomes a national coverage policy. Dr. Watson added that it is going to take a lot of creativity to figure out how to finance newborn screening and the subsequent followup and treatment of affected individuals.

Dr. Thoene, in the audience, stated that he believes the interactions between the primary care provider and the patient are the weakest link in the newborn screening process and asked Dr. Watson if any thought had been given to improve accountability and quality assurance mechanisms in this realm. What if a practitioner ignores the ACT sheet? Dr. Watson said the practitioner is likely to get sued. Often only about 50 percent of providers will make patients aware of things; others go down the legal trail; then there are stronger guidelines based on liability; then things move faster. Dr. Thoene asked whether the state screening laboratory could take on the responsibility of finding out whether contact and referral to the appropriate specialist has been made. Dr. Watson said some states do take on that responsibility, but there is variability in how far they go.

IV. REPORTS ON ACTIVITIES FROM THREE REGIONAL GENETIC AND NEWBORN SCREENING COLLABORATIVES

The seven Regional Genetic and Newborn Screening Collaboratives supported by HRSA are doing regional needs assessments for improving the health of children and families with genetic disorders, identifying barriers to genetic and newborn screening services, and working on issues that are relevant to improving services in their regions. In this session, representatives of three of the regional collaboratives gave reports on their activities: Region 1: New England Regional Genetics Group (Dr. Comeau); Region 4 Collaborative: previously the Great Lakes Genetics Network (Dr. Rinaldo); and Region 3: Southeastern Regional Genetics Group (Dr. Thoene).

A. Epidemiology: Mapping Genetic Needs Relative to Services for Cystic Fibrosis, Hemoglobinopathies, and Metabolic Disorders

Anne Marie Comeau, Ph.D.
Deputy Director
New England Newborn Screening Program
University of Massachusetts Medical School
From Region 1: New England Regional Genetics Group

Dr. Comeau reported on the activities of the regional collaborative in Region 1, the New England Regional Genetics Group, which operates in the states of Connecticut, Massachusetts, Maine, Rhode Island, Vermont, and New Hampshire. The New England Regional Genetics Group has been working (1) to develop and implement methods for the assessment of regional needs for genetic services using three newborn screening groups—cystic fibrosis, hemoglobinopathies (e.g., sickle cell anemia), and biochemical genetic disorders (e.g., medium-chain acyl-CoA dehydrogenase [MCAD])—as a model; and (2) to develop best practice models (e.g., related to border babies, laboratory backup, and clinical backup) based upon current need and epidemiologic data.

Newborn screening is a successful and universal public health model, and it can provide powerful early indicators of current and future needs of the population for specialized services. The New

England Regional Genetics Group has divided each state in the region into several distinct public health service areas that public health service people use to devote to their regional coordinators for health services. It then looks for where there are cases of the specific conditions, where the services are, what the service needs are, and what the service capacities are.

Dr. Comeau illustrated the process using cystic fibrosis, sickle cell disease, and MCAD. The New England Regional Genetics Group maps the locations of the babies who screen positive for a particular condition to their place of residence and then maps the location of centers that offer services available in a particular state to determine the mean and median miles to services for families. The collaborative also does a regional map to ascertain the adequacy of the distribution of facilities. In some cases, a person who lives in one state may want to go to another state for treatment (e.g., a person southern Vermont probably would want to go to Albany, N.Y.), so the collaborative does regional mapping as well.

In Vermont, of 32,000 infant resident births, more than 10 percent are born in New Hampshire; this poses problems for tracking. Sharing data is a privacy issue. The New England Regional Genetics Group has been working with state privacy officers to try to define exactly what data states can share with one another. It is also working to help sort out some of the technical issues related to sharing data to ensure all babies have newborn screening and that there is appropriate follow-up even for babies who cross state lines either for the screening or for the followup and treatment.

B. Performance Metrics and Harmonization of Cutoff Values for Newborn Screening by Tandem Mass Spectrometry

Piero Rinaldo, M.D., Ph.D.
Professor of Laboratory Medicine and Pathology
Mayo Clinic College of Medicine
Chair, Division of Laboratory Genetics
Mayo Clinic Rochester
From Region 4: Great Lakes Genetics Collaborative

Dr. Rinaldo reported on the newborn screening tandem mass spectrometry (MS/MS) project of the regional collaborative in Region 4 Collaborative, which includes Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio, and Wisconsin. The MS/MS project is one of the three ongoing regional projects..

Dr. Rinaldo explained that the three objectives of the Region 4 Collaborative MS/MS project are the following:

- Achieve uniform implementation of testing by MS/MS to maximize detection of affected newborns within the region.
- Improve the overall analytical performance of MS/MS testing.
- Set and sustain the lowest the achievable rates of false-positive results with MS/MS testing.

As of December 2005, the first objective—uniform implementation of MS/MS testing in Region 4—had been nearly achieved. Region 4 had 99 percent uniform implementation of MS/MS screening for the 20 primary targets in the American College of Medical Genetics (ACMG) uniform newborn screening panel and 80 percent implementation of screening for the 22 secondary targets in the panel. Kentucky—the state in the region that was the farthest behind in terms of MS/MS testing—began testing with the full panel on December 13, 2005.

In conjunction with the second objective, the Region 4's MS/MS project is seeking to obtain the lowest possible range of false positives with MS/MS testing. The first step in achieving this objective is the collection of data from MS/MS testing in the states in Region 4 (and beyond). The project is collecting two types of anonymized data from states: (1) data on testing in the normal population, and (2) data on true-positives found with MS/MS testing. A password-protected Web site on newborn screening by MS/MS done by the Michigan Public Health Institute ("National Genetics File Libraries") allows states to files in templates and brings the files up for viewing. A detailed 8-page "scorecard" developed to synthesize the data from each state lists all the markers and ratios used for testing by MS/MS. It consists of three sections: (a) one showing the 50^{th}, 90^{th}, and 99^{th} percentiles of the ranges for specific analytes in the normal population; (b) one showing cutoff values for specific analytes; and (c) one showing disease ranges on the basis of data from true-positive cases. Once the data are collected from states across the region, they can be used to look for similarities or differences from state to state (or from the literature).

According to Dr. Rinaldo, Region 4's MS/MS project team is trying to get data on at least 50 confirmed cases for each of the 42 MS/MS primary and secondary conditions in ACMG newborn screening panel. Because of the small number of true positives for these conditions, data on true positives must be collected collaboratively, not by individual states. As of Feb. 11, 2006, Region 4's MS/MS project had collected a total of 1,375 confirmed true-positive cases for the 42 MS/MS conditions in the uniform panel, including 235 confirmed cases from Minnesota, 630 from other states in Region 4, and 351 from states outside Region 4 that are contributing data (New York, Florida, California, Colorado, Ohio, and Alaska). To be included in the sample, the specimen must be the first specimen and must be collected within the first 7 days of life. The project team is close to having 50 confirmed cases for some newborn conditions—including MCAD (medium-chain acyl-CoA dehydrogenase), PKU (phenylketonuria), and SCAD (short-chain acyl-CoA dehydrogenase)—but not for most of the conditions. Some data are being provided from Italy, Japan, Saudi Arabia, and Australia; the project team welcomes these data, as well as data from states outside the region.

Finally, Dr. Rinaldo discussed how the MS/MS project is using the raw data it collects from the states using its scorecard to identify appropriate cutoff ranges in MS/MS testing for specific conditions. The MS/MS project defined two boundaries for the cutoff range: (1) the boundaries for a normal population (use an average value as the "lower range" of the cutoff rate); and (2) the disease range. The idea is to broadly define the cutoff range as the range of concentration between the 99^{th} percentile of a normal population and the 5^{th} percentile of the disease range. A cutoff value that lies somewhere between these two extremes is likely to provide the greatest specificity and sensitivity in testing. The project is making good progress to lead to the revision of cutoff values and feedback data to stage and see what impact it has. The MS/MS project is also issuing "quality" report cards to give states in Region 4 feedback on their performance in MS/MS testing.

Questions & Comments

Dr. Gregg asked whether variability across states was due to subpopulation difference (e.g. Amish communities). Dr. Rinaldo said this is a factor, but he does not think it is a major factor. It would be fairly easy to translate into multiples of the median. He plans to do this at some point.

Dr. van Dyck asked whether the goal of 50 cases of each of the diseases was enough. Dr. Rinaldo said 50 cases is an arbitrary number, but if the project team gets to 50 cases of each disease, it will have an unprecedented set of data. If all 4 million babies in the United States were screened each year using the ACMG uniform panel, Dr. Rinaldo thinks there probably would be about 1,500 true-positive cases found each year.

Dr. Hawkins asked what the false-positive cases in MS/MS screening are primarily attributable to—the way the testing is performed or the criteria for cutoffs. Dr. Rinaldo said most false positives come from (1) the arbitrary nature of the cutoffs; and (2) the limited importance attributed to the post-analytical interpretation (a low hanging fruit that could be addressed by training people to do this). He emphasized that most of the data collected currently by the Region collaborative MS/MS project team are descriptive statistics; more sophisticated statistical analyses on the data will be done in the future.

C. Preparing for Disasters: Genetic/Metabolic Health Care Delivery During and After Hurricanes Katrina and Rita

Jess G. Thoene, M.D.
Director, Hayward Genetics Center
School of Medicine
Tulane University
From Region 3: Southeastern Regional Genetics Group (SERGG)

Dr. Thoene, from the Region 3 Southeastern Regional Genetics Collaborative, gave a compelling presentation about what happened with respect to health care delivery for patients with rare metabolic/genetic disease in the wake of Hurricane Katrina, and to a lesser extent, Hurricane Rita, in the late summer of 2005. Hurricane Katrina was a horrific experiment of nature that caused health systems in the region to fall apart and starkly revealed just how fragile the continued existence of patients with rare diseases really is. These patients are the "canaries in the coal mine." Their medical problems are analogous to those encountered by common disease patients in Third World countries (remote from sources of good medical care, no therapeutic modalities or modalities that are very difficult to come by or of uncertain supply).

In the wake of Hurricane Katrina, there were more than 1,000 dead and more than 100,000 homes lost due to flooding in Louisiana alone. Fewer than 70,000 residents now live in New Orleans, as compared with more than 500,000 prior to the storm. There are no public schools open, and only four private schools open. Forty percent of the city lacks power, water, and gas. Cell phones, land lines, and computers all went down. Tulane and Louisiana State University were flooded. But when the levee broke, they were trapped in a building without air conditioning and the temperatures were around 100 degrees inside the building. There was no electricity. They had food and water, but no functioning toilets. And they stayed that way for 4 days until being evacuated from the roof of the parking structure, along with the patients that were in the Tulane Hospital, by helicopters provided by the HCA Corporation that runs the hospital.

The experience with Hurricane Katrina led Dr. Thoene to consider a number of questions related to the care of patients with rare metabolic/genetic diseases:

- How do doctors and clinicians and nutritionists and laboratorians find each other when there is an urgent and immediate diaspora such as occurred after Hurricane Katrina?
- How do patients with rare metabolic/genetic diseases find doctors and other health care personnel in the wake of such an event?
- How do we obtain lab testing when the entire infrastructure of the sate is down? (In Louisiana, all of the genetic testing had been concentrated in the city of New Orleans.)
- How do we meet ongoing needs for formula and orphan medications for patients with rare metabolic/genetic diseases when we don't know where the patients are and all the supply lines are down?

According to Dr. Thoene, in the immediate aftermath of the hurricanes, they were aided in trying to solve these problems by HRSA and SERGG. As they started to look for each other, they realized they were able to send text messages even though their cell phones didn't work. People could call in from other area codes to area code 504 when people in area code 504 could not call out, so they text messaged people and told them to call in. The president of SERGG arranged conference calls so that the genetic services personnel could call in and reassemble itself as a group. Telemedicine capabilities in the region were used to consult with some members who stayed in the disaster zone and began providing genetic service care and followup the week after Katrina. Several critically ill patients with metabolic/genetic diseases were all dealt with appropriately. They got help from laboratories in other areas. Parents willingly shared scarce medicines with strangers who had the same diagnosis as their child. And the Federal Emergency Management Agency (FEMA) granted blanket emergency approval to pay for certain medications for genetic/metabolic patients not only in Louisiana, but also in other states. A metabolic nutritionist and advocacy groups helped with patients' names and phone numbers and with coordinating referrals to other clinics and obtaining formulas and other medicines.

For the future, Dr. Thoene proposed the following:

- Develop a better system for communications, perhaps a centralized emergency number for providers and patients: 1-800-911-GENE
- Develop stockpiles of orphan medications (e.g., urea cycle medications, carnitine, Cystagon, B12, tetrahydrobiopterin) for distribution within the disaster area.
- Institute a guaranteed courier service to deliver the medicines (possibly use Federal or National Guard troops initially).
- Create a fact sheet for genetic/metabolic patients with emergency instructions, including the 1-800-911-GENE phone number.
- Create a hierarchy of labs and clinicians in all of the major regions of the United States willing and trained to respond to such events.
- Involve interested Federal agencies in reviewing whether rare disease patients can access the strategy for orphan drugs being talked about for biodefense to protect these vulnerable patients during a mass natural disaster.
- Develop mutual aid agreements, Emergency Management Assistance Compacts (EMACs), so that states not affected by a disaster can provide aid to states that are affected.

Questions & Comments

Mr. Robertson commented the National Hemophilia Foundation coordinated requests and helped patients get in touch with treatments after the hurricanes, demonstrating the benefit of having a strong central parent advocacy group. Dr. Howell asked whether Louisiana was going to move forward with a plan for infants and children with genetic/metabolic disorders. Dr. Thoene said there is no plan yet, but they hope their experience will help. Dr. Steven Groft agreed with Dr. Thoene that it is important to consider issues related to products for rare disorders in emergencies.

V. NIH OFFICE OF RARE DISEASES—RARE DISEASE CENTERS OF EXCELLENCE

Stephen Groft, Pharm.D.
Director
Office of Rare Diseases (ORD)
National Institutes of Health (NIH)

As Dr. Groft had explained in his presentation to the Committee in January 2005, ORD was established statutorily within the Office of the Director of NIH by the Rare Diseases Act of 2002 (Public Law 107-280). The office works with NIH institutes and centers to support (1) an extramural research program; (2) an intramural research program (a bench-to-bedside grants program that primarily has involved several different NIH institutes and programs within the institutes in collaborative projects for rare disorders); (3) a scientific conferences program; (4) a trans-NIH working group on rare diseases research that brings together all of the NIH institutes and centers to focus on rare diseases (currently looking at the collection, storage, and distribution of biomaterials); and (5) a center for developing and disseminating information about rare diseases. Its budget is about $15.5 million. General information about ORD is available on its Web site: http://rarediseases.info.nih.gov/.

Dr. Groft said that he views ORD as a stimulus for collaboration and bringing partners together to tackle rare disorders. ORD's extramural research program has provided support for more than 640 scientific conferences related to rare diseases since 1995, including 112 in the past year. All of the conferences supported by ORD are offered in conjunction with at least one of the research institutes at NIH. ORD believes the scientific conferences are a good way to develop a research agenda in collaboration with the research institutes, the academic research community, the pharmaceutical industry, and patient support groups. Anyone who would like to see a conference or workshop on a specific disease or group of diseases can contact ORD about that.

ORD also tries to foster collaborations among the partners it believes are essential to the successful development of orphan products: (1) industry (domestic and international, large and small); (2) academic and research community (multidisciplinary efforts); (3) medical specialty societies; (4) patient advocacy groups; and (5) the Federal Government (including regulatory agencies, those providing reimbursement, and those supporting intramural and extramural research). In the years since the Orphan Drug Act in 1983, there have been nearly 280 products approved by the Food and Drug Administration (FDA) for rare diseases. The fact that there are 6,500 or 7,000 rare disorders sometimes makes it appear that not much work is being done on rare diseases. According to ClinicalTrials.gov (http://www.clinicaltrials.gov/), though, there are currently nearly 4,600 ongoing studies involving 820 rare diseases.

The Rare Diseases Clinical Research Network was authorized in the Rare Diseases Act of 2002. That act called for ORD, in collaboration with relevant NIH research institutes and centers, to establish a network to support (1) collaborative clinical research in rare disorders (including longitudinal studies of individuals with rare diseases, clinical studies, phase one and two trials, and/or pilot demonstrations projects); (2) a test bed for distributed clinical data management that incorporates novel approaches and technologies for data management, data mining, and data sharing across rare diseases, data types, and platforms (to address small number of patients at one site); and (3) promote training of new clinical investigators in rare diseases.

The Rare Diseases Clinical Research Network has 10 rare diseases clinical research consortia, which not only perform research but also help train new clinical investigators in rare diseases. Various NIH institutes are partners with ORD in giving guidance and oversight over the various consortia. The 10 consortia are as follows:

1) Angelman, Rett, and Prader-Willi Syndromes—Dr. Art Beaudet
2) Bone Marrow Failure Diseases—Dr. Jarek Maciejewski
3) Genetic Diseases of the Mucociliary Clearance Consortium—Dr. Michael Knowles
4) Rare Genetic Steroid Disorders Consortium—Dr. Maria New
5) Consortium for Clinical Investigation of Neurological Chanelopathies—Dr. Robert Griggs
6) Cholestatic Liver Disease Consortium—Dr. Ron Sokol
7) Rare Lung Disease Consortium—Dr. Bruce Trapnel
8) Rare Thrombotic Diseases Consortium—Dr. Tom Ortel
9) Urea Cycle Disorders Consortium—Dr. Mark Batshaw
10) Vasculitis Clinical Research Consortium—Dr. Peter Merkel

A major problem in conducting research in rare diseases has always been the small number of patients available at one site. At the heart of the Rare Diseases Clinical Research Network is the centralized Data and Technology Coordinating Center in Tampa, Fla. This center collaborates in the design of clinical protocols, data management and analysis; develops a coordinated clinical data management systems for collecting, storing, and analyzing data from multiple diseases and multiple clinical sites; develops tools for Web-based recruitment and referral; constructs a portal for access and integration of public data sources; and promotes communication and coordination within the Rare Diseases Clinical Research Network (including Internet videoconferencing, a centralized secure Web site). Additional information about the Rare Diseases Clinical Research Network and each of the 10 clinical research consortia identified above is available online at http://rarediseasesnetwork.epi.usf.edu/.

Finally, Dr. Groft reviewed ORD's CETT Program (Collaboration, Education, Test, Translation) for Rare Genetic Diseases, a model of cooperation between researchers, diagnostic laboratory, and a patient advocacy group to translate diagnostic tests from research to a clinical laboratory. The process is flexible enough to allow for the development of different types off genetic tests, collaborations, and sources of test development.

Questions & Comments

Dr. Robertson asked whether ORD worked in the areas of genetic privacy with patient advocacy groups. Dr. Groft said the patient advocacy groups do a good job in their own right, and ORD sometimes helps them behind the scenes.

Dr. Brower asked Dr. Groft to talk about the diagnostic laboratories that are a part of this effort. Dr. Groft stated that six laboratories were involved at: Baylor University, University of Chicago, Emory University, Toronto Hospital for Sick Children, UCLA, and GeneDx. They wanted to partner with labs that would agree to make the genetic tests available for 5 years. They also wanted laboratories to be working with an active patient advocacy group. At this time, tests from these labs probably will not seek the Food and Drug Administration approval.

VI. NOMINATION PROCESS FOR CANDIDATE CONDITIONS ON THE UNIFORM NEWBORN SCREENING PANEL

A. Framework for the Overall Nomination Process—Criteria Workgroup Report

Nancy Green, M.D.
Medical Director
March of Dimes Birth Defects Foundation

Dr. Green presented the report of the Criteria Workgroup established at the October 2005 meeting to consider what criteria should be used to evaluate whether conditions should be added to the uniform newborn screening panel recommended by the American College of Medical Genetics (ACMG) expert panel report *Newborn Screening: Toward a Uniform Screening Panel and System*. The workgroup consisted of Dr. Brower, Dr. Boyle, Dr. Dougherty, Dr. Rinaldo, Dr. Green, and Dr. Coggins. Dr. Lloyd-Puryear and Dr. Marie Mann from HRSA assisted the workgroup.

As a prelude to considering the process for adding conditions to the uniform panel, the Criteria Workgroup agreed on several concepts. Specifically, it agreed there should be broad access to the nomination process; considered review of nominations; streamlined processes for nomination and review; transparency of processes for nomination and review; consistent criteria throughout the nomination and review process; and consideration of three broad areas (condition, test, and treatment) and references for each.

The Criteria Workgroup proposed that there be three steps in the process of nominating conditions to the ACMG uniform panel.

- Step #1: Nomination form submitted by proponent(s) of adding a condition
- Step #2: Federal administrative review of the nomination form
- Step #3: Review by the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children
    a. Evidence-based review by an external body
    b. Committee review

Step #1: Nomination form submitted by proponent(s) of adding a condition. Dr. Green presented the Criteria Workgroup's draft of a proposed nomination form (included in TAB #9 of the briefing book distributed to Committee members). The nomination form had the following components:

- *Heading* (with name of proponent, condition, type of disorder, screening method, and treatment strategy)
- *Condition* (with space for information about the incidence, timing of clinical onset, and severity of disease)
- *Test* (with space for information about the screening test to be used, the modality of screening, clinical validation; laboratory performance metrics, confirmatory [diagnostic] testing, and risks)

- *Treatment* (with space for information about the nature of the treatment modality, urgency of initiating treatment after birth, efficacy of treatment, availability of treatment, and potential medical or other risks from treatment)
- *References and submission information* (with space for up to 15 key reference citations, as well as submission checklist and contact information).

Step #2: Administrative review of the nomination form. The Criteria Workgroup thought the purpose of this step should be to complete and clarify the nomination form. The administrative body would neither reject a nomination form nor evaluate the quality of the data. Instead, it would either (a) request additional information for the form; or (b) forward the nomination form to the full Advisory Committee for consideration. The administrative review process would be transparent, with all relevant correspondence documented for the Committee's access. The administrative body reviewing the nomination form remains to be determined (it could be HRSA, but might involve other Federal agencies too).

Step #3: Review by the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. The Criteria Workgroup did not delineate this step in any detail other than to note that the step requires external expertise and transparency. Options for the Committee include (a) expedited review (or rejection); (b) request more information from the proponent nominating the condition; (c) evidence-based review prior to full Committee's consideration; and (d) possibly other steps.

Dr. Green concluded by identifying what the next tasks are with regard to each of the three steps.

- Step #1: The nomination form has to be finalized, with input from the full Committee so it can be piloted to potential users, then modified and ratified by the full Committee.
- Step #2: The Federal review process for the nomination form has to be clarified.
- Step #3: The processes for evidence-based review by an external body and review by the full ACHDGDNC have to be delineated.

Questions & Comments

Dr. Lavenstein asked how many individuals would need to be screened for a disease to validate the test. Dr. Green said the Criteria Workgroup hoped that there would be a cross-section of people helping to validate the nomination form. She thought that decisions about how many people would be needed to validate the test could be worked out with the evidence-based review group.

In response to a question from Dr. Kahn, Dr. Green explained that "expedited review" by the Committee actually meant rejection, not bypassing evidence-based review for acceptance. Dr. van Dyck said he didn't like "expedited review" meaning rejection and suggested changing this language.

Dr. Dougherty commented that the Criteria Workgroup still had to consider what the evidence-based review group would be looking for, so that the workgroup knows that the nomination form is congruent. The Advisory Committee should not deliver the nomination form to an evidence-based review group that has not been part of development of the form.

Dr. Howell asked the Criteria Workgroup to comment on how it envisioned the evidence-based review group and the format of its review. Dr. Green, noting that the Committee had heard various presentations on evidence-based review in the past year, said she wouldn't want to describe that in detail; however, there should be consistency in what is valued throughout the process. Dr. Lloyd-

Puryear added that HRSA was in discussion with Dr. David Atkins at the Agency for Healthcare Research and Quality (AHRQ) and was awaiting a proposal from AHRQ to determine whether or not the Advisory Committee should or could use the existing evidence-based practice centers, the cost of using the centers, and what expertise would be needed. The extent to which the group will follow the process used in the selecting conditions in the ACMG report remains to be determined. Dr. Howell noted that because the diseases are so rare, the expert group that reviews them is going to have to be formed for each disorder.

Dr. van Dyck returned the discussion to the flow of the three steps in the process of nominating conditions to the ACMG uniform panel. He asked two questions related to Step #2 (Federal administrative review). First, was the possibility of rejecting a nomination in Step #2 (Federal administrative review) considered? Dr. Green said that there would be no rejection of a nomination form at this point; the only action for a form with which there was some problem would be to send the form back to nominator for clarification or more information. Second, Dr. van Dyck asked, had there been any consideration of having Step #2 (Federal administrative review) end in the submission of the nomination to the evidence-based review group (bypassing the full Advisory Committee). Dr. Green replied that the Criteria Workgroup thought, given the expense and depth of an evidence-based review, the full Advisory Committee should get the application through the nomination process prior to the evidence-based review group to deliberate on whether to go forward, to stop, or to communicate to the reviewer that the time was not yet propitious for this disorder.

Dr. Boyle said the Criteria Workgroup thought the proposed nomination form had the criteria that would be the starting point for the evidence-based review, but it recognized that the evidence-based review group might refine the nomination form.

Dr. Dougherty added that the Committee still needs to work out specific criteria, or cutoff points, it will use to review the information in the nomination form and to accept or reject nominations. In order to develop these, the Committee needs to know what the evidence-based review group will use. Dr. Rinaldo commented that there is tremendous variation by disorder, and any criteria that are selected must take this into account. Dr. Dougherty reminded Committee members that the evidence-based review group only assesses the evidence; the full Advisory Committee makes the final decision.

Several raised points for additional consideration were raised by people in the audience:

- Dr. Jess Thoene asked whether any consideration had been given to alternative opportunity costs every time a new entity is approved. Dr. Rinaldo said there was a decision by the Criteria Workgroup to eliminate cost considerations at this stage.
- Dr. Anne Marie Comeau asked if the nomination form would include questions about both the screening test and the confirmatory test. She also asked whether the goal of testing was to identify the whole spectrum of disease, or just to look for the most severe form of a disorder and hopefully gain information about the clinical utility of screening for other forms of the diseases. Finally, she asked what would happen if multiple nomination forms were submitted for a single condition. It was agreed that these points should be considered.

Dr. Alan Hinman, saying he foresaw the possibility that dozens of nominations might be submitted, asked whether the conditions would be considered in isolation or whether there would be a comparison of different conditions in terms of the relative burden of disease and costs of different diseases and tests. Dr. Hinman also asked whether there were plans to develop a tracking system with numbers assigned to nominations, so that people could check up on their status. Dr. Green said the tracking system was a good idea.

Finally, Dr. Hawkins suggested that in addition to having a list of references in the back of the form, it would be helpful to list the references in the sections on the substantive sections, as well. Dr. Howell agreed that this was a good idea.

B. A Trial Run of Conditions Using the Proposed Nomination Process

Piero Rinaldo, M.D., Ph.D.
Professor of Laboratory Medicine and Pathology
Mayo Clinic College of Medicine
Chair, Division of Laboratory Genetics
Mayo Clinic Rochester

Dr. Rinaldo presented a trial run of a draft nomination form for submitting conditions to be added to the uniform newborn screening panel recommended in the American College of Medical Genetics (HRSA/ACMG) expert panel report *Newborn Screening: Toward a Uniform Screening Panel and System.* It is hoped that proponents of adding a particular condition to the newborn screening panel will join forces to submit a single form rather than submit nominations independently.

The purpose of the trial run of the nomination form that proponents of adding a condition would submit in Step #1 of the nomination process was to make it easier for Advisory Committee members to assess and comment on the form. The format of the proposed nomination form, Dr. Rinaldo said, is similar to that of the condition-specific Fact Sheets in the ACMG newborn screening report. In addition to the nomination form (with up to 15 references), Dr. Rinaldo said, he expected each nomination would include a cover letter. In the trial run, Dr. Rinaldo used MCAD (medium-chain acyl-CoA dehydrogenase deficiency) as the candidate condition to be nominated (TAB #9 of the briefing book distributed to Committee members).

Questions & Comments

Length and content of the nomination form. Dr. Rinaldo asked Committee members to comment on the content and length of the nomination form, given that the purpose of the form is to provide information that can be used to determine whether to proceed to Step #3 (an evidence-based review of the condition and review by the full Committee. Committee members agreed that Dr. Rinaldo's trial run of the proposed nomination form had made the process clearer to them. They also agreed that the two-page nomination form (10 pt. type) with information about MCAD seemed to contain about the right amount of information.

Dr. Alan Hinman, from the audience, noted that Dr. Rinaldo had filled out the form in a relatively sophisticated way and asked whether the nominations submitted by proponents would be expected to have as much clear data. Dr. Howell said that parent groups have sophisticated professionals working with them, so he would expect that the forms would be filled out in a similar manner. Dr. Hinman then asked whether the example of the nomination for MCAD presented by Dr. Rinaldo would be completed and sent out with blank nomination forms as an example of what was expected. Dr. Rinaldo said the MCAD example was a seat-of-the pants effort, so he'd do that only if and when the Committee and evidence-based review group thought it was a good example. Dr. Telfair suggested that limitations of participation in treatment might be an area to be elaborated on in the form.

Purpose and content of the cover letter. The purpose of the cover letter that Dr. Rinaldo said could be submitted with the nomination form was also addressed. Dr. Rinaldo had said that the graphs showing the results of spectroscopic scans he had included in the trial run of the MCAD nomination could be incorporated with the cover letter. Dr. Kus agreed. Dr. Dougherty expressed concern that the

accompanying cover letter with additional information might jeopardize fairness and an expedited process for reviewing uniform submissions using a standard nomination form. Dr. Alexander and Dr. Lloyd-Puryear urged Committee members not to burden the nomination form with what belongs in more detailed evidence-based review process. Other Committee members concurred that it was best to keep the nomination simple. Dr. Howell said that the consensus seemed to be that the cover letter should be limited.

Whether to evaluate submissions in terms of economic criteria. Dr. Becker, reminding Committee members that the Advisory Committee on Immunization Practices (ACIP) considers economic analysis in the development of its policies, raised the question of whether nominations of conditions to the uniform newborn screening panel should be evaluated in terms of economic criteria. After some discussion, Committee members reached a consensus that economic criteria should NOT be included on the nomination form or be used to evaluate conditions for inclusion in the newborn screening panel.

Dr. Dougherty noted that evidence-based practice centers typically do not look at economics; she added that if economic analysis were to be used, the Committee would have to develop a set of criteria to be used in the analysis. Dr. Hawkins said patent issues enter into economic analyses, and these are very complex and beyond the expertise of this Committee. Dr. Telfair stated that the Committee would have to develop an economic model to consider the economic factors because the model used would determine what the costs would be. Dr. Alexander thought it would be unwise to include an economic analysis.

Dr. Hinman said although economic information should not go on the nomination form, he thought that economic analysis should be used if it is available as part of the evidence-based review. He noted that the U.S Preventive Services Task Force does consider economic factors. Dr. Kahn, reading from page 19 of the minutes from the previous meeting, agreed with that it would be best to leave costs out of the nomination process, but to consider issues of cost, particularly the cost of followup and downstream management, in later decisions by the Committee.

Setting priorities among submissions. Dr. Gregg asked how the Committee would set priorities among submissions if there was no economic analysis or consideration of societal impact. Dr. Howell asked whether the Committee discussed a litmus test. Dr. Green said the Criteria Workgroup avoided that, but the point is well taken that the floodgates may be opened. Dr. Rinaldo said the Criteria Workgroup decided there would be no scoring in the nomination form, just a global consideration of the form. Dr. Kus said he would be concerned about coming up with a weighting scheme. Dr. Alexander and other Committee members agreed that there was no need to quantify what is in a nomination form.

Dr. Rinaldo said there is unlikely to be a flood of nominations because of the requirement that there be both (1) a test for a condition and (2) an active pilot study. Still the question of how to set priorities among them remains. Dr. Boyle suggested that the Criteria Workgroup consider what the process should be used to set priorities among the submissions as a next step.

VII. COMMITTEE BUSINESS—SUBCOMMITTEE REPORTS

The Followup & Treatment Subcommittee, Education & Training Subcommittee, and the Laboratory Standards & Procedures Subcommittee of the Advisory Committee gave reports on their meetings on Feb.13, 2006.

A. Followup & Treatment Subcommittee Report

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 following the full Committee's discussion the previous day, the Followup & Treatment Subcommittee had decided to step back and identify the goals of followup and treatment. Subcommittee members believe that arriving at a consensus about the goals will make it easier to arrive at consensus about what the components of followup and treatment are. Yesterday, the subcommittee was charged with coming up with a process to achieve that.

Participants at Followup & Treatment Subcommittee's meeting on Feb. 13, 2006, agreed that having the Advisory Committee state what the goals of followup and treatment are and achieving consensus about the components of the followup and treatment system would be very helpful to state health departments, state newborn screening programs, families and children, and others. Various approaches for reaching a consensus, including a Delphi process, were discussed at the meeting. People leaned toward having a formalized workshop with representatives of a broad range of stakeholders and perspectives (funding sources, family and patient, newborn screening program, primary and specialty care, state health department, data systems, and research). There are many documents that describe the components of long-term followup that will be examined, but the subcommittee hopes that it and the full Committee can develop consensus recommendations about what the goals and components of followup and treatment should be. The subcommittee plans to present a proposal for a process for arriving at a consensus to the full Committee at the June 2006 meeting.

Questions & Comments

Dr. Howell added that the long-term followup of the uncommon conditions will also involve research.

B. Education & Training Subcommittee Report

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

Dr. Becker reported that the Education & Training Subcommittee meeting on Feb. 13, 2006, was a lively meeting attended by approximately 20-25 people, including members of the public and all members of the subcommittee (some of whom participated via a conference call).

The Education & Training Subcommittee started off on the topic of finding a public spokesperson for newborn screening. The idea of a spokesperson or spokespersons has relatively good support from the subcommittee, but the concept needs to be discussed further.

As the discussions went on, though, a consensus emerged that the priority the subcommittee should address before recruiting a spokesperson for newborn screening should be to ensure that health care providers have the information and resources they need to withstand a potential onslaught of questions about newborn screening from their patients. The medical association partners on the subcommittee emphasized that the importance of identifying Web-based resources about newborn

screening that health care providers could use, so that is going to be the Education & Training Subcommittee's first priority.

Interest was expressed in developing a Web site to put a variety of newborn screening links on it. It was reported that the National Library of Medicine (NLM) has an Info RX toolkit on the Web to educate and assist physicians in prescribing health information to their patients, and it provides information about the conditions in the uniform newborn screening panel (http://www.ghr.nlm.nih.gov/). A coalition of Federal agencies convened by the National Institute of Child Health and Human Development has proposed a one-stop Federal Web site on newborn screening that links to Federal information about newborn screening.

Questions & Comments

Dr. Green added that the Education & Training Subcommittee had also discussed a couple of other points. First, it identified nurses and obstetric providers as primary care providers that are a higher priority in the newborn screening educational efforts for the subcommittee. Second, it agreed that the subcommittee should try to delineate what primary practitioners need to know about newborn screening (which will vary depending on the clinical setting and timing and immediate need). Dr. Terry Davis boiled down the essential points for parents, and something similar needs to be done for health care providers.

Dr. Howell commented that the material that Dr. Watson had presented on the previous day would be on the Web site of the American College of Medical Genetics (www.acmg.org). He observed that the NLM Web site is great and a wonderful place to have information; he encouraged Committee members to take a look at it. Dr. Howell concluded by saying that he hoped that the Education & Training Subcommittee will come back with information on the Web site at the June meeting.

C. Laboratory Standards & Procedures Subcommittee Report

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

Dr. Brower reported the issue the Laboratory Standards & Procedures Subcommittee wants to consider next is the use of a routine second test in newborn screening. Currently, nine states (representing 750,000 babies, or about 20 percent of the babies born in the United States each year)—Oregon, New Mexico, Maryland, Texas, Nevada, Utah, Colorado, Delaware, and Arizona—routinely obtain a second specimen. There are anecdotal reports of cases being missed with the first specimen and then identified through a second specimen.

Over the last few months, a working group of the Subcommittee held a series of conference calls and came up with the idea of a data mining effort to help facilitate the identification of parameters that would be useful to include in a larger study, including all of the routine second specimen sites. This data mining effort will focus on parameters like detection, positive predictive value, recall rates, time of specimen collection, etc.

This idea of a data mining effort was discussed in the meeting of the Laboratory Standards & Procedures Subcommittee attended by 17 people on Feb. 13, 2006. Meeting participants thought that a data mining effort would be useful as step to a larger nationwide study. They emphasized that a protocol would need to be written to identify the goals and expectations of the data mining effort and

that a specialist in epidemiology would be needed to help in the effort. Dr. Hannon agreed to identify a resource within the CDC. It was agreed that the data mining effort should be limited to congenital adrenal hyperplasia (CAH) and congenital hypothyroidism (CH) as a start. The data mining set will include 20,000 matched cases originating in the state of Maryland. A summary of the findings of the data mining will be shared with the Laboratory Standards & Procedures Subcommittee; and a draft proposal for a larger study will be presented for review by the subcommittee and the Advisory Committee as a whole.

Dr. Brower noted the Laboratory Standards & Procedures Subcommittee supports the efforts of Region 4 and the National Coordinating Council, described to the full Committee by Dr. Watson and Dr. Rinaldo the previous day, will be monitoring the findings and outcomes.

VIII. LYSOSOMAL STORAGE DISEASES WORKSHOP

Robert Vogt, Jr., Ph.D.
Research Chemist
Newborn Screening Branch, Division of Laboratory Sciences
Centers for Disease Control and Prevention (CDC)

Dr. Vogt reported on a workshop entitled "Issues in Presymtomatic Diagnoses of Lysosomal Storage Diseases" held on Dec. 6-7, 2005, in Bethesda, Md. The workshop was hosted by the National Newborn Screening and Genetics Resource Center in collaboration with the Health Resources and Services Administration (HRSA), the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), the American College of Medical Genetics (ACMG), and Genzyme.

The agenda for the two-day workshop was included in the briefing book distributed to Committee members (Tab #10), and Dr. Vogt reviewed the highlights.

Day #1: Dec. 6, 2005

- Dr. Vogt, Dr. Joan Keutzer from Genzyme, and Dr. Ken Pass from the New York Department of Health opened the meeting by explaining that the impetus for the meeting came from the fact that there is a test available for newborn screening for Krabbe disease (one of the lysosomal storage disorders) and that New York State has announced that it will do population-based newborn screening for Krabbe disease in 2006.
- Dr. Paul Fernhoff, from Emory University Medical School, gave an introductory talk on lysosomal storage disorders. Then various individuals gave presentations on the biology and current clinical situation for specific lysosomal storage disorders— mucopolysaccharidosis, Pompe disease, umbilical cord blood transplantation for the treatment of infantile Krabbe disease, Fabry disease, Gaucher disease, acid sphingomyelinase deficiency—and on X-linked adrenoleukodystrophy (which is a paroxysmal storage disease).

Day #2: Dec. 7, 2005

- Dr. Howell moderated a session on various followup issues related to lysosomal storage diseases. In that session, there were discussions of a broad spectrum of therapeutic modalities for these disorders: enzyme replacement therapy, stem cell transplants, hematopoietic stem cells, and gene therapy. The therapies discussed range from Food and Drug Administration (FDA)-approved therapies to investigational animal models.

- Dr. Deborah Marsden from Children's Hospital in Boston highlighted some of the downstream issues that result when one obtains a positive test result for a presymptomatic screen of one of the lysosomal storage disorders.
- Dr. Ed Kaye from Genzyme gave a talk on an independent registry, which is monitored by the Genzyme Foundation and an independent board that compiles therapeutic and followup information on all patients undergoing Genzyme enzyme replacement therapy. This registry model is one that the Committee might consider in terms of trying to collect data on the benefits and risks of screening and treatment for disorders. The registry is available to researchers, and a number of papers have been published using data from the registry.
- Dr. Vogt talked about a program of CDC's Newborn Screening Branch to collect dried blood spot specimens of particular interest, either because they come from infants with known disorders or as research tools for method evaluation and development. Some are diagnosed prenatally. They have made the first steps toward developing a collection of blood spots from infants with lysosomal disorders. Sometimes the disorders are diagnosed prenatally if there is a family history.
- Dr. Lloyd-Puryear gave an overview of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Dr. Jim Hanson, from the National Institute of Child Health and Human Development (NICHD), spoke about a new technologies request for proposals that is available on the Web.
- The day concluded with an open session led by Dr. Howell and Dr. Celia Kay that covered a wide range of topics.

In December of 2006 or January of 2007, a report with broad public health recommendations from the "Issues in Presymtomatic Diagnoses of Lysosomal Storage Diseases" workshop will be published in *Morbidity and Mortality Weekly Report.* The report will not advocate newborn screening for any particular disorders. Instead, the report will include very broad public health recommendations.

Questions & Comments

Dr. van Dyck asked Dr. Kus to comment on what New York is doing with respect to Krabbe disease. Dr. Kus explained that the New York legislature passed a law that requires the state to do universal population-based screening for Krabbe disease. The New York State Department of Health is in the process of developing a protocol for the Krabbe disease screening procedure, as well as for what happens after the screening and the treatment. It appears that the state's newborn screening program for Krabbe will be live in a couple of months, using dried blood spot. One of the issues that arose is how to deal with the various forms of Krabbe disease (infantile, juvenile, and adult onset).

Dr. van Dyck asked what prompted the legislature to pass the legislation. Dr. Kus said that Jim Kelly, the Buffalo Bill's quarterback who started the Hunter's Hope Foundation after his son Hunter was diagnosed with Krabbe disease, pursued this. Then suddenly there was a test and promising treatment, even though there is limited data, for Krabbe disease. Ms. Gartzke confirmed that the Hunter's Hope Foundation was active in advocating for this with Ms. Jill Fisch from Save Babies Through Screening, but they never asked for a law to be passed and don't know how that occurred.

Ms. Gartzke said most of the individuals with Krabbe disease in the registry at the Hunter's Hope Foundation have early infantile onset. Dr. Lavenstein again emphasized the heterogeneity of Krabbe disease and various forms (infantile, juvenile, and adult onset). He said sometimes people present in middle childhood with the onset of a seizure or learning disability, and an MRI scan is diagnostic.

Dr. Robertson asked whether Krabbe disease would have met the criteria that the Committee is looking for on the Nomination Form presented by Dr. Green and Dr. Rinaldo. Dr. Rinaldo replied that at the time of the ACMG newborn screening report, Krabbe disorders scored among the lowest of the potential disorders for inclusion in the uniform panel, but that was before there was a breakthrough in treatment reported in the New England Journal of Medicine (cord blood) and the test for Krabbe disease became available. Now it has risen quickly to the top. This is where the challenge is. Newborn screening is a very dynamic field. The criteria for the nominations submitted to the Advisory Committee are that there be a test and a treatment and that there be someone prospectively screening for the condition. Right now there is no pilot test, so it would not meet the criteria.

Dr. Nancy Green noted that New York's Krabbe disease screening will in essence be a pilot program, because it will be the first time that population-based screening for Krabbe disease occurs. She is not sure the state views the program as a pilot, but she hopes the state takes the responsibility for prospectively collecting and reporting on the data. She also said she hoped any recommendations in the *Morbidity and Mortality Weekly Report* would take into account the lack of any population-based data whatsoever. Dr. Vogt assured her that they would.

Dr. Carol Greene, from the Society for Inherited Metabolic Disorders (SIMD), in the audience asked whether anyone had done an anonymized test to see what the variants of Krabbe disease in the population are. If the treatment is a bone marrow transplant, that is not a trivial thing and should not be given to someone unless they have a form of the disease that will produce serious symptoms. Dr. Howell said we would not learn the answer without population screening, which New York is now doing.

Finally, a question was asked about what the cycle for reviewing conditions in the uniform newborn panel should be, given the rapidity with which Krabbe disease has moved up the ladder. Perhaps the Committee should consider automatic reviews periodically (e.g., every year, every 3 years). Dr. Howell said he would not be surprised if several of the first applicants that come to the Committee are not on the ACMG list that says no test, no treatment, because there have been dramatic changes for diseases other than Krabbe disease.

IX. ORGANIZATIONS REPRESENTING STATE POLICYMAKERS AND LEGISLATURES

A. Newborn Screening: The Role of State Legislatures—National Conference of State Legislatures

Alissa Johnson, M.A.
Program Principal
Health Program
National Conference of State Legislatures (NCSL)

Ms. Johnson gave an overview of NCSL and then discussed the role of state legislatures in newborn screening. NCSL is a bipartisan organization that serves state legislatures. Headquartered in Denver, the organization was founded (1) to improve the quality and effectiveness of state legislatures; (2) to promote policy innovation and communication among state legislatures; and (3) to ensure state legislatures a strong cohesive voice in the Federal system. Its work is supported by dues from states, foundations, and grants.

NCSL has an executive committee of approximately 60 members, including both Republicans and Democrats, and the leadership of that committee rotates every year. NCSL also has a set of standing committees on various topics like health and education. In order for NCSL to take a policy position that its representatives in Washington will lobby for, two-thirds of NCSL's members must vote to take the position. NCSL has a policy position to encourage the promotion of public health.

NCSL has a Genetic Technologies project that was begun in 1999 with a grant from the National Human Genome Institute. The project is currently supported by the National Coordinating Center (NCC) for the seven Regional Genetics and Newborn Screening Collaboratives established by HRSA at the American College of Medical Genetics (ACMG) and by the American Academy of Neurology. The project provides technical assistance to the NCC for the collaboratives regarding policy matters of mutual concern to states and the NCC (e.g., access to treatment and other services for disorders diagnosed through newborn screening). More information about NCSL's Genetic Technologies project is available at the Web site http://www.ncsl.org/programs/health/genetics.htm.

State legislatures are involved in several aspects of newborn screening:

- Determining the state's newborn screening panel
- Appropriations and fees
- Coverage/reimbursement –fees, treatment (e.g., medical foods)
- Informed consent (two states and D.C.) or authorization
- Parent education (e.g., a law might require that a brochure be given to parents prior to newborn screening; regulations might specify content)
- Voluntary vs. mandatory nature of programs and exemptions (e.g., whether religious exemptions are appropriate)
- Privacy and confidentiality of information
- Information and data sharing
- Use and retention of residual dried blood spots

- Laboratory standards
- Role of providers, hospitals, and state agencies

NCSL maintains a state legislative database of genetic legislation that includes newborn screening. It is updated at least once a month. In 2005, several states enacted legislation related to newborn screening: Arizona, Arkansas, Kentucky, Mississippi, Montana, Nebraska, New Mexico, North Carolina, Oklahoma, Texas, and Virginia. State legislatures are aware of the ACMG newborn screening report, and most of the states that passed legislation in 2005 expanded screening or paved the way to expand screening in the future. Kentucky chose to remove the legislature from determining the list of disorders that will be screened for in the future and handed that decision over to the state health department. Another hot issue in 2005 was treatment for disorders identified through newborn screening.

In the first month of 2006, the trend toward the expansion of newborn screening in the states appears to be continuing. By mid-January 2006, nine states had enacted legislation that expanded newborn screening: Georgia, Michigan, Mississippi, New Hampshire, New Jersey, New York, Pennsylvania, Washington, and West Virginia. Michigan seems to be on the verge of establishing a quality assurance committee that will recommend to the state health department which conditions to add to the newborn screening panel. Three states (Iowa, Missouri, and Virginia) have introduced bills related to coverage for treatment of medical foods.

Questions & Comments

Dr. Hawkins asked Ms. Johnson to comment on whether the trend in some states (e.g., Kentucky) to have determinations about the composition of the newborn screening panel move from the state legislature to the state health department is a good thing or not. She replied that it depends on what one thinks is an appropriate level of oversight. A state health department has more expertise and allows for a speedier process (e.g., the Texas legislature only meets every other year); however, a state legislature has a key role in financing. NCSL has no position on where the responsibility should be located. Dr. Becker observed that most state health departments have administrative regulations that require public comment opportunities. Mr. Robertson said that from the point of view of patient advocacy groups, which of these bodies—the legislature or the state health department—is going to be more effective varies from state to state and from issue to issue.

Dr. Becker asked Ms. Johnson to comment on the educational activities for legislatures that NCSL sponsors. Ms. Johnson said that NCLS has a magazine that comes out 10 times a year and they have recently done an article on newborn screening. They also have done issue briefs on newborn screening. In addition, NCSL meets with legislatures three times a year—at the spring forum, fall forum, and annual meeting. This coming April, the NCSL health committee will address integrated public health information systems. Finally, NCSL has had a number of smaller regional workshops in conjunction with the Association of State and Territorial Health Officials (ASTHO) and HRSA to educate legislatures about genetic issues. They held a large genetic policy forum in 2001 and may consider that again someday.

B. State Health Policymakers Perspectives on Newborn Screening—Association of State and Territorial Health Officials

Christopher A. Kus, M.D., M.P.H.
Pediatric Director, Division of Family Health
New York State Department of Public Health
Association of State and Territorial Health Officials (ASTHO)

Dr. Kus explained that ASTHO is a national nonprofit organization representing the chief officials of state and territorial public health agencies. These officials are dedicated to formulating and influencing sound public health policy and to ensuring excellence in state-based public health practice ASTHO had for a while a genetic advisory committee on which Dr. Kus served. Dr. Kus is a past president of the Association of Maternal and Child Health Programs (AMCHP), an affiliate of ASTHO that represents the maternal and child health directors and children with special health care needs program directors,

Next Dr. Kus outlined state health policymakers' general views and concerns with respect to newborn screening:

- The overarching principle is that newborn screening is a comprehensive and coordinated system.
- The entire newborn screening system, including followup, must have adequate resources.
- Newborn screening is referred to as a Federal-state partnership, but the system clearly involves private health care providers.
- Guidelines are preferred over mandates.
- Population-based, public health principles should be applied to newborn screening.
- Access to care is a critical issue.
- A trained workforce (public and private sectors) is vital.
- Evaluation of programs is essential.
- Building the infrastructure for long-term followup is necessary. This means monitoring continuously the medical management and care coordination of affected individuals; assessing the efficacy, sustainability, and safety of early treatment intervention; uncovering new disease treatment outcomes; and demonstrating the utility and limitations of testing.

Finally, Dr. Kus identified some ASTHO publications in this area, all of which are on ASTHO's Web site www.astho.org:

- Issue Brief: "State Strategies to Promote Coordination of the Newborn Screening System" (2004).
- Report: *Financing State Newborn Screening Systems in an Era of Change* (2005).
- Position statement: "Newborn Screening," passed by the ASTHO Executive Committee, July 2005.

For more information, contact any of the following: Dr. Kus at the New York State Department of Health; Ms. Lauren Raskin Ramos, Principal Director, Public Health Prevention and Promotion, ASTHO; or Ms. Lauren Ratner, Director, Maternal and Child Health Policy, ASTHO.

Questions & Comments

Dr. Green asked Dr. Kus to make the ASHTHO reports available to the Committee. Dr. Kus said he would be happy to do this. Dr. Howell said it would be a good idea to send the ASTHO reports out to Committee members, because there have been some changes in the Committee's membership.

X. PUBLIC COMMENT SESSION

The following individuals made public statements on the afternoon of Tuesday, Feb. 14, 2006. The written text of their statements appears in Appendix A.

1. Jana Monaco
Parent & Board Member
Organic Acidemia Association

Ms. Monaco said she was glad to share a parent's perspective on behalf of the Organic Acidemia Association in support of the efforts to achieve a uniform newborn screening program. She noted that Virginia will expand its newborn program on March 1 and people are working hard to prepare for the screening by producing educational materials for families and medical professionals. In addition, the New York-Mid-Atlantic for Genetic and Newborn Screening Collaborative is also working on such education and attaining some uniformity within the regional collaborative. Nevertheless, Ms. Monaco identified several areas of concern: (1) the distance that families of children affected with genetic or heritable disorders have to travel for care (e.g., "border babies" such as those born in northern Virginia are referred to Richmond, Va., rather than to Children's National Hospital in D.C.); (2) the need for education of health care providers; and (3) the need for greater standardization of newborn screening and care. Finally, Ms Monaco urged the Committee to involve metabolic physicians who care for affected children in its work, noting that the need for their expertise will increase as newborn screening is expanded and more babies are diagnosed and require long-term followup.

2. Jill Levy-Fisch
Parent & President
Save Babies through Screening Foundation

Ms. Fisch reported that she is the newly elected president of the Save Babies Through Screening Foundation and hopes the Advisory Committee will view the foundation as a partner. She is looking forward to making changes at the foundation and providing information and guidance on newborn screening on an international level. Ms. Fisch emphasized the need for education of families and medical providers about newborn screening and the needs of individuals found to have disorders. She urged the American Academy of Pediatrics and the American Academy of Family Practitioners to send a letter to all of their members making them aware of the Web site http://www.newbornscreening.info/ and link to it on their own websites. Ms. Fisch also suggested that an educational CD on newborn screening prepared by the Georgia March of Dimes be distributed nationwide. Ms. Fisch stated that there is a desperate need for metabolic food and formula legislation and said that she hoped that other states would follow Kentucky's lead in this matter. Finally, noting that she and Ms. Micki Gartzke had recently attended meetings in New York State, which is preparing to screen newborns for Krabbe disease, Ms. Fisch expressed support for getting a mechanism in place to add disorders to the uniform newborn screening panel expeditiously.

3. Deb Lee Gould, M.Ed.
Director, MCAD Parent and Grief Consultant
Fatty Oxidation Disorders Family Support Group
(presented by Jill Levy-Fisch, Save Babies through Screening Foundation)

Ms. Gould, the parent of a college-age son with MCAD (medium-chain acyl-CoA dehydrogenase) deficiency, sent a letter illustrating the importance of educating medical professionals about MCAD and other disorders. Her son recently went in for oral surgery at a large teaching hospital in North Carolina. She discussed her son's emergency protocol with the surgeon and anesthesiologist 5 days before the surgery and gave both doctors a copy of the protocol, but the anesthesiologist arrogantly overrode the protocol. Her son strongly voiced his concerns, as well, having had a sister who died under similar circumstances, but the anesthesiologist refused to listen. The result was that her son experienced a serious metabolic crisis that could easily have caused his death or serious brain damage.

4. Micki Gartzke
Parent & Director of Education & Awareness
Hunter's Hope Foundation

As the parent of a child who died from early infantile Krabbe disease after a long diagnostic odyssey and as a representative the Hunter's Hope Foundation, which supports research and families dealing with Krabbe disease and related disorders, Ms. Gartzke are said she could not stress enough the great importance of progress towards a nomination process to add a disease to the core panel. Krabbe disease is now treatable with cord blood transplant if detected early, and she looks forward to the day when Krabbe disease is deemed appropriate for the uniform newborn screening panel. Ms. Gartzke applauded the efforts of the Education & Training Subcommittee to increase public awareness, educate health care providers, and educate state health departments and legislatures about newborn screening. She said she thought the idea of a one-stop Web site is excellent. She agreed with Ms. Fisch that the Web site www.newbornscreening.info is an excellent resource for disease-specific information targeted to both parents and physicians. Finally, Ms. Gartzke reported that the Hunter's Hope Foundation is working with New York State to help the state prepare to begin screening newborns for Krabbe disease. Ms. Gartzke promised to update the Committee with additional information from New York and when the time is right, the Hunter's Hope Foundation will seek guidance on how it can best assist with the nomination of Krabbe disease to the core panel.

5. Peter Sybinsky, Ph.D.
Chief Executive Officer
Association of Maternal and Child Health Programs (AMCHP)

Dr. Sybinsky said that AMCHP supports a system of newborn screening for serious and potentially fatal genetic disorders, and an evidence-based uniform panel of screening tests that form the starting point for such a system, but it believes that more attention and resources need to be devoted to long-term followup of newborns found to have disorders as part of a comprehensive and coordinated newborn screening system. Short-term followup includes those activities that ensure all infants are screened, abnormal results are appropriately and expediently handled, and affected infants are promptly identified, appropriately referred, and treatment is initiated where applicable. Long-term followup extends the period of followup substantially to monitor continuously the medical management and care coordination of those affected who require such; assess the efficacy, sustainability, and safety of early treatment intervention, and uncover new disease or treatment outcomes that might be evidenced. AMCHP is committed to facilitating developmental work in the

area of long-term followup and plans to survey its members, state maternal and child health programs, to obtain information about the current status of long-term followup activities.

6. Arthur Burghes, Ph.D.
Associate Professor
Molecular & Cellular Biochemistry at Ohio State University
Families of Spinal Muscular Atrophy (SMA)

Dr. Burghes, noting that SMA is the leading genetic killer of children under the age of 2 and the second most common autosomal recessive genetic disorder, said he strongly supports Dr. Rinaldo's recommendation that SMA be the chosen disease for the trial run of the modified process for adding disorders to the uniform newborn screening panel. Dr. Burghes' research and Dr. Kathryn Swoboda's research at the University of Utah suggest that the successful treatment of SMA will require administering drugs to affected newborns before symptoms appear. Consequently, newborn screening will be vital to identify SMA-afflicted children and initiate treatment immediately. A DNA-based test for SMA that has been adapted to mass spectrometry detects 95 percent to 98 percent of cases. This or other tests can be developed to move DNA testing into newborn screening.

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

Dr. Greene explained that the members of SIMD are scientists and clinicians, including physicians, nutritionists, nurses, and counselors, who developed or have improved the screening diagnosis and treatment for inborn errors of metabolism and who provide diagnosis and treatment to preserve life, health, and development for those with inborn errors of metabolism. SIMD members deeply appreciate the Committee's efforts to develop a process of nomination of new conditions to the uniform newborn screening panel and to ensure access to appropriate followup diagnostic and treatment services for every baby and family identified by newborn screening. SIMD is willing to help the Committee in any way it can. Dr. Greene would be happy to take any questions or requests from the Committee to the SIMD Board if the Committee thinks SIMD can be of assistance.

XI. 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

Written Protocols for the Committee. Dr. Howell reported that he had asked Dr. Lloyd-Puryear to convene a workgroup consisting of Dr. van Dyck, Dr. Becker, Dr. Boyle, and himself to come up with similar written protocols for the ACHDGDNC. It is not common for Federal advisory committees to have written protocols, but one committee that does have them is the Advisory Committee on Immunization Practices (ACIP). Information on ACIP protocols was included in materials given to Committee members in their briefing books at October 2005 meeting; and there is additional information on Center for Disease Control and Prevention's (CDC) Web site.

Agenda for the Next Committee Meeting. The next meeting of the Committee is scheduled for June 5–6, 2006. Dr. Howell asked for members to suggest possible agenda items. Dr. Dougherty

first asked whether an expert in evidence-based review could be added as a Committee member, so that the Committee would have its own independent advice independent of the evidence-based review group. Dr. Lloyd-Puryear replied that there are no slots for members but that a consultant might be hired who would come to the meetings on an ongoing basis.

The following topics were identified by Dr. Howell and other Committee members for possible inclusion on the next meeting's agenda:

1. A report from the newly formed workgroup on written protocols for the Committee
2. A discussion or presentation on barriers to sharing data (state laws, lack of infrastructure, patents, etc.)
3. Continued work and reports by the subcommittees
4. A presentation on the National Library of Medicine's Genetics Home Reference Web site (http://ghr.nlm.nih.gov/) from Dr. Cathy Fomous.
5. Work on refining Step #2 and especially Step #3 in the process for adding conditions to the uniform newborn screening panel:

    - *A presentation from the Criteria Workgroup* on (a) additional modifications to the nomination form for nominating conditions to be added to the uniform newborn screening panel; (b) methods for prioritizing nomination forms that are submitted; and (c) thoughts related to the evidence-based review group's structure and criteria.
    - *A presentation from someone from an evidence-based review group*. Noting that refining Step #4 is particularly important because of the necessity of aligning the nomination process with the evidence-based review criteria, Dr. Becker suggested that the Committee invite one or two people from an evidence-based review group to make a presentation to (1) provide the Committee with an overview of the kinds of things they would be looking for in a submission; and (2) provide the committee with an idea of the kinds of processes that they would go through externally to bring their findings back to the Committee. Dr. Lloyd-Puryear said that this would be possible. Dr. Boyle mentioned the evidence-based review process being established at CDC called the Evaluation of Genomic Applications in Practice and Prevention (EGAPP); perhaps Dr. Linda Bradley could be invited to discuss that, as well as how that group prioritizes nominations. Dr. Howell said that these were suggestions worth pursuing.
    - *Report on pilot testing of nomination form for adding conditions to the uniform newborn screening panel*. Dr. Green suggested having sort of a pilot of the nomination form for adding conditions to the uniform newborn screening panel. Dr. Howell said the Criteria Workgroup had made wonderful progress on the form and that a pilot test was an excellent idea. The following questions were addressed and it was decided that the pilot should be reported on at the next meeting.
        - Should Dr. Rinaldo's MCAD model response be distributed along with the draft nomination form in the pilot? Dr. Dougherty said some changes needed to be made first (e.g., put the references near the statements, not just at the end, as someone suggested earlier).
        - What groups will be included in the pilot? Dr. Dougherty said part of CDC has a cognitive testing group to see how people are responding in real time to questions to see how user friendly the nomination form is, so if some group would be willing to fill out the form, that would help the Committee see how

user friendly the form is (might have to have a sophisticated group and a not sophisticated group). Dr. Carol Greene from the Society for Inherited Metabolic Disorders (SIMD) offered to have her organization help pilot the form, and she thought the Genetic Alliance could help pilot, too.

- What is the deadline for the pilot? Dr. van Dyck said he expected the pilot to be ready to be presented by the next meeting, because he was envisioning a pilot in one or two places that fill out the form using one or two conditions. Dr. Howell agreed we should have the pilot at the next meeting. If the evidence-based review group says that things need to be added, they can be added when the Committee redoes the pilot. Dr. Howell wanted to get things moving as quickly as possible.

After asking if there were any more comments or questions, Dr. Howell concluded the meeting at 2:05 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