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

Summary of Tenth Meeting
May 17-18, 2007
Washington, DC

The Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children was convened for its 10th meeting at 9:08 a.m. on Thursday, May 17, 2007, at the Ronald Reagan Building and International Trade Center in Washington, D.C. The meeting was adjourned at 1:58 p.m. on Friday, May 18, 2007. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments on May 18, 2007.

Committee Members Present

Amy Brower, Ph.D.
Executive Director
Medical Informatics and Genetics
Third Wave Molecular Diagnostics
315 South Fork Place
South Sioux City, NE 68776

Gregory A. Hawkins, Ph.D.
Associate Professor
Department of Internal Medicine
Section on Pulmonary, Critical Care, Allergy and Immunologic Diseases
Center for Human Genomics
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157-1054

R. Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children
Professor, Department of Pediatrics (D820)
Leonard M. Miller School of Medicine
University of Miami
P.O. Box 016820
Miami, FL 33101

Jana Monaco
Board Member
Organic Acidemia Association
3175 Ironhorse Drive
Woodbridge, VA 22192

James A. Newton, M.D.
President
Alabama Neonatal Medicine, P.C.
7203 Copperfield Drive
Montgomery, AL 36117

Piero Rinaldo, M.D., Ph.D.
Professor of Laboratory Medicine
T. Denny Sanford Professor of Pediatrics
Vice-Chair of Academic Affairs and Intramural Practice
Department of Laboratory Medicine and Pathology
Mayo Clinic College of Medicine
200 First Street, Southwest
Rochester, MN 55905

Michael Skeels, Ph.D., M.P.H.
Director
Oregon State Public Health Laboratory
1717 SW Tenth Avenue
Portland, OR 97201

Liaison Members

Joseph Telfair, Dr.P.H., M.S.W., M.P.H.
Secretary's Advisory Committee on Genetics, Health, and Society
Professor, Public Health Research and Practice
Department of Public Health Education
School of Health and Human Performance
University of North Carolina at Greensboro
437 HHP Building
1408 Walker Avenue
P.O. Box 26170
Greensboro, NC 27402-6170

Ex-Officio Members

Coleen Boyle, Ph.D., M.S.
Director, Division of Birth Defects and Developmental Disabilities
Division of National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
1600 Clifton Road, Mailstop E86
Atlanta, GA 30333

Denise Dougherty, Ph.D.
Senior Advisor, Child Health and Quality Improvement
Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, MD 20850

Peter C. van Dyck, M.D., M.P.H., M.S.
Associate Administrator
Maternal and Child Health Bureau
Health Resources and Services Administration
Parklawn Building
5600 Fishers Lane, Room 18-05
Rockville, MD 20857

Executive Secretary

Michele A. Lloyd-Puryear, M.D., Ph.D.
Chief, Genetic Services Branch
Maternal and Child Health Bureau
Health Resources and Services Administration
Parklawn Building
5600 Fishers Lane, Room 18A-19
Rockville, MD 20857

Organization Representatives Present

American Academy of Family Physicians
Norman B. Kahn, Jr., M.D.
Vice President, Science and Education
American Academy of Family Physicians
11400 Tomahawk Creek Parkway
Leawood, KS 66211-6272

American Academy of Pediatrics
Tracy L. Trotter, M.D., FAAP
200 Porter Drive, 3rd Floor
San Ramon, CA 94583

American College of Obstetricians and Gynecologists
Anthony R. Gregg, M.D.
Director, Maternal Fetal Medicine
Medical Director of Genetics
Department of Obstetrics and Gynecology
University of South Carolina School of Medicine
Two Medical Park, Suite 208
Columbia, SC 29203

Child Neurology Society
Bennett Lavenstein, M.D.
Associate Professor, Neurology & Pediatrics
Neurology Department
Children's National Medical Center
111 Michigan Avenue
Washington, DC 20010

Department of Defense
Lt. Col. David S. Louder, III, M.D.
Chief Consultant for Maternal-Child Medicine
Air Force Medical Corps
AFMSA/SGOC
110 Luke Avenue, Room 405
Bolling AFB, DC 20032

Food and Drug Administration
Ethan D. Hausman, M.D., FAAP, FCAP
Medical Officer
Inborn Errors of Metabolism Team
Division of Gastroenterology Products
WO-22, Room 5171, HFD-180
US FDA, CDER, OND, ODE-3
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Genetic Alliance
Sharon Terry, M.A.
President and Chief Executive Officer
Genetic Alliance
4301 Connecticut Avenue, N.W., Suite 404
Washington, D.C. 20008-2304

March of Dimes Birth Defects Foundation
Diane Ashton, M.D., M.P.H.
Deputy Medical Director
March of Dimes
1275 Mamaroneck Avenue
White Plains, NY 10605

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I. WELCOME, OPENING REMARKS

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

New Committee Members and Liaisons. Dr. Howell opened the meeting by recognizing two new nonvoting organizational liaison representatives to the Advisory Committee: Ms. Sharon Terry from the Genetic Alliance and Dr. Timothy Geleske from the American Academy of Pediatrics (AAP). Dr. Geleske was unable to attend this meeting, and Dr. Tracy Trotter represented the AAP in his absence. Dr. Howell also noted that Dr. Michael DeBaun, a pediatric hematologist and associate professor at Washington University School of Medicine in St. Louis, Missouri, has joined the Committee as a new member. Dr. van Dyck reported that a solicitation for new Advisory Committee members to replace members whose terms are ending in September 2007 was published in the *Federal Register*. The nomination process closed in March and the U.S. Department of Health and Human Services (HHS) is reviewing the nominations.

Agenda for the Day. Dr. Howell said that the agenda for the 2-day meeting would include the following:

- **Process for nominating and evaluating conditions for inclusion on the uniform newborn screening panel.** Dr. James Perrin would present a proposal for the structure and process for the new external Evidence Review Group (ERG) that will be involved in the process for adding conditions to the uniform newborn screening panel. The ERG will be cochaired by Dr. Perrin and a Committee member.
- **Long-term followup after newborn screening.** Dr. Boyle and Dr. Alex Kemper would report on the April 2007 workgroup 1-day meeting on long-term followup for newborn screening.
- **Activities of the HRSA-Funded Regional Genetics and Newborn Screening Collaboratives**:
    - Dr. Stephen Downs, Dr. Rani Singh, and Dr. James Eckman would report on long-term followup projects related to newborn screening undertaken via two HRSA-funded Regional Genetics and Newborn Screening Collaboratives: the Region 4 Genetics Collaborative and the Region 3/Southeastern Regional Genetics Group (SERGG).
    - Dr. Rinaldo and Dr. Marzia Pasquali would report on projects to improve the performance of newborn screening by tandem mass spectrometry (MS/MS) in two Regional Genetics and Newborn Screening Collaboratives: the Region 4 Genetics Collaborative and the Region 6/Mountain States Genetics Regional Collaborative Center.
- **Report on the status of the States with respect to newborn screening.** Dr. Brad Therrell would give the Committee an update on the current status of State newborn screening programs and report on two recent meetings related to newborn screening.

- **Report on newborn screening at the Department of Defense.** Dr. Louder would report on the newborn screening program at the U.S. Department of Defense.
- **Federal legislative update**. Mr. Emil Wigode from the March of Dimes Birth Defects Foundation would provide an update on Federal appropriations and authorizing legislation of relevance to the Advisory Committee.
- **Subcommittee meetings and reports.** The Advisory Committee's Education & Training Subcommittee, Followup & Treatment Subcommittee, and Laboratory Standards & Procedures Subcommittee would meet on Thursday, May 17, 2007, and give reports to the full Committee on Friday, May 18, 2007. All of the subcommittee meetings would be open to the public.

Committee Correspondence. Letters were sent to the Secretary's Advisory Committee from several organizations requesting formal representation on the Committee as a nonvoting liaison representatives: (1) the American College of Medical Genetics (ACMG); (2) the Society for Inherited Metabolic Disorders (SIMD): (3) Pediatrix Medical Group; and (4) PerkinElmer Life and Analytical Sciences, Inc. (included under TAB #5 in the binder prepared for the May 17-18, 2007, Advisory Committee meeting). Dr. Howell asked Committee members to review the letters so that they could come to some decision about them later in the meeting when standard operating procedures for the Committee were discussed.

Approval of Minutes. The minutes from the December 18-19, 2006, meeting of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children were approved.

Meeting Dates for 2008. Dr. Lloyd-Puryear said that dates for May and September 2008 meetings have not yet been set and asked Committee members to indicate on calendars provided in their binders (TAB #17) which dates they would not be available.

II. PROCESS FOR NOMINATING/EVALUATING CANDIDATE CONDITIONS FOR THE NEWBORN SCREENING PANEL

A. Proposal for an External Evidence Review Group (ERG)

James Perrin, M.D.
Professor of Pediatrics, Harvard Medical School
Director, MassGeneral Hospital Center for Child and Adolescent Health Policy
Director, Maternal and Child Health Bureau Evidence Review Group, Systems of Care for Children and Youth with Special Health Care Needs

Dr. Perrin presented a proposal to the Advisory Committee for the structure and process for the Evidence Review Group (ERG) to be involved in the nomination and evaluation process for candidate conditions on the uniform newborn screening panel. The proposed ERG, he emphasized, would *not* make recommendations to the Advisory Committee. The primary role of the ERG would be to review the evidence relevant to the Advisory Committee in making recommendations about which conditions to add or remove from the uniform newborn screening panel recommended by the American College of Medical Genetics (ACMG).

Composition of the ERG. Participants at an October 23, 2006 meeting convened to think through strategies for developing better evidence for the Advisory Committee's use in evaluating conditions for inclusion in the uniform newborn screening panel. They recommended that the ERG consist of a core evidence group staff with a project director who is knowledgeable about epidemiology/methods; a consumer; someone representing public health, someone with experience in economic assessment; and someone who brings content expertise in genetics). The full Advisory Committee, including some members who would be regular participants, would assist the core ERG. Individuals with ad hoc expertise in the disorder or specific tests under consideration or in methods would also assist the core group. Dr. Perrin said a clear conflict-of-interest policy would be established for ERG participants. In addition, an external advisory group for the ERG would be created to bring additional expertise in review methods, in genetics, and among health care providers.

Tweaking the Nomination Form. The process approved by the Advisory Committee for nominating and reviewing conditions involves three steps:

- **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. Advisory Committee review
    b. Evidence-based review by an external ERG
    c. Advisory Committee review and decision

The nomination form approved by the Committee provides some evidence relevant to four questions: (1) does the information clearly define a disease (in different populations); (2) what is the prevalence of the disease (in different populations); (3) can the condition be identified reasonably well in screening; and (4) are there actions after screening that can lead to positive outcomes?

Participants at an October 23, 2006, meeting convened to think through strategies for developing better evidence for the Advisory Committee's use in evaluating conditions for inclusion in the uniform newborn screening panel generally affirmed the Advisory Committee's proposed nomination form and process (as reported to the Committee in December 2006), but they agreed that some refinements to the form by the ERG and Advisory Committee will be necessary.

To help refine the nomination form, the ERG will seek greater clarity with members of the Advisory Committee about the definitions of terms such as accuracy (test), available (test), efficacy (treatment), and urgency (treatment). The ERG also will seek advice from the Committee about what constitutes the minimum sensitivity and specificity of newborn screening tests. The ERG will raise issues about the evidence regarding costs, which are not on the current nomination form, as well as issues related to potential harms of screening.

In some instances, a nomination form submitted may be submitted to the Advisory Committee and the Advisory Committee may decide that there is not enough information about the specific condition, test, or treatment to move forward. In such instances, the ERG could help the Committee determine what pilot studies might be appropriate to gather additional data needed to go forward (e.g., testing and treating a condition in one State using another State as a control; better evidence of prevalence; screening effectiveness in population application).

The ERG's Evidence Review Process. The ERG would review evidence on the following: (1) the condition (prevalence, natural history, different forms of the condition); (2) screening and diagnostic testing; and (3) treatment (risks, benefits, applicability to what condition groups). The ERG would use a decision analytic framework to address risks and benefits. It would indicate clearly where evidence is absent and what information would be most critical in trying to help the Advisory Committee make decisions or recommendations.

Several issues arise in reviewing the evidence on screening for heritable disorders that the ERG will have to keep in mind. First, the ERG will not be doing a traditional level-of-evidence approach, because most of the conditions that one might screen for are extremely rare, and there are no randomized controlled trials. Second, information on costs and benefits is limited, especially if one considers all potential outcomes true and false positives and true and false negatives. Third, much of the evidence that will be available to the ERG is not published literature. Thus, it will be very important for the ERG to develop a systematic strategy for determining (a) how to assess unpublished literature, and (b) how to access unpublished literature (e.g., Food and Drug Administration data on trials for some of the drugs and proprietary data from some of the companies that are developing new treatments for some of the conditions).

The hope is that work by the ERG to frame any remaining questions on the nomination form would begin immediately. Then, at the September 2007 Advisory Committee meeting, conditions for in-depth systematic reviews would be prioritized (current nominations and possibly additional solicitations from the community). If all goes well, the ERG could then carry out evidence-based reviews to have them ready for the Advisory Committee at its meeting in the spring of 2008.

Questions & Comments

After a few questions, Dr. Howell commended Dr. Perrin and his group on their work and stated that he believed the Committee should encourage them to move ahead with plans for the ERG as Dr. Perrin described. There was no objection. Dr. Howell asked Dr. Rinaldo and Dr. Brower to serve on the ERG as liaison members from the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children.

- ***DECISION #1:*** *Dr. Perrin will proceed with plans for the external Evidence Review Group (ERG) as described, and the process of nominating and reviewing conditions for inclusion on the uniform newborn screening panel will begin. Dr. Rinaldo and Dr. Brower will serve on the ERG as the Advisory Committee's liaisons.*

B. Cover Letter for the Nomination Form

Dr. Howell asked Advisory Committee members for their comments on the draft of a cover letter to go to people nominating conditions to the uniform newborn screening panel. The draft cover letter, developed by Dr. Nancy Green and Dr. Marie Mann, was included in TAB #6 of the materials given to Advisory Committee members for the meeting.

Ms. Terry suggested broadening the conflict-of-interest portion of the form and said she would give her comments to the Committee later. Dr. Rinaldo recommended adding a paragraph encouraging people to nominate a condition using a team approach that involves patient advocacy groups, clinicians, researchers, labs, etc., rather than having separate individuals submit nominations.

Several people worked on draft language for the paragraph related to the use of a team approach, and after some discussion, Committee members reached a consensus about what language to include.

- ***DECISION #2:*** *The following language will be added as the second paragraph of the cover letter to accompany the nomination form for candidate conditions on the uniform screening panel:* ACHDGDNC encourages the preparation of the nomination form by a multi-disciplinary team effort. This team effort should reflect the provision of evidence by both advocacy and professional organizations and individuals with expertise on the condition being nominated and other issues relevant to newborn screening.

III. LONG-TERM FOLLOWUP AND TREATMENT IN NEWBORN SCREENING

Dr. Boyle and Dr. Alex Kemper reported on the Advisory Committee's Followup & Treatment Subcommittee's ongoing efforts to identify the elements of long-term followup and treatment in newborn screening and to develop a position paper on the topic for presentation to the Advisory Committee and possible publication.

A. Update on the Followup & Treatment Subcommittee's Activities and April 2007 Meeting on Long-Term Followup in Newborn Screening

Coleen Boyle, Ph.D., M.S., Committee Member
Director, Division of Birth Defects and Developmental Disabilities
Division of National Center on Birth Defects
and Developmental Disabilities
Centers for Disease Control and Prevention

Dr. Boyle summarized the April 18, 2007, workgroup meeting organized by the Advisory Committee's Followup & Treatment Subcommittee entitled "The Roadmap to Implement Long-Term Followup and Treatment in Newborn Screening." A summary of the meeting was included under TAB #7 in the binder prepared for Advisory Committee members.

As background, Dr. Boyle noted that the Followup & Treatment Subcommittee has focused for about the past year on the issue of long-term followup (including treatment) after newborn screening. Although there are a number of guidelines related to short-term followup after newborn screening, there is little guidance in the area of long-term followup and existing definitions and goals of long-term followup vary. For that reason, the Followup & Treatment Subcommittee has decided to try to step back and consider what long-term followup is and what the goals of long-term followup are.

The April 18th workgroup meeting on long-term followup and treatment in newborn screening was convened to discuss a draft position paper prepared by Dr. Alex Kemper, Dr. Stephen Downs, and Dr. James Figge that set forth (a) a working definition of long-term followup; (b) the goal(s) and major components of long-term followup and treatment; and (c) major participants/systems in long-term followup. Participants at the meeting represented the major perspectives/systems impacted by long-term followup (individuals/families, primary care, specialty care, public health, financial and regulatory, and health information systems). A

summary of the meeting was included under TAB #7 in the binder prepared for Advisory Committee members.

Dr. Boyle summarized the feedback from participants at the April 18th meeting on long-term followup and treatment in newborn screening as follows:

- **Goal of long-term followup**. The overall goal should be to achieve the best possible outcomes for children and families over the long term. Long-term followup is a process that should continue throughout a person's lifespan (focus to age 18 or 21), with an emphasis on transitions such as the transition from pediatric health care to adult health care.
- **Components of long-term followup**. The core components of long-term followup after newborn screening are the following:
    - *Clinical care/treatment.* There should be more emphasis on collating and distributing available best practices and existing evidence. Access and manpower issues figure prominently in this component.
    - *Coordination of care/services.* This component includes public health components and clinical components. The "medical home" might be the point of coordination, but coordination may require disease-specific efforts. Families need a single "point of contact" for coordination of care/services.
    - *Evaluation and surveillance.* Evaluation and surveillance are extremely important but underdeveloped public health functions. Long-term tracking of natural history/treatment history is essential.
    - *Platform for research*. Care improvement is an integral part of long-term followup and the infrastructure for clinical research should be built into the system. Translation of research findings into clinical practice is critical.
- **Models for providing long-term followup.** Most participants at the April 18th workshop thought that the medical home should be the point of coordination of care and services for individuals with conditions detected via newborn screening. Yet some thought that much of the care coordination should be disease specific. A possible model for long-term care following the detection of a condition via newborn screening might be a hybrid model combining (a) the chronic care model of a medical home for children with common diseases/disorders (e.g., asthma or attention deficit hyperactivity disorder); and (b) disease-specific models (e.g., Children's Oncology Network).
- **Family issues/individual issues.** Family issues and issues related to individuals with a genetic or metabolic condition detected via newborn screening (developmental, medical, educational, emotional/social issues) should be addressed comprehensively. Families should be empowered in the long-term followup system. Providers should be trained on how to partner with families.
- **Information technology/personal health record.** An interoperable electronic personal health record or some type of electronic information exchange will be very important in development of the long-term care system.

The second part of the day at the April 18th workshop was devoted to a session facilitated by Dr. Alan Hinman on roles and responsibilities in long-term followup in newborn screening. Dr. Boyle explained that that topic will not be a part of the position paper but will probably be among the next steps that the subcommittee will consider.

B. Draft Position Paper on Long-Term Followup in Newborn Screening

Alex Kemper, M.D., M.P.H., M.S.
Associate Professor
Department of Pediatrics
Duke Children's Hospital and Health Center
Duke University

The draft position paper that was considered at the April 18, 2007, workshop on long-term followup after newborn screening was prepared by Dr. Alex Kemper, Dr. Stephen Downs, and Dr. James Figge. In his presentation, Dr. Kemper reported on some of the thoughts that he and his colleagues have had about the definition of long-term followup, gave examples of long-term followup programs, talked about high-level conceptual models, and identified next steps.

The overarching goal of long-term followup is to achieve the best possible outcome for children and their families. Components of long-term followup include chronic disease management and provision of treatment; age-appropriate preventive care and health promotion; activities to expand the evidence base related to the condition and treatments for the condition; quality improvement. Long-term followup should extend throughout an individual's lifespan from the time of diagnosis.

There are various models for the provision of long-term followup to individuals with conditions detected via newborn screening. One model for long-term followup of children with special health needs is the medical home. An illustration of the Medical Home from Raleigh Children's Hospital is one of the best and includes coordinating and providing health care, preventive care, continuity of care, and single point of care. It is important to recognize that Medical Home is not a physical location or any specific type of provider, and the location of a person's medical home can change over time (e.g., during the transition to adult care).

One of the drawbacks of the medical home model for long-term care in newborn screening is that many individuals with special health needs do not have a medical home. Furthermore, the model of the medical home lacks specificity for the heterogeneous conditions (e.g., MCAD, sickle cell disease) detected via newborn screening. The model also does not provide any clear spot for public health.

Disease-specific models for long-term followup of children with special health needs include the Children's Oncology Group (which provides recommendations on how to monitor for the late effects of cancer treatment and does some surveillance of survivors, but does not specify how followup care should be coordinated); the 11 Comprehensive Sickle Cell Centers funded by the National Heart, Lung, and Blood Institute (which help coordinate the care of those children who receive care through the clinics and conduct basic and translational research); and the clinics accredited by the Cystic Fibrosis Foundation (which provide comprehensive care and are involved in quality improvement and research).

The Followup & Treatment Subcommittee has been trying to develop a high-level conceptual model to improve child and family outcomes following newborn screening. The four primary types of things that affect these outcomes are (1) elements related to the specific condition; (2) elements related to the affected individual; (3) the health care system; and (4) the environment. Next steps include developing a "staged" vision for the future, with explicit and achievable practice goals, perhaps as logic model; and defining the relationship between public health, care providers, and researchers.

Questions & Comments

Dr. Skeels asked how one decides which individuals to follow in long-term followup given that there is significant biological variation and a spectrum of affectedness for specific conditions. Dr. Boyle replied that that question was discussed at the April 18th meeting as an issue that needs to be addressed.

Period of Followup. Dr. Kahn asked whether thought had been given to extending the vision of long-term followup into adulthood. Ms. Monaco asked whether the Followup & Treatment Subcommittee had considered looking at current adults living with the disorders (e.g., under what conditions and circumstances did they reach adulthood, success stories) to benefit the research that is being done on children and for long-term followup.

Dr. Kemper stated that the goal should be to ensure appropriate long-term followup for all ages, but he focused on ages 18 to 21 for the position paper because of the magnitude and importance of transitions such as the transition from pediatric health care to adult health. Dr. Telfair stated that he believed that issues related to the transition to adult care were part of the Advisory Committee's purview. Dr. Howell, noting that the Advisory Committee's legal charter is to focus on heritable disorders and genetic diseases in "newborns and children," emphasized that the adult age group is not within the Committee's purview.

Dr. Boyle reported that the Followup & Treatment Subcommittee had heard from all perspectives that the lifespan approach is very important and that there are critical points of transition that must be highlighted. Although the subcommittee has not yet developed a specific agenda in terms of looking at adults, Dr. Boyle said she believes that once a followup program is created, much could be learned from surveillance data, observational data.

Medical Home. Dr. Skeels and other Committee members suggested that the medical home as the point of providing comprehensive primary care and coordination of services is a great concept but is still "a work in progress"—i.e., not the reality for many families. Dr. Kahn noted that the term medical home has been around since the American Academy of Pediatrics (AAP) created it in 1968 but stated that the concept is really just beginning to catch on. Dr. Kahn volunteered to share with the Advisory Committee a set of principles that several primary care organizations—the AAP, the American College of Physicians, the American Academy of Family Physicians, and the American Osteopathic Association—had recently adopted a set of principles on what constitutes a medical home. Dr. Howell said this would be helpful.

Speaking from the audience, Dr. Bonnie Strickland, who has responsibility for medical home in HRSA's Maternal and Child Health Bureau, said surveys show that more than half of families of children with special health care needs and all children say they do have a medical home. She believes the medical home is an interesting concept for long-term followup of children with conditions detected via newborn screening, because it is grounded in primary care with comanagement with subspecialties and promotes well-child care. She emphasized the importance of thinking of children first, not their diseases. Dr. Telfair observed that Dr. Richard Antonelli has done a considerable amount of work on the medical home.

IV. NATIONAL INSTITUTES OF HEALTH'S RESEARCH ACTIVITIES RELATED TO NEWBORN SCREENING

Dr. Howell noted that there are many research questions related to newborn screening that remain to be addressed and added that he would like to establish a working group that will look at research issues and ask Dr. Michael Watson, chair of the National Coordinating Committee at the American College of Medical Genetics (ACMG), to chair it. Adding that the National Institutes of Health (NIH) has an active research program in newborn screening, Dr. Howell asked Ms. Gilian Engelson, project officer for the current research program in newborn screening, to come up and make a presentation to the Committee on this.

Gilian Engelson, M.P.H.
National Institute of Child Health and Human Development
National Institutes of Health (NIH)

Ms. Engleson discussed newborn screening research activities at NIH, as well as the potential development by NIH of a Newborn Screening Translational Research Network. As background, Ms. Engelson explained that several NIH institutes are interested in newborn screening.

The lead NIH institute for newborn screening is the National Institute of Child Health and Human Development (NICHD). NICHD's current research priorities related to newborn screening are (1) the development of translational research infrastructure programs; (2) the development of screening technology; (3) improved therapies; (4) studies of the natural history and long-term outcomes of treatment; (5) behavioral and social sciences research; and (6) creation of appropriate public policies.

NIH institutes apart from NICHD that are interested in specific conditions or topics related to newborn screening are the following:

- National Institute of Neurological Disorders and Stroke (NINDS)—developmental neurological disorders
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)—metabolic conditions
- National Institute of Biomedical Imaging and Bioengineering (NIBIB)—point of care technologies
- National Human Genome Research Institute (NHGRI)—ethical, legal, and social issues (ELSI), genomics, linkages to conditions
- National Heart, Lung, and Blood Institute (NHLBI)—hemoglobinopathies and cardiomyopathies
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)—neuromuscular conditions
- National Institute on Deafness and Other Communication Disorders (NIDCD)—hearing impairment
- National Institute of Environmental Health Sciences (NIEHS)—environmental factors associated with congenital defects

- National Library of Medicine (NLM)—newborn screening resource pages. including the Genetics Home Reference
- John E. Fogarty International Center (FIC)—genetics and informatics training, international research efforts
- Office of Rare Diseases (ORD)—rare diseases

NIH Research Grants and Contracts Related to Newborn Screening. One current NIH funding opportunity is a grant program cosponsored by NICHD, NIDDK, and NIDCD to develop therapeutic interventions (new, improved, or supplemental) for screenable conditions: "Innovative Therapies and Clinical Studies for Screenable Disorders." Three different types of grants are available: R01 (the standard NIH grant) and R21s and R03s (more exploratory grants). Several grants have already been awarded, among them grants researching therapeutic interventions for galactosemia, spinal muscular atrophy, hearing loss due to cytomegalovirus, and globoid-cell leukodystrophy. Application deadlines occur three times each year until 2009. Additional information about this program is available at www.grants.gov.

NIH also has contracts for novel technologies. In September 2006 NICHD awarded two 3-year contracts to support the development of novel technologies in newborn screening. One contract was awarded to Ron Scott at the University of Washington to consider the expansion of tandem mass spectrometry (MS/MS) to lysosomal storage disorders. The other contract was awarded to Ken Pass in New York State to research Luminex bead array technology. The expectation is that both of these technologies will eventually expand to other conditions beyond those currently being screened for.

Newborn Screening Translational Research Network. A potential NIH initiative is a Newborn Screening Translational Research Network. The hope is that the NIH Newborn Screening Translational Research Network would have a network coordinating center that could pull together the grants and the contracts, investigator-initiated grants, clinical research centers and State labs and diagnostic labs, as well as current registries and other databases and repositories. This coordinating center could also link in with the HRSA-funded Regional Genetics and Newborn Screening Collaboratives.

A Newborn Screening Translational Research Network could validate new treatments and technologies, as well as provide increased access to dried blood spots and other samples for researchers. The network also could be used to look at longitudinal health outcomes on individuals identified through newborn screening. Such a network would require an informatics system to link researchers with potential human subjects for clinical trials in the network. It would also require informed consent and recommended research policies.

InfoRx. NLM is taking the lead on a project called InfoRx. InfoRx pads are prescription pads to help health care providers refer patients to the up-to-date, consumer friendly Web page: the Genetics Home Reference Page (http://glr/nlm.nih.gov). A health care provider can just write the name of the condition down on this prescription pad and give it to the family to go to the Website and get more information that is authoritative and consumer-friendly. There has been direct outreach by American Academy of Pediatrics (AAP), the American College of Medical Genetics (ACMG), American College of Obstetricians and Gynecologists (ACOG), as well as the American Academy of Family Physicians (AAFP), and InfoRx pads can be ordered free at http://www.informationrx.org.

How the Advisory Committee Can Help. Ms. Engelson said that NIH welcomes the Advisory Committee's guidance on what the research needs are in newborn screening, as well as its advice regarding the development of the Newborn Screening Translational Research Network (e.g., what the infrastructure might look like, what the components might be, linkage to public health programs, policy and legislative issues, ELSI issues).

Questions & Comments

Dr. Howell urged the Advisory Committee, as it starts looking at long-term followup, to think about what the important research questions are and to try to get those conveyed to NIH and other research funders to help support that. He added that some of the awarded grants and contracts have encountered significant problems with institutional review board (IRB) clearance, so addressing IRB issues is important.

Dr. Dougherty reported that the Agency for Healthcare Research and Quality and the Centers for Medicare and Medicaid Services had just developed a handbook on patient registries. The 210-page handbook, *Registries for Evaluating Patient Outcomes, A User's Guide,* addresses IRBs and other research issues. The full report and a 13-page summary, which will contain a checklist for registry developers, will be published soon.

Dr. Telfair commented that the Secretary's Advisory Committee on Genetics, Health, and Society works on issues of three contexts, launching new outcomes, social and behavioral sciences, and ELSI issues, related to newborn screening, and asked what NICHD's interest in these topics is. Ms. Engelson replied that NICHD is broadly interested in how newborn screening results might impact the families, how best to educate families about newborn screening to get informed consent, etc.

Returning to a point brought up earlier about the Advisory Committee's purview being limited to newborns and children, Dr. Telfair emphasized that it is important to take a long-term perspective of long-term followup for newborn screening, especially if one includes the family. Dr. Howell agreed and noted that NIH did not have the same limits as the Advisory Committee.

V. REGIONAL COLLABORATIVES' LONG-TERM FOLLOWUP PROJECTS

Dr. Stephen Downs, Dr. Rani Singh, and Dr. James Eckman reported on some pilot long-term followup projects related to newborn screening undertaken via two HRSA-funded Regional Genetics and Newborn Screening Collaboratives: the Region 4 Genetics Collaborative (Downs) and the Region 3/Southeastern Regional Genetics Group (SERGG) (Singh and Eckman).

A. Region 4 Genetics Collaborative: Adaptive Turnaround Documents, Newborn Screening, and the Medical Home

Stephen M. Downs, M.D., M.S.
Associate Professor and Director
Indiana University
Children's Health Services Research
Regenstrief Institute

Dr. Downs observed that expanded newborn screening has resulted in the potential to screen newborns for well over 50 conditions; however, the diagnosis and treatment of affected infants

must be timely or the potential health and other benefits that can be realized will not be achieved. A major challenge when there is a positive screen or a questionable screen or a missed screen can be finding the affected infant to make sure that the response is timely.

With a supplemental grant from HRSA to the Region 4 Genetics Collaborative, Dr. Downs and his colleagues at Indiana University and the Regenstrief Institute are working with the Indiana Department of Public Health to develop new ways to address this problem. Their approach involves two components: (1) a regional health information network —the Indiana Network for Patient Care (INPC); and (2) a mechanism for two-way communications with providers—computer-generated paper documents known as "adaptive turnaround documents" (ATDs).

The INPC in Indianapolis and central Indiana links five hospital systems, county and State health departments, pharmacy clearing houses, Medicaid and other insurers, and other participants. The network uses a federated data repository model, in which data from different hospitals, clinics, etc., are stored in separate physical files. The INPC relies on the widely accepted Health Level 7 (HL7) communication standard and standard clinical vocabularies such as Logical Observation Identifiers Names and Codes (LOINC) to facilitate the exchange and pooling of results. A global patient index links the data about a single patient from different sources. A concept dictionary has a set of coded terms it applies to terms used by different organizations to match up different terms that mean the same thing. The global patient index and a concept dictionary allow the INPC to combine the data from multiple sources.

Dr. Downs and his colleagues are taking advantage of the INPC and an information delivery mechanism that exists through this network called Docs4Docs to allow the sharing of information about newborn screening results using ATDs. ATDs are computer-generated sheets of paper that deliver tailored information from one place to another. When the documents are scanned or faxed, their structured data are automatically put back into the database. The way the system works is that the INPC monitors all results that come in for a particular patient. Thus, when hospitals or labs send screening results to the INPC using HL7 messages, the messages get grabbed by the Docs4Docs system, and ATDs get sent by fax or through secure inboxes to the physicians who ordered the tests. The primary care physician can then respond, indicating what action has been taken, then send the ATD through a fax machine back to the INPC, where there the information will be added to the data repository and where subsequent messages can be sent to the Indiana State Department of Health.

Dr. Downs and his colleagues believe that ADTs will enhance newborn screening programs by providing just-in-time information to the medical home, preventing missed opportunities to screen, and facilitating the long-term tracking of children with identified conditions. The INPC is continuously receiving HL7 messages throughout central Indiana. The system can capture the HL7 messages from neonates who are seen for any reason (emergency room visits, well-child checks, laboratory tests, physician visits, or whatever); check those against newborn screening reports that match those children; and then alert the child's primary care physician when there is an abnormal or a missing screen. The system can also facilitate long-term followup of newborns, because once it is known that a child has a particular primary care physician, the system can on a regular interval send that physician a letter asking for followup information about that child.

B. Region 3/Southeastern Regional Genetics Group: Newborn Screening Long-Term Followup Project

Rani Singh, Ph.D.
Assistant Professor of Human Genetics and Pediatrics
Director, Nutrition Section
Department of Human Genetics
Emory University School of Medicine

Dr. Singh discussed a 5-year project on long-term followup for patients and families that she and her colleagues are about to begin in Region 3 (Alabama, Florida, Georgia, Louisiana, Mississippi, North Carolina, Puerto Rico, South Carolina, Tennessee, and the Virgin Islands). The goals of the newborn screening long-term followup project of the Southeastern Regional Genetics Group (SERGG) are to construct an information system to provide care coordination, address stakeholders' information needs, create data linkages, and build evidence for standards of practice and infrastructure for future research. For now, the focus will be primarily on long-term followup for conditions detected via tandem mass spectrometry (MS/MS) and the hemoglobinopathies.

The project team's vision is that a long-term newborn screening followup program should do the following: (1) integrate the public health infrastructure and private sector (i.e., use public-private partnerships); (2) incorporate medical home and support services, transitioning, emergency preparedness issues in the region; (3) provide timely management and treatment services; (4) develop data systems for monitoring outcomes and quality improvements; (5) utilize robust communications to facilitate and maintain access to services; and (6) remain flexible to accommodate changes in knowledge.

Dr. Singh summarized the first three of four planned project activities in the Region 3 newborn screening long-term followup project, all of which are all related to MS/MS conditions:

1. *Evaluate capacity and performance of newborn screening long-term followup information systems.* The project team will collaborate with the Public Health Informatics Institute in a phased approach over 5 years to determine, engage and utilize stakeholder groups to identify an information system for long-term followup that practitioners, State public health departments, and consumer groups can use. There is a 5-year plan for this activity that culminates in having all States and territories in Region 3 begin to use the information system and system evaluation strategies in newborn screening.
2. *Develop a regional information system for all analytes of positive newborn screens and treatment protocols.* The project team will gather and compile nutrition care and management plans for affected newborns, then share the results and use them to help develop best practice models for medical management and nutrition protocols. The 5-year plan for this activity ends with the dissemination of best practice models for management strategies and nutritional care plans for individuals with positive newborn screens.
3. *Analyze positive newborn screen outcomes to improve management practices and decrease inequities in Region 3.* The project team will start building evidence through activities such as a literature review, interviews with families and health care professionals. It will then form a library of this information, with links and other information made available to patients, families, and practitioners. A regional journal club of experts will be formed in the third year of the project. The team will be partnering with other organizations like Genetic Metabolic Dieticians, and it has already talked to American Dietetic Association. The 5-year plan for this activity ends with the development of an action model for

improving management practices and decreasing inequities in Region 3 that is shared both regionally and inter-regionally.

It is hoped that the outcomes of the project on long-term followup for individuals with conditions detected via screening via MS/MS in Region 3 will be (1) the identification and initiation of components of the newborn screening information system as a resource for improving care coordination; (2) a data tracking system that includes positive cases, analyte biomarkers, screening diagnosis and management, and an evidence-based library; and (3) management protocols for medical nutrition and support.

C. Region 3/Southeastern Regional Genetics Group: Followup Initiatives Related to Sickle Cell Disease

James Eckman, M.D.
Professor, Department of Hematology, Oncology, and Medicine
Adjunct Professor of Pediatrics
Winship Cancer Institute
Emory University School of Medicine
Director, Georgia Comprehensive Sickle Cell Care Center, Grady Health System

Dr. Jim Eckman discussed the Region 3 long-term followup project activity related to hemoglobinopathies. Dr. Eckman said that when he started out taking care of sickle cell patients in Georgia in the late 1970s, most patients were dying in childhood. Now 85 percent of sickle cell disease patients survive to adulthood. There seems to be continuous benefit at all ages for individuals who are detected in newborn screening programs.

The growing numbers of individuals who survive into adulthood with sickle cell disease face a number of challenges. Sickle cell exacerbates in the late teens and 20s, both in terms of the frequency of pain crisis and deaths. Many patients with sickle cell disease do well medically but lack independence (i.e., exhibit helplessness; exhibit chronic illness behavior rather than chronic healthy behavior). Many recent improvements in pediatric outcomes have been obtained through the aggressive use of transfusions, and some patients develop transfusion-related problems (venous access; alloimmunization; iron overload) and end up in chronic pain states.

Among the ways that these problems might be addressed, Dr. Eckman suggested, are the following:

1. *Provide early intervention using newborn screening as an opportunity to educate the parents and family about sickle cell disease.* Early intervention is needed to address medical issues related to sickle cell; provide parent education; provide extended family education; and improve social support, psychological functioning, and economic function of patients with sickle cell disease. The family, young adult, and provider are imbued with a future orientation for the affected individual—the idea starting at birth that they are going to become successful adults. One model that might be adapted for sickle cell is the Nurse Home Visitor Program (David Olds), a prenatal and postnatal intervention for high-risk mothers that had positive effects on their children.
2. *Develop effective transition programs to establish an effective adult medical home*. As Dr. Telfair and others have reported, individuals with sickle cell disease, their care providers, and their family all need transitioning. The problem is that there are no adult providers now for sickle cell disease, and there is a lack of knowledge about sickle cell disease in the adult population. When adults with sickle cell disease need care, they go to emergency departments. A hospital-based physician takes care of them. They may have a medical

home, but if they do it is going to be in general internal and family medicine. Oncologists and hematologists take care of only a minority of these patients.

3. *Support a system of primary care with backup.* One requirement is adequate funding for primary care. Beyond that, it is possible to develop protocols for primary health maintenance for and with generalists and physician extenders; protocols for and with emergency room physicians; and protocols for and with hospitalists. In addition, the network of Centers of Excellence in Sickle Cell Disease is well equipped.

Dr. Eckman said that Region 3 is undertaking an initiative in primary care backup that focuses on pain control as the most important issue for adult sickle cell patients. The project will develop pain control protocols for home management, emergency rooms, and inpatient services. The assessment tools for managing patients and assessing outcomes in the project will probably be patients' pain diaries. Region 3 is also well poised to do a transition project, because Dr. Telfair is in Region 3, as are the authors of a 2002 American Academy of Pediatrics position paper on transitions (J. Reiss, R. Gibson, Health Care Transition: Destinations Unknown," *Pediatrics*, 110:1307, 2002).

Dr. Eckman concluded his presentation by noting that additional information about sickle cell is available at the Sickle Cell Information Website: www.scinfo.org. A monthly newsletter is available via e-mail.

Questions & Comments

Dr. Dougherty asked for comments from health information technology experts present at the Committee meeting how hard it will be to integrate individual long-term followup initiatives being undertaken across the country with national standards. Dr. Downs explained that the ease or difficulty will depend on whether individual efforts adhere to the standards for data transfer and for data coding that currently exist or work collaboratively with the standards organizations to create the standards that they need where they do not already exist.

Dr. Howell observed that HHS Secretary Leavitt has as one of his major interests at the current time electronic medical records and personalized health records. In conversations with his office, Dr. Howell has been told that one of the areas that they are going to focus on in this effort is newborn screening.

Speaking from the audience, Dr. Danuta Krotoski from the National Institute of Child Health and Human Development said developing analyte coding across States is good and asked if there was work being done with Canada. Dr. Downs said the LOINC Consortium, the group that certifies LOINC codes as standard, is an international organization, and one of the people who works most closely with him, Gilbert Hill, is in fact Canadian.

VI. UPDATE ON THE STATUS OF STATE NEWBORN SCREENING PROGRAMS AND REPORT ON TWO MEETINGS

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

Dr. Therrell gave an update on the current status of State newborn screening programs and reported on two recent meetings related to newborn screening that he attended. A 2-page grid entitled "National Newborn Screening Status Report—Updated 04/30/07"—showing State requirements with respect to the core American College of Medical Genetics (ACMG) panel of 29 conditions and secondary conditions amenable to newborn screening—was included under TAB #9 in the binder prepared for the Advisory Committee members. Dr. Therrell also briefly summarized the high points of two meetings related to newborn screening that he attended in May 2007.

Update on Newborn Screening in the States. Dr. Therrell noted that State newborn screening programs reported the following recent changes in response to a request asking what they would want to have reported by NNSGRC to the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children:

- Arizona now mandates screening of newborns for 27 disorders, up from just 8 in April of 2006, and it will add screening for cystic fibrosis on June 30, 2007. Hearing screening is not mandated, but many children are screened nonetheless, and the State has implemented a centralized hearing screening followup program.
- Arkansas, which was one of the States with the fewest disorders covered by newborn screening, is now seeking legislative approval for full expansion. The State plans to hire additional staff by January 2008, to begin a public awareness campaign in March, and then to begin expanded screening by July of 2008. The newborn screening fee is expected to increase from $14.83 to $89.25 per newborn.
- California, which previously did not screen newborns for BIO (biotinidase deficiency) and cystic fibrosis, has gone through pilot testing for those two conditions and will start screening for them officially on July 17, 2007.
- Delaware began screening for BIO in June 2006, cystic fibrosis screening using an IRT/IRT protocol* in October 2006, and CUT (carnitine update deficiency) screening in December 2006. It is initiating steps to move toward a Web-based reporting system.
- Florida's expanded newborn screening program began in January 2006, and screening for cystic fibrosis is expected to begin in July 2007.
- Georgia began expanded newborn screening in January 2007 with a fee of $40 per newborn. It is currently using an automated voice response system and an auto fax system to respond back to physicians on a 24/7 basis. The State screens for cystic fibrosis using an IRT/DNA protocol. It is planning linkages to vital records, as well as the electronic transfer of demographic data from some hospitals. Georgia, like many States, had a lot of legislative

*An IRT/IRT protocol consists of an immunoreactive trypsin (IRT) protocol without mutation analysis of the cystic fibrosis transmembrane conductance regulator (CFTR) gene; an IRT/DNA protocol includes mutation analysis.

difficulties with its newborn screening program, and once the program got through the legislature, the budget was vetoed by the governor. So now Georgia is back to square one in terms of looking at expansion and who is going to do the expansion, whether it's going to be done by the State lab or an outside laboratory. An audit showed the State lab was the most cost-effective in Georgia.

- Illinois is working on a rule change to add screening for cystic fibrosis using an IRT/DNA protocol, and the State is expected to start cystic fibrosis screening in the summer of 2007. The plan is to do 6-months of limited screening and increase the fee to cover this, from $47 to $59. The State is putting out $600,000 in grants for genetic counseling related to cystic fibrosis. Illinois's legislature has been quite active. Somewhat to the surprise of the screening program, the Illinois Senate just passed a bill to add screening for five lysosomal storage disorders (Krabbe, Pompe, Gaucher, Nieman-Pick, Fabry). The House is slowing the bill down, because Krabbe is the only one of that group being screened for right now (in New York), and there is some question as to what to do about the others. A bill to support Fragile X screening was introduced in the Illinois legislature, too.
- Kansas finally passed a law allowing the expansion of newborn screening. The expansion start date is July 2008, and there is $800,000 available to do that expansion. A Kansas law saying that the newborn screening program has to pay for everything related to newborn screening has been holding things back, but new legislation would allow the program to cover treatment products on a sliding scale.
- Louisiana is working to expand screening to include the 29 core conditions in the ACMG uniform panel. Screening for all the conditions except cystic fibrosis is in place, and screening for cystic fibrosis is supposed to start in July 2007. Louisiana's laboratory testing, which has been done in Iowa since Katrina, is expected to return to Louisiana's State lab in the summer of 2007.
- Maine is planning cystic fibrosis screening, with implementation expected in January 2008.
- Maryland added cystic fibrosis screening in June 2006 using an IRT/IRT protocol, and it also has obtained new lab instrumentation and software.
- Michigan's legislature approved expansion of the State's newborn screening program to include 49 of 54 recommended conditions. The State expects to begin screening for cystic fibrosis in October 2007.
- Missouri started screening for cystic fibrosis in a pilot program in January 2007. It is expected to start real screening for cystic fibrosis in July 2007. Cystic fibrosis followup has been contracted to the cystic fibrosis centers, and BIO screening will be added late 2007 or early 2008, at which time the State will be screening for the full core panel.
- Montana has a bill to expand the mandatory blood spot screening from 4 conditions to 28 conditions, and the bill may even have passed by now.
- Nebraska's newborn screening committee recommended changing the optional tandem mass spectrometry (MS/MS) newborn screening tests (96 percent compliance) to mandated tests. The program decided to go ahead and mandate, but it has not yet been able to reach accords on that with the health department director to ask for funds from the legislature.
- New York last year added screening for Krabbe disease, becoming the first State in the country to screen for a lysosomal storage disease. New York found 2 high-risk babies and 2 moderate risk babies of the 16 referred in the first 166,000 newborns, and it reportedly found one confirmed case of Krabbe disease. The State has recently modified its

hemoglobin procedures to use high-performance liquid chromatography (HPLC), with confirmations using HPLC/ion-exchange chromatography (IEC).

- New Hampshire screens newborns for 13 conditions, including toxoplasmosis. It anticipates that screening for the 19 additional MS/MS conditions will begin July 1, 2007.
- Ohio began screening newborns for cystic fibrosis in August 2006, and it also began CUD screening.
- Oklahoma began screening for MCAD (medium-chain acyl-CoA dehydrogenase deficiency) last June. The State now offers genetic counseling with certified genetic counselors for conditions including sickle cell trait. Oklahoma is adding in the MS/MS conditions in a staged process that it hopes to have completed by December 2008; it will add screening for BIO after that.
- Oregon reported that on January 1, 2007, New Mexico was added to the Northwest Regional Screening Program. Cystic fibrosis was added to Oregon's newborn screening panel in 2006 and to New Mexico's and Alaska's screening program in 2007.
- Rhode Island added 17 conditions to its newborn screening panel, and as of July 1, 2006, it screened for all 29 core conditions included in the ACMG uniform newborn screening panel.
- South Carolina began screening for TYR I, II, and III (tyrosine I, II, and III) in April 2007, and it has a contract with the Mayo Clinic to provide second-tier succinylacetone testing.
- South Dakota will add screening for cystic fibrosis on June 1, 2007. South Dakota uses an in-State laboratory for contract newborn screening services, and that laboratory subcontracts with Texas and Massachusetts for some tests. The State recently issued a new request for proposals and awarded a comprehensive contract to Iowa's newborn screening lab.
- Texas has had quite a few changes in its newborn screening program. On December 6, 2006, Texas added 19 MS/MS conditions using MRM, which means they are targeting those conditions and are not doing a full scan to see what other conditions might be there. On January 8, 2007, Texas began screening newborns for BIO. The legislation said they should expand to meet the core conditions within available funds. Right now Texas has decided that available funds will not cover cystic fibrosis, but the plan is to add cystic fibrosis as soon as possible. Texas has implemented a new reporting format which has been fraught with some other issues in Texas that are being worked out right now, and they're updating their voice response system for 24/7 coverage, and they are considering improving their demographic entry system that are now in some of the hospitals to directly download demographic entry to the State laboratory.
- Vermont is screening newborns for 28 of the 29 core conditions in the ACMG uniform newborn screening panel and is working to add screening for cystic fibrosis by end of 2007.
- Washington State is reviewing additional disorders for possible inclusion in its newborn screening program. The University of Washington has applied for institutional review board approval to do a pilot study to detect lysosomal storage diseases.
- West Virginia has mandated expansion of its newborn screening panel from 7 to 29 conditions in two phases: Phase I—July 1, 2007, CAH (congenital adrenal hyperplasia), cystic fibrosis, and BIO (non MS/MS); and Phase II—July 1, 2008, MS/MS, ending July 2008. The State also is exploring telemedicine opportunities.

Dr. Therrell showed several maps indicating which MS/MS conditions are screened for in the United States as of May 2007; the percentage of newborns screened in the United States for specific disorders; and which States screen newborns for the core 29 conditions or other conditions in the uniform newborn screening panel. He noted that screening for cystic fibrosis has been expanding rapidly. In June 2006, 12 States were screening for all 29 core conditions in the ACMG uniform newborn screening panel; as of mid-May 2007, there were 16 States screening for all 29 core conditions.

Dr. Therrell ended this portion of his presentation with a report of news about a CAH kit change, problems with the manufacture of the filter paper and work by the Clinical Laboratory Standards Institute. He stated that controversy about whether the IRT/DNA or IRT/IRT protocol is best for screening for cystic fibrosis remains.

Report on Two Recent Meetings Related to Newborn Screening. Dr. Therrell briefly summarized the high points of two recent newborn screening meetings he attended:

- **G6PD Meeting, May 11-12, Washington, D.C.** This meeting, with about 16 people, was convened to look at the utility of assessing G6PD (glucose-6-phosphate dehydrogenase) deficiency in newborns, with emphasis on certain high-risk populations, in helping to prevent severe neonatal hyperbilirubinemia and kernicterus (a type of brain damage that can result from high levels of bilirubin in a baby's blood). G6PD screening is currently required in Washington, D.C., and is also used in Pennsylvania, but there are hardly any outcome data, so it was decided that the research agenda should be centered on information gathering.
- **SCID Meeting May 14-15, 2007, San Francisco**. The meeting on SCID (severe combined immunodeficiency) was convened by Dr. Jennifer Puck at the University of California, San Francisco, to discuss how best to organize and implement newborn screening programs) and to identify possible investigations and collaborations that might be useful in moving the process ahead. SCID newborn screening tests actually have been worked out. The tests that Dr. Puck has are called TRECS. Wisconsin, which is going to begin screening for SCID within the next year, will be the beta test site for SCID, as New York is for Krabbe disease.

VII. COMPREHENSIVE NEWBORN SCREENING FOR INFANTS IN THE MILITARY HEALTH SYSTEM

Lt. Col. David S. Louder, III, M.D.
Chief Consultant for Maternal-Child Medicine
Air Force Medical Corps
AFMSA/SGOC

Dr. Louder discussed the recent development of a comprehensive newborn screening program for infants covered by the military health program of the U.S. Department of Defense. As background, Dr. Louder noted that the military health system has a global mission that is primarily focused on the nation's war fighters: "to enhance our nation's security by providing health support for the full range of military operations and sustaining the health of all those entrusted to our care." Although pediatric care is not at the center of the system, prevention and early detection are embraced. The individual military services, the Navy, the Army, and the Air Force, have a focus on a healthy population and want to ensure that the people, who are going to war, as well as their spouses and children at home, are as fit and healthy as possible.

The military health system faces several challenges in performing newborn screening. One is that military families travel frequently. Another is that the military health system is located in 42 States and 14 foreign nations. Historically, clinical newborn screening practices for infants born to military health system beneficiaries have mirrored local newborn screening practices; overseas screens have been sent to several States, including Maryland and Oregon. Yet another challenge is that patients move between military and civilian network providers in the military health system. The fact that military families often live far from extended family support systems, and spouses deploy overseas, creates additional challenges.

In 2002, following an incident in which a newborn with sickle cell disease in a location overseas where the baby was not tested and did not have a good outcome, the Army Surgeon General ordered policy development for newborn screening. In 2005, the TriCare Management Agency, with broad oversight for military health care, approved a plan to improve newborn screening in the military health system. The vision for the military health system's newborn screening program is a program that will be global, comprehensive, responsive, uniform, and universal. The strategic assumption is that the military health system possesses valuable and unique resources. The concept of a medical home, for example, is well established in the military. In addition, the military has its own electronic medical record system called AHLTA; and command and control mechanisms.

A Newborn Metabolic Screening Integrated Project Team has been meeting since June 2005 to work on the new system. The project team has agreed to accept the uniform newborn screening panel recommended by the American College of Medical Genetics (ACMG). The project team's other activities include evaluating newborn screening clinical activities, developing a registry, developing an educational plan, and establishing a liaison with the Advisory Committee. The military health system will contract with a centralized laboratory to provide results from newborn screening tests within days, not weeks, and to maintain secure, Internet-accessible data. Families will have immediate access to credentialed genetic counselor for response guidelines if a screening result is abnormal. Case management, oversight, and quality improvement will all be very important. The project team is eager to collaborate and participate in data sharing initiatives with State, regional, and national entities.

Questions & Comments

Dr. Telfair asked Dr. Louder to talk about role of nurses, technicians, and physician extenders in assisting what goes on in newborn screening. Dr. Louder replied that the military health system tries to foster focusing on the primary care team. It has a modular approach to primary care, in which specific technicians (often LPN equivalents), registered nurses, and medical assistants are combined as a team. The plan is to work even more with registered nurses to improve their ability to case manage patients and be available for patients n the phone.

Dr. Telfair then asked whether the military health system uses a case coordination approach to the medical home or some other approach. Dr. Louder replied that he views the medical home as a two-way relationship: the family knows that a clinic, a physician is there for them, and just as importantly the clinic, the physician, the provider team goes out and finds the family if they need something (e.g., immunizations) to optimize their health. In response to a question from Dr. Howell, Dr. Louder confirmed that the military does screen for hearing loss.

VIII. COMMITTEE BUSINESS—SUBCOMMITTEE MEETINGS & REPORTS

The Advisory Committee's Followup & Treatment Subcommittee, the Laboratory Standards & Procedures Subcommittee, and the Education & Training Subcommittee held meetings that were open to the public from 2:00 p.m. to 5:00 pm on Thursday, May 17, 2007. On the second day of the meeting, May 18, 2007, each subcommittee gave a report to the full Committee, as discussed below.

A. Followup & Treatment Subcommittee Report

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

In lieu of Dr. Coleen Boyle's absence, Dr. Dougherty reported that the Followup & Treatment Subcommittee's meeting had a twofold agenda: (1) to discuss the subcommittee's next steps in the wake of the April 18, 2007, expert meeting held to discuss a draft position paper on long-term followup in newborn screening prepared by Dr. Alex Kemper, Dr. Stephen Downs, and Dr. James Figge; and (2) to discuss draft survey tools and next steps for the subcommittee with respect to metabolic foods and formulas.

Next Steps on Long-Term Followup in Newborn Screening. The Followup & Treatment Subcommittee agreed that the summary of the April 18th meeting on long-term followup ("The Roadmap to Implement Long-Term Followup and Treatment in Newborn Screening") needed some revisions, and Dr. Carol Greene will make them. More importantly, the subcommittee will develop a 3-page report to the Advisory Committee summarizing agreements at the April 18th expert meeting on long-term followup goals, long-term followup definitions, and the four essential components of long-term followup, as well the organizations and individuals who need to be involved. The plan is to present a version of the 3-page document to the full Advisory Committee at the September 2007 meeting for discussion and potential endorsement, as well as possible publication either by the Advisory Committee or in a journal.

The subcommittee will also develop a longer paper, along the lines of the draft prepared by Dr. Kemper and his colleagues as background for the expert meeting, for possible publication. Finally, the subcommittee will develop an action plan to actually implement the components of long-term followup, if the Advisory Committee agrees to them, and put the roles and responsibilities next to the specified components.

Next Steps on Metabolic Foods and Formulas. Because foods and formulas are not considered drugs, insurance coverage is variable. This problem is well known to the patient community and the nutrition and dietician communities, but there is no source of systematic data on what the gaps and needs are. The subcommittee and others discussed the development and implementation of several surveys to collect such data on metabolic foods and formulas—a survey of metabolic dieticians, a survey of parents, a survey of legislation, and a survey by Dr. Susan Berry—and other strategies to gather facts about insurance coverage for metabolic foods and formulas. The subcommittee also discussed using compelling examples and data to get insurance companies to pay. A task force of the subcommittee will consider whether there are enough data to bring to the Advisory Committee to make a recommendation or endorsement related to medical foods and

formulas. Otherwise, the task force will engage in a fact-finding activity or use Susan Berry's data to arrive at a national strategy for the Advisory Committee to address.

Questions & Comments

Dr. Howell encouraged the Followup & Treatment Subcommittee to publish its definition and report on long-term followup in newborn screening in a peer- reviewed journal. He noted that it is hard to get funding for medical foods and formulas when virtually everyone in the United States is on a special diet for a variety of medical "needs" and encouraged the group to think out of the box to address this issue.

Dr. Howell also asked about what financial, staffing or other implications of the Followup & Treatment Subcommittee's taskforce on metabolic foods were. There was further discussion on what was agreed to at the May 17th meeting of the Followup & Treatment Subcommittee. Dr. Dougherty and Dr. Greene clarified that the subcommittee had discussed several surveys related to metabolic foods and formulas being done by outside groups: (1) a survey of parents; (2) a survey of legislation being developed by Ms. Alissa Johnson at the National Conference of State Legislatures; (3) a survey of metabolic dieticians; and (4) a survey by Dr. Susan Berry. Dr. Singh said she is involved with a committee, which is separate from the Followup & Treatment Subcommittee that has been working on medical foods and providing guidance for the parents' survey. She thought the idea was to continue with the parents' survey and to bring the information back and get some final commitment in terms of guidance from the Advisory Committee. Dr. Telfair said he left with the impression that the subcommittee agreed that it would continue to support the parents' survey but that a task force would engage in fact-finding related to other surveys and survey proposals to help make a decision as to what the subcommittee would support and how it would move forward.

B. Laboratory Standards & Procedures Subcommittee Report

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

Dr. Brower reported on the study of the utility of the routine second screen of newborns and a number of other topics that were discussed at the Laboratory Standards & Procedures Subcommittee's meeting.

Update on the Subcommittee's Study of Routine Second Specimens. One of the Laboratory Standards & Procedures Subcommittee's first priorities for the short term is to perform a study to assess the utility of the routine second screen of newborns. Dr. Harry Hannon reported to the subcommittee that the Centers for Disease Control and Prevention (CDC) institutional review board (IRB) has completed its review of the study, which will focus on second screens for CH (congenital hypothyroidism) and CAH (congenital adrenal hyperplasia). The IRB determined that the retrospective study (which involves collecting data for the past 2 to 5 years from States that routinely do a second screen) is category IV exempt and that the prospective study may not be considered human research.

The next step is to obtain State-specific IRB approvals. The Association of Public Health Laboratories (APHL) is going to create a spreadsheet to track the progress of the States that are participating in this study as they move through their IRB process. It is also working on an electronic data collection form. The subcommittee discussed expanding the study to include tandem

mass spectrometry (MS/MS). It views this study as a first step and hopes that it will create a template for future studies regarding routine second specimens.

Update on the Region 4 Genetics Collaborative Project on Laboratory Quality Improvement in Newborn Screening by MS/MS. Dr. Rinaldo provided an update to the subcommittee on the newborn screening laboratory quality improvement project of the Region 4 Genetics Collaborative. The project is seeking data on at least 50 true positives (cases) for each of the 42 MS/MS primary and secondary conditions in the uniform newborn screening panel, with a view toward improving overall analytical performance. This study is progressing very well, and national and international participation have significantly increased. In addition, Dr. Rinaldo and his colleagues have established performance metrics focused on detection rates, false positive rates, and positive predictive value for these 42 conditions. The collection of the data and the analysis tools being generated enable data comparisons across labs within regions, across regions, within a single lab as a single entity, and around the world with the international participants.

FDA Regulation in Newborn Screening. The Laboratory Standards & Procedures Subcommittee was interested in understanding FDA's role in the oversight of newborn screening laboratories. Dr. Hausman gave the subcommittee an overview of Dr. Harper's presentation to APHL on FDA's role in newborn screening. Currently, FDA regulation in newborn screening is focused on the manufacturers of the reagents, whether they are for research use only, analyte-specific reagents, or in vitro diagnostic kits.

Specimen collection cards used in newborn screening are regulated by FDA as a medical device. Only one company makes the cards, and labs are having difficulties acquiring the cards. APHL and CDC have sent a joint letter to the company to alert them to this crisis, but Laboratory Standards & Procedures Subcommittee wanted to make sure everyone on the full Committee was aware of the problem.

Variability in Cystic Fibrosis Screening Practices. Cystic fibrosis screening involves DNA analysis. The subcommittee agreed that current variability in cystic fibrosis screening practices (e.g., variability in the screening algorithms, the makeup of the DNA panels, approaches to carrier identification and communication to families) and associated outcomes would be a good research topic. In addition, the subcommittee discussed Dr. Phil Farrell's efforts with respect to facilitating laboratory adoption of cystic fibrosis screening.

Secondary Conditions in the ACMG Newborn Screening Panel. Dr. Therrell offered to have the National Newborn Screening and Genetics Resource Center do a survey and report back to the full Advisory Committee in September 2007 regarding how many States are mandating, offering, and reporting secondary conditions in the uniform newborn screening panel. Dr. Therrell stated that most States offer all of the secondary conditions, but they choose not to indicate that they mandate certain ones because of some legal responsibilities.

The Laboratory Standards & Procedures Subcommittee would like to ask the Education & Training Subcommittee to consider the need for the education of providers and the public regarding secondary targets in its efforts. In addition, the subcommittee would like to remind everyone of a very helpful *Pediatrics* supplement called "Counting Conditions," which explains the issues of primary targets and secondary conditions.

Guidance for Pilot Studies for Newly Nominated Conditions. The Laboratory Standards & Procedures Subcommittee talked about pilot studies related to conditions nominated as candidates for the uniform newborn screening panel. Although the nomination form approved by the Advisory

Committee includes components for ensuring a test is available, pilot studies planned for SCID (severe combined immunodeficiency disorder) may not be including these components. The subcommittee is taking on as an action item the development of some additional education and guidance for pilot studies to make sure that they capture the key data points that will be needed in consideration of the new condition.

Questions & Comments

Dr. Gregg stated that educating providers about secondary conditions on the newborn screening panel is very important. Dr. Howell agreed that coming up with some really thoughtful and accurate descriptions of the secondary conditions was a good idea, noting that much of the discussion around secondary conditions derives from the fact that when one is looking for specific analytes to diagnose a condition, you without question have the ability to identify other conditions. At Dr. Howell's request, Dr. Rinaldo put up a slide showing that only two of the secondary conditions detected via MS/MS on the uniform panel are unrelated to a differential diagnosis of the primary conditions in the ACMG newborn screening panel. All of the others are linked to differential diagnosis of a primary target.

Dr. Gregg stated that it is important to have performance metrics for newborn screening that encompass disorders such as cystic fibrosis, hemoglobinopathies) in addition to the performance metrics that Dr. Rinaldo has proposed in his work on MS/MS disorders. Dr. Howell agreed. Speaking from the audience, Dr. Harry Hannon from CDC reported that he had talked to Dr. Lloyd-Puryear about a potential project with getting APHL involved to look at disorders other than MS/MS disorders in terms of the performance metrics that Dr. Rinaldo has proposed in his work on MS/MS disorders.

Dr. Howell added that the fact that there is a single manufacturer that provides all the filter paper for newborn screening brings up a number of interesting questions.

C. Education & Training Subcommittee Report

Gregory A. Hawkins, Ph.D.
Assistant Professor
Section on Pulmonary, Critical Care, Allergy, and Immunologic Diseases
Department of Internal Medicine
Wake Forest University School of Medicine

Dr. Hawkins began his presentation on the Education & Training Subcommittee's activities by reminding everyone that the subcommittee's approved charges are as follows:

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

Changes in Subcommittee Membership. Dr. Hawkins reported that there have been some significant changes in membership on the Education & Training Subcommittee. Dr. Steve Edwards stepped down from the American Academy of Pediatrics (AAP), Dr. Nancy Green moved from the March of Dimes to Columbia University, and Ms. Gail Johannes retired. Dr. Hawkins thanked them for their participation. He also thanked Dr. Tracy Trotter from the AAP and Dr. Diane Ashton from the March of Dimes and others for attending the Education & Training Subcommittee meeting of the previous day.

Update on Activities of the Subcommittee. A letter to the HHS Secretary Leavitt recommending that HHS "develop and fund a mechanism to study the distribution of existing newborn screening educational material and acquisition of knowledge about newborn screening by expectant parents in the context of the healthcare provider-patient relationship" was sent to the Secretary; a copy of the letter was included under TAB #5 of the binder for the Advisory Committee members. No response has yet been received.

On conference calls in February and March 2007, Education & Training Subcommittee members discussed newborn screening materials in different languages and for different ethnic/cultural groups. An overall question that arose was whether the HRSA-funded Regional Genetics and Newborn Screening Collaboratives could work better to produce such materials. To shed light on this topic, the subcommittee invited two individuals to speak on cultural and language communication issues related to newborn screening at its May 17th meeting.

Report on the May 17th Subcommittee Meeting. Education & Training Subcommittee members and other participants heard presentations on cultural and language communication issues related to newborn screening and reviewed newborn screening materials for parents in many different languages that were prepared in California:

- **Cultural communication issues.** Dr. Murray Brilliant, from the University of Arizona College of Medicine, discussed cultural communication issues in performing genetic studies in Navajo, Hopi, and Havasupai tribes. The Navajo and Hopi have moratoriums on genetic studies, because they view them in a negative perspective. One reason is that during the development of the genome project, they were told that if they were not studied, they might become extinct. And during the Havasupai study, they did mitochondrial testing and were told their origin was from Asia, so they were not happy with that because their religious background suggested they arose from the Grand Canyon. Interestingly, both populations are part of newborn screening. They do not consider them to be "genetic studies," because they do not think DNA is involved. These cultural issues are something to consider when educating people about newborn screening. So this brings up question, how do you educate them? What happens when newborn screening becomes DNA based?

- **Language issues.** Ms. Kristi Zonno, from the newborn screening program at the Rhode Island Department of Health, discussed the development of different educational materials in different language by the New England Public Health Genetics Education Collaborative. They have made the brochure entitled "Newborn Screening Test: They Could Save Your Baby's Life" available in English, Spanish, Portuguese, Chinese, Arabic, Spanish, Vietnamese, and Khmer (Cambodian). They used quality control testing with native speakers to control for spelling and language errors. They are now working on Bosnian, French, Italian, Somali, Laotian, Russian, Haitian (Creole), and simplified Chinese. Interestingly, a couple of people at the subcommittee meeting noted that Haitian Creole is not a spoken language; French is the language used by Haitians for writing. In addition to the materials presented by Ms. Zonno, a large folder of newborn screening educational materials in different languages (Chinese, Laotian, Chinese, and Spanish) was provided by Ms. Kathleen Velasquez, from California's newborn screening program.

Participants at the May 17th meeting agreed on the following points clear with respect to developing newborn screening education material:

- Newborn screening educational material for different cultural and ethnic groups involves more than simple language translations. The material must reflect relevant knowledge of the cultural characteristics of target groups.

- The development of newborn screening education material for different ethnic and cultural groups is time consuming and costly. Duplication of this time and expense are unnecessary. Probably a lot of material developed in California could be used in other areas of the country.
- Newborn screening educational material for different ethnic and cultural groups must undergo quality testing. Quality testing should involve relevant reviews and a feedback process that directly involves the target groups.
- Newborn screening educational material must relay a consistent national message.

To simplify and streamline the development of newborn screening educational materials for different ethnic and cultural groups, participants at the Education & Training Subcommittee meeting thought that it would be helpful to have coordinated development plan and an online resource created and maintained by the National Coordinating Center (NCC), the HRSA-funded Regional Genetics and Newborn Screening Collaboratives, and the National Newborn Screening and Genetic Resource Center (NNSGRC) that would make culturally and linguistically appropriate newborn screening educational materials they could use at their discretion. The key language translation and cultural specific issues would have been addressed in the materials made publicly available. Some materials have already been prepared and are ready to be deposited.

The Education & Training Subcommittee voted to make the following recommendation to the Advisory Committee:

Education & Training Subcommittee's
Recommendation to the Advisory Committee—May 18, 2007

The Education & Training Subcommittee recommends the National Coordinating Center (NCC) for the Regional Genetics and Newborn Screening Collaboratives work with all regions to create a national repository for newborn screening educational materials in multiple languages and multiple formats, paying special attention to cultural diversity and quality translation. Such a repository would eliminate the duplication of efforts by regions and States to maximize the efficiency, finances, and resources. The NCC also should develop a committee in coordination with the National Newborn Screening and Genetic Resource Center (NNSGRC) that will develop guidelines for the translation of materials to be tested prior to deposit in the national repository.

Questions & Comments

Dr. Howell observed that the Advisory Committee does not have the authority to direct the NCC for the Regional Genetics and Newborn Screening Collaboratives to do anything. He asked Dr. Mike Watson, the director of the NCC at the American College of Medical Genetics (ACMG), and Dr. Therrell, the head of the NNSGRC to comment.

Dr. Watson explained that all of the questions that involve the regional collaboratives have an underlying issue—namely, that for the most part, most of the money is in the States. The States are charged with mandating what will be screened in newborn screening and, as part of that process, they also develop educational materials. The problem is that the States are not playing well together—and that is a fundamental issue that has to be addressed in moving forward on issues such as data collection activities, research involving newborn screening, and educational materials. A

meeting is planned for September 2007 to bridge HRSA's interests and the National Institute of Child Health and Human Development's interests in figuring out how to get the States to function a bit more together. Perhaps figuring out how to pool resources to reduce the duplication of efforts in educational materials could be put on the agenda.

Dr. Therrell said that the NNSGRC collects all the newborn screening educational materials in English, but not in all the different languages. NNSGRC staff knows where to get the materials in other languages, so it would not be hard to get them and put them in to NNSGRC's repository. Dr. Therrell said he believed that having such a repository would be a good idea. Getting a group to review the educational materials and exercise quality control would raise some difficult issues with the States, some of which do not even use the ACMG Action (ACT) sheets for different disorders. The NNSGRC has just hired a new genetic counselor whose role is to work on educational materials, and perhaps that person could help with this.

Dr. Skeels said he thought the Education & Training Subcommittee's proposal was a terrific idea. He also stated that he believes that States do work well together in this area on a State-by-State basis, but there has been no national attempt to coordinate or encourage that. He would welcome this.

Dr. Rinaldo commented that there are additional issues to consider with respect to foreign languages—for example, there is not really one Italian. Thus, if this project is done, it will be important to focus on very basic, fundamental messages.

Several audience members liked the proposal but agreed there would be challenges involved. Dr. Harry Hannon from CDC said he the State lab in Minneapolis has a handmade newborn screening pamphlet for the Amish population with little quilts and a ribbon. Dr. Anne Comeau from the New England Newborn Screening Program said she believed that there is room for national collaboration. To keep costs down, it would be good to block out specific phrases from one language to another. Ms. Sylvia Au from the Hawaii Department of Public Health said that State programs in her region do play well together. State-level educational materials have to follow specific state guidelines, and California's booklet could not be used in Hawaii, but it would be possible to take phrases out of it. Dr. Trotter clarified that what the Education & Training Subcommittee envisioned was a modular translation of newborn screening materials that would allow States to create their own booklets. The idea of the collaboration is to reduce the cost of translation and the cost of making it accurate.

Dr. Howell concluded the discussion by saying that although the Advisory Committee could not direct the NCC, perhaps Dr. Watson and Dr. Therrell could discuss the idea put forth by the Education & Training Subcommittee and then come back and report to the full Committee.

IX. STANDARD OPERATING PROCEDURES FOR THE ADVISORY COMMITTEE

The document entitled "ACHDGDNC: Policies and Procedures for Operation and the Development of Recommendations for Screening Newborns and Children for Heritable Disorders and for the Heritable Disorders Program," was included in the materials distributed to Committee members in their briefing books for the December meeting (TAB #12). The plan was to have the Advisory Committee vote to approve the document at the end of the meeting, but no vote could be taken at the end of the meeting, because there was no longer a quorum. Dr. Lloyd-Puryear said that she

would work to get the document approved via e-mail rather than wait until the September meeting of the Advisory Committee.

A. Substitute Section D on Nonvoting Organizational Liaison Representatives

The Advisory Committee discussed a substitute version of section D, "Liaison Representatives" for page 6 of the draft operating procedures presented by Dr. Howell and Dr. Lloyd-Puryear. Several comments were made:

- Dr. Kahn said change "subspecialty expertise" in the first paragraph to "specialty expertise."
- Dr. Howell suggested changing the upper limit on the number of organizational representatives to 12 instead of 11 in the second paragraph.
- Dr. Dougherty suggested deleting "and strongly encouraging their membership to adopt recommendations" in the first paragraph. Dr. Hausman agreed, noting that FDA's functionality is such that it reviews and regulates medical devices, so it could not recommend things, although it wants to be involved with the Advisory Committee very much. Dr. van Dyck suggested changing the language to something like "inform the organization of the activities of the Committee." Dr. Howell suggested the language "strongly encouraging their membership" to "stay informed" about the Committee's activities. Committee members agreed that someone could work on the specific language for this section, and the Committee could reconsider it later in the day.

B. Appropriate Mechanism for Representation from Industry

Dr. Howell asked the Advisory Committee to consider whether industry as a whole or specific industry groups should be represented on the Advisory Committee and what the appropriate mechanism for industry participation would be. Dr. Lloyd-Puryear explained that there are currently three voting members of the Committee from industry who were appointed by the White House, presumably because they represent industry. The Committee's draft standard operating procedures conflict-of-interest provisions will significantly limit the presence of industry representatives as voting members on the Committee.

Committee members generally agreed that the voice of industry should be heard during the Committee's deliberations. There are many different groups involved in newborn screening and genetic testing. One question, therefore, is how to get representation from such a broad group? Several possible mechanisms for allowing industry to send liaison representatives who do not vote to the Committee were discussed:

- **Reserve a single liaison representative seat for industry on the Committee.** One possibility would be to have one of the 12 liaison seats reserved for industry. Dr. Lloyd-Puryear said some Federal advisory committees (e.g., the Secretary's Advisory Committee on Genetic Testing) do have at least one position at the table that serves to represent industry broadly. The industry representative does not vote but can bring up important issues more easily than a person sitting in the audience; sometimes industry actually has a voting membership on a committee. Two mechanisms for designating a single industry liaison seat to the Advisory Committee were discussed:
    - ***Designated liaison seat for industry with rotating membership.*** Some Committee members said they did not think that rotating an industry liaison seat from one

meeting to another made any sense. The lack of continuity would mean that there would be little difference between appearing at a single meeting as the "industry liaison" and participating as a member of the audience.

- ***Designated liaison seat for industry with no rotating membership.*** Some Committee members supported this approach, but the question was raised: If the role of the liaison is to report back to a constituency, and a person from one organization is selected to "represent industry," who is the constituency? Some suggested that having a single company represent "industry" would not be appropriate. Some Committee members suggested that industries related to newborn screening might develop a mechanism for selecting a single industry liaison representative. One member said he did not think that it would be possible to find one person to represent all the competing interests of industry. Virtually all Committee members agreed that it would be inadvisable for the Committee to get involved in the difficult and probably contentious process of choosing a single liaison representative for industry.

- **Allow flexibility to choose industry liaison representatives on the basis of the Committee's needs.** Dr. Newton said he did not think that the Advisory Committee should limit the number of nonvoting industry liaison representatives; it should decide how many (none, one, or more than one) and which industry liaison representatives to have on the basis of the Committee's needs. Several other Committee members agreed.

After this discussion, the Committee voted to approve the following motion (6 for, 0 against, 3 abstaining):

- ***MOTION #1****: The Advisory Committee will not reserve a designated seat for industry to send a nonvoting liaison representative to the Committee. Instead, the Committee will seek advice and expertise and representation as needed from industry.*

C. Consideration of Specific Organizations' Requests to Send Nonvoting Liaison Representatives

Dr. Howell stated that four organizations had sent letters to the Secretary's Advisory Committee from several organizations requesting formal representation on the Committee as a nonvoting liaison representatives: (1) the American College of Medical Genetics (ACMG); (2) the Society for Inherited Metabolic Disorders (SIMD): (3) Pediatrix Medical Group; and (4) PerkinElmer Life and Analytical Sciences, Inc.

Dr. Brower and other Committee members spoke in favor of allowing SIMD and ACMG to send liaison representatives, noting that both organizations have well-defined missions, as well as a constituency that the Committee wants to engage. The Committee voted to approve the following motion by Dr. Brower (6 for, 0 against, 3 abstaining):

- ***MOTION #2:*** *The Advisory Committee will invite the Society for Inherited Metabolic Disorders (SIMD) and American College of Medical Genetics (ACMG) to send nonvoting organizational liaison representatives to the Committee.*

The Committee next discussed Pediatrix Medical Group or PerkinElmer's requests to send liaison representatives. Dr. Dougherty suggested getting more information from those two companies as to why they think they meet the criteria to be a liaison representative, given that the Committee has not voted on procedures for appointing liaison representatives. Dr. Howell said his understanding

was that the Committee had implicitly turned down both requests in deciding not to allocate a liaison seat for industry. Dr. Hawkins noted that one voting member of the Committee, Dr. Peter Coggins, is with PerkinElmer, so allowing that company to send a liaison representative would give that company two slots. The Committee voted to approve the following motion by Dr. Rinaldo (6 for, 0 against, 3 abstaining).

- ***MOTION #3****: The Advisory Committee declines the requests of Pediatrix Medical Group and PerkinElmer Life and Analytical Sciences, Inc., to send nonvoting organizational liaison representatives to the Committee.*

Dr. Brower volunteered to report back at the next Advisory Committee meeting about professional organizations that represent industry that play that role of communicating across all industries related to newborn screening.

X. REGIONAL COLLABORATIVES' PROJECTS TO IMPROVE LABORATORY PERFORMANCE IN NEWBORN SCREENING

Dr. Rinaldo and Dr. Marzia Pasquali reported on projects to improve laboratory performance in newborn screening by tandem mass spectrometry (MS/MS) in two HRSA-funded Regional Genetics and Newborn Screening Collaboratives: the Region 4 Genetics Collaborative and the Mountain States Genetics Regional Collaborative Center in Region 6.

A. Region 4 Genetics Collaborative: Laboratory Quality Improvement in MS/MS Newborn Screening

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 gave the Committee an update on the collaborative newborn screening laboratory quality improvement project of the Region 4 Genetics Collaborative (which includes Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio, and Wisconsin). A defining characteristic of the project, he said, is the active and frequent participation and submission of data on newborn screening by MS/MS from newborn screening labs in the United States and other countries. The study is progressing very well, and momentum in national and international participation appears to be gaining strength.

State newborn screening labs and other participants are asked to submit data once a month on the percentiles of values for the normal population, cutoff values, and true positive cases. The data are posted on a cumulative basis on the Region 4 Website (www.region4genetics.org). Dr. Rinaldo and his colleagues have been seeking data on at least 50 true-positive cases for each of the 42 primary and secondary conditions in the ACMG uniform newborn screening panel that are detectable via MS/MS, with a view toward improving overall analytical performance. The researcher team now has at least 50 true positives (cases) for 14 of the 20 primary conditions detectable via MS/MS on the ACMG uniform panel; they also have 50 true positives for 3 of the 22 secondary conditions detectable via MS/MS on the panel.

Dr. Rinaldo illustrated how he and his colleagues manipulate the data that have been submitted by newborn screening labs on percentiles, cutoff values, and true positives to generate percentiles of various markers and disease ranges. They use a very objective and dynamic approach to specify the cutoff range for a particular condition, which involves comparing the normal population and disease population and variability in cutoff values. The cutoff range is the range of concentration between the 99th percentile of a normal population and the 5th percentile of the disease range. The reason the 5th percentile is used rather than the 1st percentile is to minimize the undue impact of any very unusual outliers.

The data and the tools available through the MS/MS project in Region 4 also enable the comparison of newborn screening laboratories within regions, across regions, within a single lab as a single entity, and around the world with respect to the following performance metrics: (1) the detection rate of a newborn screening program (defined as the number of neonates that on average need to be tested to detect one affected patient); (2) the false-positive rate of a newborn screening program (the proportion of positive tests in subjects proven by followup evaluation not to have one of the conditions targeted by a given screening program); and (3) the positive predictive value of a test (the probability that the patient has a disease when restricted to those patients who tested positive).

On the basis of their experience to date, Dr. Rinaldo and his colleagues have proposed the following targets as evidence of the adequacy of a newborn screening program's analytical and postanalytical performance: a detection rate of 1 in 3,000 or higher, a positive predictive value greater than 20 percent, and a false-positive rate of less than 0.3 percent. (See article P. Rinaldo et al., "Making the Case for Objective Performance Metrics in Newborn Screening by Tandem Mass Spectrometry," *Mental Retardation and Developmental Disabilities Research Reviews*, 2006, which was included under TAB #13 in the binder distributed to Committee members.

As the Region 4 Genetics Collaborative MS/MS laboratory quality improvement project has evolved, many other activities have developed, including a round-robin sample exchange project, monthly conference calls, training courses, and face-to-face meetings of a working group. The targets of the sample exchange program are to get 100 percent correlation of true-positive cases with a threshold of 95 percent; 90 percent of primary analyte(s) values within 20 percent of submitters' corresponding values; 100 percent active participation in the exchange process from all States within Region 4; and increased participation from at least three States outside Region 4. The training courses are week-long training sessions at the Mayo Clinic in which the MS/MS data and tools developed through the project are discussed and reviewed. The next training session will be held at the end of June 2007.

Dr. Rinaldo, who thanked the Michigan Public Health Institute for its help in making the Region 4 Genetics Collaborative MS/MS project happen, reported that his team had recently been notified that they had received a grant for a 5-year sequel to the project. The project objectives for 2007 are include more of the same, including the development and implementation in screening practice the clinically validated cutoff valves and postanalytical tools; the provision of six or seven training courses a year, etc. What will really be different and exciting is the development of customized software (Web based, password protected) to manage data collection, analysis, and reporting. This new software will allow peripheral data submission (i.e., participants will enter their own data) and facilitate the production of project tools such as scorecards, plots, and customized reports. It will also allow adding new conditions and markers with potential applicability beyond conditions detectable via MS/MS screening.

Questions & Comments

Audience member Dr. Kenneth Pass from the New York-Mid-Atlantic Consortium for Genetics and Newborn Screening in Region 2 complimented Dr. Rinaldo on his work and asked whether his dataset included data from private newborn screening laboratories or Pediatrix. Dr. Rinaldo said his project team did not have data from private labs or Pediatrix. Mr. Bill Slimak from Pediatrix explained that the data from newborn screening belong to the States, and Pediatrix cannot give the data to anyone unless the States give approval. All Pediatrix does is format the data and electronically send it. At Dr. Rinaldo's request, Mr. Slimak agreed to e-mail Dr. Rinaldo within the next few days – the name and contact information for individuals in the States who have the authority to give approval.

Dr. Pass also asked whether Dr. Rinaldo had considered using multiples of the mean rather than percentiles and what attention he had given to using newborn specimens to develop new assays vs. comparing performances among states. Dr. Rinaldo replied that they intended to move toward using multiples of the mean and that their database would easily convert absolute values into multiples. He also said that his philosophy is that samples are precious, but there is not a finite supply of samples, so even if you run out of a sample, there will be more.

B. Region 6/Mountain States Genetics Regional Collaborative: Improving the Quality of Newborn Screening by MS/MS

Marzia Pasquali, Ph.D.
Associate Professor of Pathology (Clinical)
University of Utah School of Medicine
Medical Director, Biochemical Genetics and Supplemental Newborn Screening

Dr. Pasquali reported on a laboratory quality assurance project being undertaken by the Mountain States Regional Collaborative in Region 6 (Arizona, Colorado, Montana, Nevada, new Mexico, Texas, Utah, and Wyoming). This project, which involves the exchange of blood spots for educational purposes to improve the quality of newborn screening by MS/MS, will complement Dr. Rinaldo's collaborative MS/MS laboratory quality improvement project in Region 4 and proficiency testing by the Centers for Disease Control and Prevention.

Currently, there is no consensus on how to deal with borderline/abnormal profiles in newborn screening. Such profiles may be due to iatrogenic effects, hyperalimentation, or medication, or metabolic or other disorders. In some cases, physicians admit the patient with an abnormal newborn screening result, until confirmatory tests have been done. In others, physicians just say get the confirmatory test done within 72 hours.

The goals of the Region 6 project are (1) to improve recognition of these abnormal profiles in newborn screening; (2) decrease the number of the unnecessary confirmatory tests that are done on these infants; (3) when possible, promote the use of second-tier tests that will help clarify whether there is an abnormal profile due to a metabolic disorder or not; and (4) ultimately, decrease the number of false positives and also false negatives that can derive from these tests.

To do this, the Mountain States Regional Collaborative will encourage all of its States to participate in the collaborative project of Region 4 and attend the training sessions. The collaborative will send "educational challenges"—i.e., blood spots from real patients with metabolic disorders or with clinical conditions resulting in abnormal amino acids or acylcarnitines)—and compile a report on

the analytical part of testing and the followup/clinical aspect of testing. Evaluation forms will be distributed by electronic mail. One meeting a year will be organized to discuss the educational challenges. Results will also be discussed at the regional meetings. Tracking over time will determine the impact of the training sessions and educational challenges on performance. The challenges for the project include obtaining blood from patients in many centers in order to increase the number of cases, developing consent forms, and tracking data from participating laboratories.

Although the project will start as a regional effort, enrollment will be open to every lab performing newborn screening by MS/MS. There will be no cost for labs to participate. Participating labs will be asked to analyze two to three sets of blood spots twice per year, fill out the results form, e-mail the results, and attend one meeting per year.

Questions & Comments

Dr. Howell suggested that Dr. Pasquali might find it helpful to work in collaboration with the National Institute of Child Health and Human Development to identify neonates with special issues and that Pediatrix might be able to help in getting appropriate samples of infants who are getting special treatments that would affect newborn screening.

XI. FEDERAL LEGISLATION: AN UPDATE

Emil Wigode
Director, Federal Affairs
Office of Government Affairs
March of Dimes Birth Defects Foundation

Mr. Wigode reported on the status of Federal appropriations and authorizing legislation related to newborn screening. He also noted that HHS Secretary Michael Leavitt was asked by Rep. Lucille Roybal-Allard during the House Appropriations Committee hearings about the letter from the Advisory Committee encouraging the Secretary to facilitate the adoption of the 29 core conditions in the uniform newborn screening panel. Secretary Leavitt said he had not received the letter but would look into it and would get back in writing to the Committee.

According to Mr. Wigode, it is probably going to be a long process to get increases in fiscal year 2008 Federal funding for newborn screening—or even to get overall some extra money in the fiscal year 2008 appropriations bills. For fiscal year 2007, Congress provided level funding for most of the agencies that deal with newborn screening, including the Maternal and Child Health Block Grant, which funds most of HRSA's newborn screening activities, the National Institute on Child Health and Human Development and many programs at the Centers for Disease Control and Prevention (CDC).

The fiscal year 2008 appropriations process just got underway, and the March of Dimes has made it a priority to urge members of Congress to increase HRSA's fiscal year 2008 budget for newborn screening to $9 million (from about $6 million in 2007). The framework to guide congressional spending decisions for the year is the fiscal year 2008 congressional budget resolution. The budget resolution included a $23 billion increase for domestic discretionary funding, but that money will be allocated among different health, education, environment, and other domestic bills by the House and Senate Appropriations Committees. The director of the Executive Office of Management and Budget has publicly stated that because the budget resolution is $21 billion above what the President's budget was, he will recommend that the President veto several appropriations bills that

go above the President's level. It will be a long process to get some funding increases and get overall extra money in this year's appropriations bills.

Mr. Wigode noted that some authorization bills related to newborn screening along with several other bills included under TAB #14 in the binder prepared for Advisory Committee members:

- **Newborn Screening Saves Lives Act.** This bill would authorize several grant programs (e.g., for education and training for health care professionals, education for parents and families, followup care for newborn screening, assistance to States to help improve their screening programs). In addition, the bill would reauthorize the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children for another 5 years, and within that reauthorization, make changes to reflect better what the Committee is doing right now. It would also require CDC to inspect labs and develop a national contingency plan for newborn screening for health emergencies. Senator Chris Dodd and Senator Orrin Hatch have reintroduced this bill (S. 364) in the Senate, and Rep. Roybal-Allard and Rep. Mike Simpson have introduced a counterpart (H.R. 1634) in the House
- **The Screening for Health of Infants and Newborns (SHINE) Act.** This bill would authorize an Internet clearinghouse for educational materials related to newborn screening. It would also authorize several grant programs to help States increase their capacity and also study the benefits of screening for additional disorders beyond the core 29. Finally, it would also require the development of guidelines for States to report newborn screening data. Senator Hillary Clinton is planning to reintroduce this bill (S. 3743) in the Senate, but there is no House counterpart.

The Senate Health, Education, Labor, and Pensions Committee is interested in moving a newborn screening bill in June or July 2008, and both these bills are under its jurisdiction. The March of Dimes is encouraging Senator Dodd and Senator Clinton to come up with a consensus bill in the Senate to get action there, and then try to get the House to move on the bill.

Finally, Mr. Wogode reported that one provision from Senator Barack Obama's Genomics and Personalized Medicine bill discussed at the meeting had passed the Senate. A provision requiring an Institute of Medicine study on the safety and quality of genetic tests was included as an amendment to the recent Food and Drug Administration reform bill that passed the Senate.

XII. PUBLIC COMMENT SESSION

The following individuals made public statements to the Advisory Committee on the afternoon of Friday, May 18, 2007. The written text of their statements appears in Appendix A.

1. Paula Brazeal
President
United Leukodystrophy Foundation

Ms. Brazeal, who lost two sons, a brother, and an uncle to adrenoleukodystrophy (ALD), said that she had appealed to the Committee in June 2006 to understand the necessity and the critical need for newborn screening for ALD. She urged Committee members not to get bogged down in matters of process and said that she and others are committed to nominating ALD as a condition to be added to the uniform newborn screening panel as soon as possible.

2. Kathleen Huntington
Genetic Metabolic Dieticians International (GMDI)

Ms. Huntington stated that she is a clinical dietician and member of GMDI, a new group formed to meet needs of genetic metabolic dieticians serving patients identified via newborn screening. GMDI supports the efforts of Advisory Committee to expand and improve and reform newborn screening. Its members are in a unique position to understand treatment, implementation, and adherence to therapy. GMDI is doing a survey of State coverage of medical food and would like to share the results with the Committee and collaborate with the Advisory Committee to make sure that medical foods are covered.

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

Ms. Gartzke applauded the Advisory Committee for finalizing the form for nominating conditions to the uniform newborn screening panel and stated that the Krabbe disease team would be submitting a form to nominate Krabbe disease. She reported that New York, which began screening for Krabbe disease last year, identified two children at high risk and two children at low risk. It also identified one child with early infantile onset Krabbe who has been transplanted and is doing very well—a huge milestone. Ms. Gartzke noted that she has made comments at every one of the Advisory Committee's 10 meetings to date and thanked the Committee for allowing her to share her views as a parent who lost a child to Krabbe disease 10 years ago.

4. Jill Levy-Fisch
Parent & President
Save Babies Through Screening Foundation

Ms. Fisch said she was proud of the New York program for Krabbe disease, was glad that the Committee was at the point where nominations for conditions to be added to the newborn screening panel were going to be accepted. She reported that she had attended the April 18, 2007 workgroup meeting on long-term followup and thought that what was accomplished that day would help redefine the long-term followup system for affected newborns. She emphasized that long-term followup should take a developmental, lifetime perspective. Ms. Fisch also urged the Advisory Committee to act expeditiously once recommendations addressing the lack of reimbursement for medical foods are made by the Followup & Treatment Subcommittee.

5. Andrea M. Williams
Executive Director
Children's Sickle Cell Foundation, Inc.

Ms. Williams said that although she had heard Committee members refer to genetic diseases and heritable disorders as being "rare" diseases, sickle cell disease is not rare. Approximately 1 in 400 African Americans have sickle cell disease and 1 in 12 with sickle cell trait. These carriers are at risk for having a child with sickle cell disease. Every child that tests positive for sickle cell trait has at least one parent that also has sickle cell trait, possibly two. Should both be carriers, they are at a 25 percent risk of having a child with sickle cell disease. It is important to educate these parents about their situation, and it is important to educate providers to view sickle cell trait as a diagnosis requiring an action plan that includes referring parents for genetic counseling.

6. Carol Greene, M.D.
Board of Directors
Society for Inherited Metabolic Disorders (SIMD)

Dr. Green said SIMD, the professional organization of clinicians and scientists focused on inborn errors of metabolism, appreciated the opportunity last month to participate in the April 2007 meeting on long-term followup and treatment issues. She indicated that she would like to submit for the record SIMD's statement on improving the collection of outcome data for therapies for clinical use for the record and SIMD's policy statement on medical foods. She also stated that SIMD appreciates the vote from the Advisory Committee to allow SIMD to send a nonvoting organizational liaison representative to the Advisory Committee.

7. David Whiteman, M.D.
Principal Medical Director
Medical Affairs
Shire Human Genetic Therapies

Dr. Whiteman congratulated the Advisory Committee on having approved the nomination form and external Evidence Review Group for the expansion of the uniform newborn screening panel. He said his main interest in newborn screening is lysosomal storage diseases, especially Hunter's syndrome. We intend along with the clinicians who treat such patients and with the support of family organizations to submit a nomination for Hunter's syndrome as a condition to be added to the newborn screening panel. Finally, Dr. Whiteman said he would like to see the Committee strengthen its communications with industry.

8. Spencer Perlman
Government Relations Director
Families of Spina Muscular Atrophy (FSMA)

Speaking on behalf of the spinal muscular atrophy (SMA) community, Mr. Perlman urged the Advisory Committee to explicitly permit the addition of disorders to the uniform newborn screening panel for which there is no demonstrated treatment or cure. Newborn screening is an issue of paramount importance within the SMA community. There have been several exciting research breakthroughs in SMA research in the past 5 years, and this research, along with clinical trials now in progress and drug discovery programs that are moving forward rapidly, could benefit from identifying affected individuals at birth and hold tremendous promise in developing a treatment or cure for SMA. Sixteen researchers haves signed a letter to the Advisory Committee giving reasons to screen for SMA, and Mr. Perlman summarized the letter and asked that it be placed in the record along with his oral testimony.

9. Kimberly Symonds
Executive Director
Wilson's Disease Association

Ms. Symonds reported that the Wilson's Disease Association is working with the Mayo Clinic on a newborn screening pilot study for Wilson's disease in Minnesota and hopes to submit a nomination for Wilson's disease to be included on the uniform newborn screening panel in the near future. She urged the Advisory Committee to consider Wilson's disease for inclusion in the uniform newborn screening panel. Although there are effective treatments and therapies for the disease, without screening, there is no easy way to obtain a diagnosis, because Wilson's disease mimics many other disorders.

10. Bill Slimak
VP Operations
Pediatrix

Mr. Slimak explained that the organization requesting formal representation on the Committee as a nonvoting liaison representative was not Pediatrix Screening but Pediatrix Medical Group, which has components (physician practices, Pediatrix University on the Web, pediatric research with a warehouse of clinical data, hearing screening, and Pediatrix screening) that touch about 1 million of the 4 million babies born each year. He stated that it would be almost impossible to find one representative of "industry" to serve as a liaison to the Committee, given the spectrum of clinical labs in the Clinical Laboratory Improvement Act world, reagent manufacturers in the Food and Drug Administration (FDA) world; and pharmaceutical houses in a different FDA world. He concluded by saying that he would continue to attend Advisory Committee meetings to advocate that all newborns get the most comprehensive screening and clinical service available.

XIII. 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

Dr. Howell asked if there were any additional items that should come before the Committee, noting that several Committee members had to leave and there was there was no longer a quorum.

Dr. Dougherty asked what was going to happen with the "ACHDGDNC: Policies and Procedures for Operation and the Development of Recommendations for Screening Newborns and Children for Heritable Disorders and for the Heritable Disorders Program," which had been considered earlier in the day. Dr. Lloyd-Puryear said that she would work to get the document refined via e-mail rather than wait until the September meeting of the Advisory Committee. Dr. Howell agreed, saying he hoped the procedures could be approved very soon.

Dr. Brower indicated she would like to know how long States keep their newborn screening cards and if there could be a mechanism to save those cards that represent positive cases so that they might be linked to the 4,000 positive cases that Dr. Rinaldo now has in his database. Dr. Therrell said information about that is available on National Newborn Screening and Genetics Resource Center's Website (http://genes-r-us.uthscsa.edu/). He said most States do retain their positive cases in some way for future studies, but they do not retain the negatives after a period of about 6 months.

Dr. Howell asked Committee members to forward suggestions for the Advisory Committee's September 17-18, 2007 meeting. Dr. Lloyd-Puryear indicated that she would set dates for future meetings after reviewing Committee members' availability. Dr. Howell adjourned the meeting at 1:58 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.
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