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

Summary of 19th Meeting
September 24-25, 2009
Bethesda, MD

Prepared for:

Genetic Services Branch
Maternal and Child Health Bureau
Health Resources and Services Administration
Rockville, MD

Prepared by:

Altarum Institute
Washington, DC

October 2009

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was convened for its 19th meeting at 8:30 a.m. on Thursday, September 24, 2009, at the Bethesda Marriott Hotel in

Bethesda, Maryland. The meeting was adjourned at 2:10 p.m. on Friday, September 25, 2009. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments.

Committee Members Present

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CONTENTS

I. WELCOME, OPENING REMARKS

Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
Professor, Department of Pediatrics
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Welcome. Dr. Howell welcomed Dr. Mary Willis, who is serving as the representative to the Advisory Committee from the U.S. Department of Defense (DOD), to the meeting. Dr. Lloyd-Puryear noted that there is a supplement to the PDF of the briefing book that was sent to Committee members on a thumb drive prior to the meeting. She also explained that the Federal Government is not permitted to give out hardware; for that reason, she asked Committee members to download the files they need from the thumb drives they received and return the thumb drives to the Committee. Finally, Dr. Lloyd-Puryear asked individuals giving presentations at the meeting to save their presentations with their name and title on the laptop at the front of the room.

Approval of Minutes. By voice vote, the Committee unanimously approved the minutes of the Committee's 18th meeting on May 12, 2009 (under Tab #5 in Committee members' briefing books).

Response to President's Commission on Bioethics. Dr. Howell reported that in June 2009, President Obama disbanded the President's Commission on Bioethics and that the commission's work is being archived. He noted that in February 2009, the Advisory Committee had discussed possible responses to a report issued by the President's Commission on Bioethics. The question now, Dr. Howell said, is what the Advisory Committee should do, if anything, given that the commission no longer exists.

Dr. Fleischman responded that he and others had published a response to the report of the President's Commission on Bioethics in *Genetics and Medicine* and said he thought the Advisory Committee should respond if for no other reason than to indicate the Advisory Committee's disagreement with the commission. Dr. Howell asked what the mechanism should be used, saying he assumed it would be a published response. Dr. Lloyd-Puryear said there was a published report in *Genetics and Medicine.* Dr. Boyle recommended that the Committee publish a response to the President's Council on Bioethics so the comments could be indexed when people look for information. Dr. Dougherty, calling in on the phone, agreed that the Committee should do have some sort of response even if it was just a report on the Committee's Website. It seemed to be the sense of the Committee that it should publish some sort of response to the report of the President's Commission on Bioethics.

Committee Correspondence and Articles of Interest. Dr. Howell drew Committee members' attention to a letter dated July 31, 2009, from the new Secretary of Health and Human Services (HHS) Kathleen Sibelius in their briefing materials (under Tab #5 in Committee members' briefing materials). The letter was a general letter, and a more detailed letter is expected in October of this year. It is clear that changes in the realm of medical foods will require legislation. Senator John Kerry's (D-Mass.) office is working on legislation pertaining to medical foods using the Advisory Committee's April 7, 2009, letter on medical foods and consultations with Dr. Howell. Dr. Howell also drew Committee members' attention to several articles of interest (under Tab #16 in Committee members' briefing materials).

II. COMMITTEE BUSINESS—SUBCOMMITTEE REPORTS

For most of the morning of September 24, 2009, the Advisory Committee's Laboratory Standards & Procedures Subcommittee, Education & Training Subcommittee, and Followup & Treatment Subcommittee held meetings that were open to the public. Before the group convened for lunch, the subcommittee chairs gave reports to the full Committee on their activities, as discussed below.

A. Laboratory Standards & Procedures Subcommittee

Gerard Vockley, M.D., Ph.D.
Chief of Medical Genetics
Children's Hospital of Pittsburgh of UPMC
Professor of Human Genetics and Pediatrics
University of Pittsburgh
Committee Member

Dr. Vockley, the chair of the Laboratory Standards & Procedures Subcommittee, reported that the subcommittee had received several updates at its September 24th meeting:

- Dr. Harry Hannon gave a progress report on the study of routine second screens for congenital hypothyroidism (CH) and congenital adrenal hyperplasia (CAH) that was begun by the National Newborn Screening and Genetic Resource Center (NNSGRC) and Association of Public Health Laboratories (APHL) on behalf of the subcommittee quite some time ago. Six states now have obtained approval from institutional review boards (IRBs), and the some of them are starting to enter data, so the study is finally moving ahead.
- Dr. Bob Vogt from the Centers for Disease Control and Prevention (CDC) provided an update on CDC's progress in making make reagents for newborn screening available. Four of the five Genzyme-produced lysosomal storage diseases enzyme substrates for tandem mass spectrometry (MS/MS) have now been validated and are being made available by CDC; the Krabbe disease substrate is not quite ready to go. Committee members were reminded of study in Minnesota comparing the antigen-based multiplex-B technology to MS/MS enzyme assays for those diseases and to a traditional fluorometry enzyme assay.

Most of the September 24th meeting of Laboratory Standards & Procedures Subcommittee was devoted to a discussion of the implications of screening for conditions such as severe combined immunodeficiency disorder (SCID) that require molecular-based newborn screening. Molecular screening technologies are to some extent less mature than MS/MS was when implemented as screening platform; and such technologies are also more variable. Michelle Kagano from New York State gave a nice overview of the history and current status of such technologies. The Laboratory Standards & Procedures Subcommittee will not be able to stay on top of all technologies; however, it can try to refresh the goals of what molecular screening technologies ought to be achieving with respect to newborn screening and make sure as new screening tests come forward using these technologies that there is some platform to fall back on that is relatively technology independent.

B. Education & Training Subcommittee Report

Tracy L. Trotter, M.D., F.A.A.P.
Senior Partner
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San Ramon Valley Primary Care Medical Group
Committee Member

Dr. Trotter, who chairs the Education & Training Subcommittee with Jana Monaco, reported that the subcommittee now includes the following members: Natasha Bonhomme, Colleen Buechner, Dr. Chen, Dr. Fleischman, Dr. Geleske, Dr. Gregory Hawkins, Joyce Hooker, Dr. Musci, and Andrea Williams.

HRSA Grant Provided for the Development of a Newborn Screening Clearinghouse. At its September 24th meeting, the Education & Training Subcommittee received a report that the Genetics Services Branch of HRSA's Maternal and Child Health Bureau has provided a 5-year, $3.8 million grant to the Genetic Alliance and the National Newborn Screening and Genetics Resource Center (NNSGRC), along with other collaborators, to start a Newborn Screening Clearinghouse. The goal of the clearinghouse is to increase awareness of newborn screening for all stakeholders, provide a central linking point for data and resource sharing, enable just-in-time and point-of-service access for parents and providers, and integrate electronic health technologies.

Organizational Updates. Updates were provided to the subcommittee by the Genetics and Newborn Screening Regional Collaboratives, the Genetic Alliance, NNSGRC, the March of Dimes, the American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Family Physicians (AAFP).

Activities and Plans Related to Educating Primary Care Physicians and the Public About Newborn Screening. The Education & Training Subcommittee is serving in an advisory capacity to entities involved in educating primary care physicians and in educating families and the public about newborn screening. The subcommittee has partnered with various organizations—including AAP, AAFP, ACOG, the National Human Genome Research Institute (NHGRI), NNSGRC, and the Genetic Alliance—to help ensure that primary care physicians and the public get the information they need. At the September 24th meeting, the subcommittee members discussed the following:

- **Update on June 2009 Workshop on Genomic Education Topics in Maternal and Child Health.** A workshop on genomic education topics in maternal and child health was organized by the Education & Training Subcommittee at "Developing a Blueprint for Primary Care Physician Education in Genomic Education," a two-day meeting convened by the National Human Genome Research Institute (NHGRI) in June 2009. The purpose of the workshop on genomic education topics in maternal and child health was to stimulate thinking about the development of an action plan for improving the genetic and genomic education of primary care physicians involved in maternal and child health. The workshop was attended by about 30 people, including representatives from organizations representing primary care providers, many of whom are at a high enough level in their organizations to make decisions. Specific topics discussed at the workshop on genomic education topics in maternal and child health were the following: (1) *knowledge areas* (genetics/genomic medicine, clinical utility of genetic tests, role in newborn screening, how to collect and act on a family health history, sources for guidelines and clinical recommendations, methods of informing families bout genetic testing and obtaining consent, and when and how to refer to a genetic counselor or geneticists); (2) *barriers to*

educating primary care physicians (e.g., lack of time, lack of geneticists to train primary care physicians, and lack of enthusiasm (due to poor literacy, lack of confidence, concerns about relevance to child health care); and (3) *educational interventions* (e.g., develop educational curriculum for residency training programs, ensure that board certification exams assess literacy, continuing medical education on practical aspects of incorporating genetic and genomic information into primary care, promoting participation in genetics and genomic medicine-related educational activities through the maintenance of the board certification process, and create a Website that would organize both clinical recommendations and practical office tools (e.g., family health history forms, risk questionnaires). Dr. Alex Kemper is working with a few subcommittee members to produce a draft report on the meeting and workshop, and the Education & Training Subcommittee hopes eventually to obtain the Advisory Committee's approval to publish it. The subcommittee also that there will be a followup meeting of the group that met at the two-day NHGRI workshop in June 2009.

- **Recommendation to Establish a "Learning Collaborative"/Genetics in Primary Care Training Institute**. To help educate primary care physicians about genetics, the subcommittee discussed and embraced an idea suggested by Dr. Lloyd-Puryear—the creation of a "learning collaborative" that would pair physicians from busy primary care physicians with expert in genetics; have all primary care physicians attend a conference to define opportunities for genetics in primary care; develop specific one-year projects; participate in frequent calls to review progress; meet at the end of the year to share results; and formally evaluate the project's impact. The Education & Training Subcommittee requests that the Advisory Committee recommend that a "Learning Collaborative"/Genetics in Primary Care Training Institute be funded.
- **Discussion of the Need for Additional Resources for Public Education Related to Newborn Screening.** Finally, the Education & Training Subcommittee discussed the need for and recommends additional resources to increase public awareness of the newborn screening system.

Dr. Trotter made the following motion, which was unanimously approved by the Committee (10 yes, 4 absent):

- ***MOTION #1 (PASSED): The Advisory Committee supports the development of a "Learning Collaborative"/Genetics in Primary Care Training Institute and recommends moving forward in next six months to find some funding and an appropriate mechanism for that project.***

After the motion passed, the suggestion was made that family members be involved in the process for developing the Learning Collaborative"/Genetics in Primary Care Training Institute.

C. Followup & Treatment Subcommittee Report

Colleen Boyle, Ph.D., M.S.
Director, Division of Birth Defects and Developmental Disabilities
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention (CDC)

Dr. Boyle, the chair of the Followup & Treatment Subcommittee, reported that the subcommittee is continuing its efforts (1) to define and characterize long-term followup (LTFU) care after newborn screening; and (2) to examine issues related to insurance coverage of medical foods. In addition, Dr. Boyle indicated that the subcommittee has recently identified some issues related to short-term followup after newborn screening that it will try to address.

Recent Subcommittee Activities Pertaining to LTFU Care After Newborn Screening

- **Paper on Roles and Responsibilities in LTFU After Newborn Screening.** Dr. Boyle reminded Advisory Committee members that Dr. Alex Kemper and other members of the Followup & Treatment Subcommittee had developed a paper outlining the major components of long-term followup in newborn screening that was published as a statement from the Advisory Committee in *Genetics in Medicine* in April 2008. The Followup & Treatment Subcommittee is now developing a second document that outlines the roles and responsibilities of major players in long-term followup (namely, affected individuals/families, primary care providers, specialty and subspecialty providers, and the public health sector at national and state levels). The hope is that when the second article is ready, it will similarly be approved by the Advisory Committee for publication in *Genetics in Medicine*.

- **Workshop Held to Identify Overarching Questions (Quality Measures) for LTFU and Treatment in Newborn Screening.** On September 23, 2009, prior to its regular meeting on September 24th, the Followup & Treatment Subcommittee convened a special workshop on LTFU after newborn screening. The purpose of the workshop, entitled "Overarching Questions in Long-Term Followup and Treatment in Newborn Screening," was to have a small group of individuals with expertise from the various sectors of the public health and health system that interface with or are critical to long-term followup after newborn screening—namely children and their families, primary and specialty care providers, state and federal public health entities, and other stakeholders having expertise in education, managed care, and health insurance. participants review and refine a list of core questions that lead to the development of the types of information needed to ensure optimal LTFU of infants with conditions detected via newborn screening. The Followup & Treatment Subcommittee had begun developing a consensus on a set of variables for the electronic exchange of information needed to ensure optimal long-term followup of infants with conditions detected via newborn screening at the beginning of 2009. It was been agreed that the variables selected should pertain to the four components of LTFU identified by the Followup & Treatment Subcommittee (care coordination through a medical home, evidence-based treatment, continuous quality improvement, and new knowledge discovery) in the article published in *Genetics in Medicine* in April 2008 and should also address the information needs of the key sectors in long-term followup (national and state entities involved in newborn screening, primary care/specialist providers, and families). A draft matrix of dozens of questions relevant to LTFU after newborn screening that was based on this framework was given to participants at the September 23rd workshop. Members of the three breakout groups at the workshop—National/State, Subspecialist/Primary Care Providers, and

Families—were asked to modify, collapse, add, and prioritize the questions so that there would be only about five to seven questions per perspective. There was generally consensus at the meeting about what the major questions in various sectors should be. The next step will be for the Followup & Treatment Subcommittee to do additional work to refine the overarching questions. Dr. Kus has agreed to spearhead the subcommittee's effort.

Recent Subcommittee Activities Pertaining to Insurance Coverage of Medical Foods

- **Committee's Letter to the HHS Secretary on Medical Foods.** Earlier this year, the Advisory Committee approved sending a letter from the Advisory Committee to the Health and Human Services Secretary Charles E. Johnson recommending a number of legislative and policy measures to ensure that families medical foods. At the subcommittee's September 24th meeting, Dr. Howell updated subcommittee members on the status of the letter, which was sent to Secretary Johnson on April 7, 2009. Legislation on medical foods is being prepared in the U.S. Congress.
- **Survey of Families on Medical Foods**. The subcommittee has been conducting a survey of affected families with the help of the New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services, the Southeastern Regional Genetics Group, and the Region 4 Genetics Collaborative. At the meeting on September 25th, Dr. Mary Kay Kenney gave subcommittee members a preliminary overview of analysis of data from the survey of families. Data are still be collected and analyzed, and the subcommittee expects to make a report on the survey to the full Advisory Committee in January 2010.

Identification of Issues Related to Short-Term Followup After Newborn Screening. Several issues came up at the subcommittee's September 24th meeting related to short-term followup after newborn screening. In many states, no linkage of newborn screening data with vital records and other state records occurs on a real time basis, so children get lost. The subcommittee discussed possibly making newborn screening conditions a reportable condition at the State level to facilitate the reporting and collection of information. The question the subcommittee is considering is what the Advisory Committee might do in terms of making recommendations to address these issues. Dr. Kemper has volunteered to shepherd the subcommittee's efforts related to these short-term followup issues.

III. NEW MEDICAL FOODS LEGISLATION

Christine Brown, M.S.
Executive Director & Parent of Children with PKU
National PKU Alliance

Ms. Brown began her presentation by explaining that the mission of the National PKU Alliance, which includes several member organizations around the United States, is to improve the lives of individuals and families with phenylketonuria (PKU) through research, support, education, and advocacy, while ultimately seeking a cure. She then reported on an advocacy campaign on Capitol Hill undertaken by the National PKU Alliance this past summer to make sure that inborn errors of metabolism were not left out of the national discussion of health reform.

The National PKU Alliance sent its advocacy chair Kelly McDonald to Capitol Hill for six weeks. She and other advocates from the National PKU Alliance visited 100 Senators and more than 200 representatives and gave them all stories from PKU families around the country about their difficulties in getting coverage for both medical foods and modified low-protein foods. They also gave them copies of the Advisory Committee's April 7, 2009, letter to the Secretary of Health and Human Services on medical foods to provide documentation of the problem, along with the Advisory Committee's recommendation for a solution.

This advocacy effort has paid off. Senator John Kerry (D-Mass.) has agreed to draft legislation to federally mandate insurance companies to cover medical foods and foods modified to be low in protein for PKU for PKU and 29 other inborn errors of metabolism. Meanwhile, the National PKU Alliance's advocacy work continues. Last week, more than 900 e-mails were sent to Members of Congress by parents, clinicians, etc., about importance of covering medical foods. There is a coordinated campaign of phone calls, e-mails, in district meetings and letters to the editor. The National PKU Alliance Working in partnership with inborn error of metabolism and rare disease organizations in this campaign. It is looking for examples of denials of coverage from Medicaid and/or Medicare and will share these with the Centers for Medicare and Medicaid Services (CMS).

Finally, Ms. Brown thanked the Advisory Committee for its April 7, 2009, letter to the Secretary of Health and Human Services on problems related to medical foods. She noted that the letter has made a huge difference for PKU families. They have used the letter as part of their talking points and it helps demonstrate their legitimacy. There is a fight ahead to advance the cause for all children and adults with inborn errors of metabolism, and it is important to work in a coalition to advance the cause.

Questions & Comments

Ms. Monaco asked whether the legislation that Senator Kerry is working on addresses issue of self-insured companies not paying for medical foods. Dr. Howell said he had seen an outline of draft legislation and the outline includes everything that is contained in Advisory Committee's April 7, 2009, letter. He thanked the PKU Alliance for its work and kind comments.

IV. UPDATE FROM THE HHS OFFICE OF THE NATIONAL COORDINATOR FOR HEALTH INFORMATION TECHNOLOGY

Ginger Price
Program Director
Nationwide Health Information Network (NHIN)
Office of the National Coordinator for Health Information Technology (ONC)
U.S. Department of Health and Human Services (HHS)

Ms. Price, who appeared on behalf of Dr. Charles Friedman, the National Coordinator of the Office of the National Coordinator for Information Technology (ONC) within the U.S. Department of Health and Human Services (HHS), first discussed ONC's activities under the economic stimulus bill enacted by Congress in 2009—namely, the American Recovery and Reinvestment Act (ARRA) of 2009 (Public Law 111-5). In the second part of her presentation, Ms. Price provided an overview of the Nationwide Health Information Network (NHIN), which is a network of networks on the public Internet that provides common legal framework for information sharing, a common infrastructure needed for network security and connectivity, and specifications for interoperable services.

The American Recovery and Reinvestment Act (ARRA) and HITECH Act of 2009. Lawmakers incorporated the Health Information Technology for Economic and Clinical Health (HITECH) Act as part of the 2009 stimulus bill. The HITECH Act is intended to promote the widespread adoption of health information technology to support the electronic sharing of clinical data among hospitals, physicians, and other health care stakeholder. The HITECH Act codifies the Office of the National Coordinator for health Information Technology (ONC).

Beginning in 2011, the HITECH Act authorizes the Centers for Medicare and Medicaid Services (CMS) to provide reimbursement incentives for eligible professionals and hospitals that using health information technology such as certified electronic health records (EHR) in a meaningful way. Under the HITECH Act, HHS has established two advisory committees—the Health Information Technology (HIT) Policy Committee and the HIT Standards Committee—that are tasked with making recommendations to ONC that will help CMS develop the initial criteria for the meaningful use of health information technology and assist in planning for future incentive programs. The incentive payments for the meaningful use of health information technology that will begin in 2011 will phased out over time.

Over time, the definition of meaningful use of health information technology will become demanding. Thus, the requirements will increase between 2011 and 2013, as well as between 2013 and 2015. The HIT Policy Committee's "June 16, 2009, Meaningful Use Matrix" identifies some of the health care goals, objectives, and discrete measures of meaningful for 2011, 2013, and 2015. In the summer of 2009, the HIT Policy Committee provided a final recommendation to CMS regarding the definition of "meaningful use. CMS is drafting a "meaningful use" Notice of Proposed Rulemaking, and this should be finalized in 2010. The meaningful use criteria for 2011 will pertain to capturing and sharing data; the 2013 meaningful use criteria will pertain to advanced care processes with decision support; and the 2015 meaningful use criteria will pertain to improved outcomes.

An informational hearing on the HIT Policy Committee's meaningful use criteria for 2013-2015 will be held in October 2009. This will address gaps in appropriate measures for assessing meaningful use, criteria for specialists (e.g., use of measures relevant to specialists, participation in national registries, development of new measures). Feedback and new ideas will be sought for meaningful use criteria for 2013 and 2015 from a spectrum of physician practices, hospitals, and safety net providers. In the phasing in of meaningful use criteria, the HIT Policy Committee will use criteria such as the following: enable health reform; focus on health outcomes, not software; feasibility (balance urgency of health reform with calendar time needed to implement health information technology; starting from low adoption rate, sensitive to under-resourced practices), provisions of the HITECH Act (e.g., timelines fixed at 2015 and 2011-12; and funding rules are defined with front-loaded incentives). The HIT Policy Committee's timeline for the next 12 months is available online at www.healthit.hhs.gov, where information is regularly updated.

Experience suggests that achieving the meaningful use of health information technology will not be easy. In recognition of this, Congress included two important grant programs in the HITECH Act to support the meaningful use of health information technology. These two programs—the State Health Information Exchange Cooperative Agreement Program, and the Health Information Technology Extension Program—have about $1.2 billion of ONC's $2 billion in discretionary funds. The State Health Information Exchange Cooperative Agreement Program, created by the HITECH Act's addition of Section 3013 to Title XXX of the Public Health Service Act, provides for grants to states and qualified state-designated entities to develop and advance mechanisms for information sharing across

the health care system. Under these state cooperative agreements, $564 million will be awarded to support efforts to achieve widespread and sustainable health information exchange within and among states through the meaningful use of certified EHRs. CMS will issue proposed criteria for meaningful use for this program by the end of 2009.

To keep up to date on meaningful use criteria, the State Health Information Exchange Cooperative Agreement, and the Health Information Technology Extension Program, Advisory Committee members can visit the Website http://health it.hhs.gov and select Recovery.

The Nationwide Health Information Network (NHIN). The Internet's widespread availability and low cost make it an attractive option for the secure exchange of health information; however, the Internet is open, and Internet-based exchanges present two critical challenges for the exchange of health information: (1) *patient, privacy, security, and trust* must be maintained; and (2) information exchange should be "*interoperable*" between systems, so that information generated in one system can be used and understood by another. The NHIN is being created to address these challenges. The NHIN is basically a network of networks that builds on the pubic Internet. It creates a "trusted" network where there is assurance that parties can be trusted (governance, directory, certificates), assurance that patient preferences are adhered to, and assurance that the transmission across the Internet is secure. In addition, the NHIN includes a set of technical protocols, industry standards, and very specific implementation guides that support interoperability and enable NHIN participants to read and understand the health information that is exchanged with minimal or "point-to-point" coordination. The architecture of the NHIN is highly distributed, and patients' health information is retained at the level of the level of the local health information exchange.

The present focus of the NIHN is on the exchange of health information between organizations (e.g., from the U.S. Department of Defense to the Veterans Administration); some day exchanges may be possible at a lower level (e.g., within the Department of Defense). The NHIN cooperative includes (1) private health information organizations (e.g., MedVirginia, HealthBridge, the Regenstrief Institute); (2) state-level health information organizations (e.g., the Delaware Health Information Network, the New York eHealth Collaborative, the North Carolina Health Care Information and Communications Alliance); (3) provider organizations (e.g., Cleveland Clinic, Kaiser), and (4) federal entities (Centers for Disease Control and Prevention, CMS, U.S. Department of Defense, Indian Health Service, National Cancer Institute, National Disaster Medical System, Substance Abuse and Mental Health Services Administration, Social Security Administration, and Veterans Administration). These entities have come together in the NHIN Cooperative, some through contract, some through grants, some through other understandings.

Each health information organization in the NHIN as its own architecture and makes its own determinations with respect to the release of patient information. The NHIN standardizes the communications between health information organizations but does not standardized implementations of NHIN services and interfaces. Finally, the NHIN is platform neutral, having adopted a stack (Web services) that can be implemented using many operating systems and programming languages. Right now what is exchanged is a C32 document, which is a summary of care. As the NHIN brings on other networks (e.g., personalized health records), other documents may be added.

Right now, limited production pilots of the NHIN are beginning to demonstrate how standards and specifications are implemented as working operational solutions for health information exchange. MedVirginia, and the Social Security Administration went into limited production pilot in February of

2009, and other organizations planning to demonstrate health information exchange include Kaiser Permanente, the Department of Veterans Affairs, the Department of Defense, and the Centers for Disease Control and Prevention. About $24 million of ARRA dollars are going into an NHIN-based exchange information with the Social Security Administration. In the next phase, a process of bringing on additional pilot partners will begin. The specifications of the NHIN can also be used by organizations that do not wish to join the NHIN.

Right now, ONC is working from the use cases developed by the American Health Information Community. With the inclusion of meaningful use criteria, ONC has a whole new vista ahead. The NHIN is implementing a process to elicit and prioritize new information exchange features from the health information community. Beyond the NHIN core services, new services have recently been submitted for consideration: (1) a request from the Centers for Disease Control and Prevention to enable the gathering of population health data from health information exchanges; (2) a request from CMS for a profile to enable health information organizations to transmit transfer of care reports to CMS via the NHIN; (3) a request from the Food and Drug Administration for a new service for analytic purposes; (4) a request for NHIN capability to support CMS' Physician Quality Reporting Initiative; and (5) a request for NHIN capability to provide alerts to providers on public health alerts and interventions. The NHIN's staff are responding to these requests to allow input and review of technical artifacts.

In early 2010, ONC will showcase NHIN demonstrations and network operational capabilities. For more information about the NHIN, Advisory Committee members can go to http://healthit.hhs.gov and click on "Nationwide Health Information Network." For regular updates, they can join the Health IT Listserv at https://list.nih.gov/archives/health-it.html and click on "Join or Leave the List, or Update Options." Questions about the NHIN can be addressed by e-mail to nnhin@hhs.gov.

Questions & Comments

Dr. Howell said that in the request for public comments on the NHIN from ONC, Dr. Lloyd-Puryear had sent a letter on behalf of the Advisory Committee noting that there were no newborn screening measures or pediatric measures included in any of the discussion and asking whether that situation might change. He asked Ms. Price to comment. Ms. Price indicated that she was unaware of that letter and would follow up with Dr. Howell about this later. She encouraged Dr. Lloyd-Puryear to submit the Committee's comments directly to Ms. Price.

Speaking from the audience, Dr. Lisa Feuchtbaum, with the Genetic Disease Screening Program of the California Department of Public Health, said that the NHIN seems to be a natural forum for unfolding some of the linkages within State databases (e.g., linking state vital statistics databases with newborn screening). Moreover, within states, it would be great if state employees were able to get access to data within their own department of health services. Ms. Price replied that she would take those ideas back and discuss them as state grants are made, but she added that one of the challenges for the NHIN is that if you are going to make something nationwide, there are different rules that are very state specific, so it considerable groundwork has to be done to make information exchanges between or within states possible.

V. UPDATE ON IMPLEMENTING THE NEWBORN SCREENING USE CASE

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Dr. Zuckerman, a consultant to the Initiative on Personalized Healthcare at HHS who has been working on newborn screening and family history interoperability, had previously given presentations to the Advisory Committee on the development by the Personalized Healthcare Workgroup of the American Health Information Community (AHIC) of the "Newborn Screening Detailed Use Case" and the "Newborn Screening Use Case Coding and Terminology Guide."

In this presentation, Dr. Zuckerman updated Advisory Committee about recent developments and coming milestones in the implementation of the newborn screening use case by the Healthcare Information Standards Panel (HITSP) and other entities. In addition, he asked Advisory Committee members to participate in the public comment process and to endorse HITSP's final newborn screening interoperability specification, which will be issued in January 2010 and put forth as one of the standards to be approved by the Health Information Technology Standards Committee.

Update on Activities Related to Newborn Screening by HITSP and Other Entities. According to Dr. Zuckerman, the enactment of the Health Information Technology for Economic and Clinical Health Act (HITECH) under the American Recovery and Reinvestment Act of 2009 (ARRA) required HITSP to translate its prior work into the new framework. The first milestone in bringing the newborn screening use case into reality is HITSP's Requirements Design Standards Selection (RDSS) for newborn screening (RDSS 153), and there are opportunities for Advisory Committee members to comment on the standards and on the coding methods that have been selected. The RDSS for newborn screening provides specific solutions for each aspect of the original newborn screening use case. Thus, it describes the information flows, issues, and system capabilities supporting newborn screening reporting and information exchanges among clinical care settings and public health and. A key feature of the RDSS is the listing of the data requirements for each information exchange. RDSS 153 is available at HITSP's Website (http://www.hitsp.org/ConstructSet_Details.aspx?&PrefixAlpha=6&PrefixNumeric=153) will be open for public comment through October 16, 2009. It is important to make sure that the key unique features of newborn screening (i.e., that cannot make use of material from other laboratory testing or maternal and child health use cases) have been identified. Among the questions to address, which will lay the foundation for long-term following after newborn screening are: What does the ordering process for newborn screening involve? What data are captured at the time a newborn screening specimen is obtained? There is also interest in whether separate documents are needed for hearing screening.

Of even greater importance than the RDSS, according to Dr. Zuckerman, is inspection testing of HITSP's draft interoperability specification for newborn screening. The draft interoperability specification for Newborn Screening is supposed to be completed by October 30, 2009, but inspection testing and public comments will continue through December 4, 2009. Dr. Zuckerman urged Advisory Committee members to comment on the draft Interoperability Specification for Newborn Screening and make sure important data are captured for the way newborn screening is done not just now and but the

way it may be done in the next five or 10 years. As a result of the HITECH Act, HITSP's interoperability specifications will eventually carry the force of regulation. The standards that are selected now will not be totally voluntary, because in addition to incentives for hospitals and physicians and their offices to adopt certified EHRs, there will be other restrictions on the way states implement systems and the way that Federal funds, such as grant funds, can be used. Key components of the draft interoperability specification for newborn screening will make extensive reuse of material from other use cases (e.g., EHR-Lab).

In January 2010, HITSP will complete its final newborn screening interoperability specification putting it forth as one of the standards to be approved by the Health Information Technology Standards Committee. HITSP will complete its final Newborn Screening Interoperability Specification in January 2010, putting it forth as one of the standards to be approved by the Health Information Technology Standards Committee. Dr. Zuckerman requested the Advisory Committee members endorse the final newborn screening interoperability specification at its January 2010 meeting.

Anticipated Use of SNOMED CT® and LOINC® in Electronic Data Transmissions. The anticipated use of Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT®) and Logical Observation Identifiers Names and Codes (LOINC®) in electronic transmissions of health information and the incentives that will go along with their use will be important for newborn screening. There will be a migration from the International Classification of Diseases, 9th Revision Clinical Modification (ICD-9-CM), which is broadly used to assign diagnoses today, to SNOMED-coded problem lists, although that will take some time, and the use of ICD-10 for billing and other statistical reporting will continue in parallel. By 2015, however, problem lists in electronic health records (EHRs) in both hospital and ambulatory settings will use SNOMED CT codes. In the same way, LOINC codes are going to be used to describe laboratory values in electronic transmission, and a special set of LOINC codes has been developed to report genetic test interpretation as well as the identification of alleles and even the recording of gene sequences. The staff at the National Library of Medicine (NLM) are counting on members of the Advisory Committee to be their clinical experts, to request corrections to the data that will be referenced in HITSP's documents.

Effort to Capture Data Fields in Filter Paper Forms Used to Order Newborn Screening Lab Tests. With the help of Dr. Brad Therrell at the National Newborn Screening and Genetic Resource Center (NNSGRC), Dr. Zuckerman and his colleagues have been analyzed filter paper forms from newborn screening laboratories in all 50 newborn states and the District of Columbia to see what types of information states are capturing in the data fields on these forms. The goal of this effort is not to get every state to capture the same data but to make sure that the data standards that are going to be promulgated for electronic transmissions can accommodate the variability of what states actually do. Some data items are used in nearly all states, while others are used in only a single state. Cluster analysis created three groups of fields that were the most prevalent (e.g., baby's sex, baby's birth date, filter paper number, baby's last name, blood draw date), frequently occurring, and used in only a few states. The next step is to verify the data. Some fields seem to be used for large number of infants, some for a large number of states but relatively few infants. Some fields, even birth date, are not universal. The plan for electronic transmissions is to have a general purpose field into which a state could add any additional coded element. Dr. Zuckerman and his colleagues would like to include some of the data elements that emerge from the workshop on "Overarching Questions in Long-Term Followup and Treatment in Newborn Screening" convened by the Advisory Committee's Followup & Treatment Subcommittee headed by Dr. Boyle.

Other Activities. Dr. Zuckerman reported that the Association of Public Health Laboratories (APHL) has approved the Newborn Screening HL7 Implementation Guide prepared by the Public Health Informatics Group. He also reported that Integrating the Healthcare Enterprise (IHE), which runs the Connectathon at the Healthcare Information and Management Systems Society (HIMSS), the health care industry's membership organization, recently completed a white paper on newborn screening; and IHE is also moving forward on programs to get vendors to implement projects in newborn screening, newborn discharge, and the capture of hearing screening results.

Actions for the Advisory Committee. In closing, Dr. Zuckerman asked Advisory Committee to take the following specific actions:

- Give public comments in HITSP's requirements design standards selection document (RDSS) for newborn screening by October 16, 2009.
- Give public comments on HITSP's inspection testing phase of the draft Interoperability Specification for newborn screening by December 4, 2009. (The question is: "Can I do what I'm doing today on paper using the electronic data standards that are proposed?)
- Propose a mechanism to assign identifier numbers to all newborn screening laboratories. (Many of the newborn screening labs do not have Clinical Laboratory Improvement Amendments [CLIA] numbers. Should there be a whole newborn screening laboratory number, or are there other standards for general laboratories that could be use?).
- Endorse implementation of HITSP's final Newborn Screening Interoperability Specification at the Advisory Committee meeting in January 2010. In January 2010, HITSP will complete its final Newborn Screening Interoperability Specification putting it forth as one of the standards to be approved by the Health Information Technology Standards Committee. HITSP will complete its final Newborn Screening Interoperability Specification in January 2010, putting it forth as one of the standards to be approved by the Health Information Technology Standards Committee.
- Participate in the National Library of Medicine's (NLM) ongoing effort to develop newborn screening codes.

Questions & Comments

Dr. Howell thanked Dr. Zuckerman for his comments and asked whether any Advisory Committee members wanted to respond to the questions he posed.

Dr. Rinaldo said that Dr. Zuckerman's point about some newborn screening laboratories' not having Clinical Laboratory Improvement Amendments (CLIA) identifier numbers was worrisome if it was true. Speaking from the audience, Dr. Brad Therrell said as far as he and Dr. Harry Hannon knew, all laboratories have either a CLIA number or a CAP (College of American Pathologists) number.

Dr. Chen asked how well coordinated HITSP's interoperability work in the Nationwide Health Information Work is with previous the work of the previous ONC. Dr. Zuckerman said that everything that HITSP is doing is very closely linked to the previous work and that rather than open a debate on which version of HL7 we should use for the newborn screening lab report, decisions that were made in developing the NHIN are going to move forward. There is a quality reporting document architecture that has been developed that could be used to collect quality measures for newborn screening. There is now a laboratory-ordering standard that is moving forward.

Finally, Dr. Zuckerman urged the Advisory Committee to think about requests for measure under "meaningful use." He said he saw at least some of the meaningful use criteria as being particular relevant (e.g., capturing orders, incorporating lab results into an EHR); however, meaningful use also deals with access to patient-specific educational resources, providing patients with timely access to their health information, providing patients with electronic copies of their information, and exchanging key clinical test results among providers. Dr. Zuckerman said he sees these as being ripe for one of those specialty-specific measures and believes that newborn screening could become a way in which practices and hospitals could show that they are making meaningful use of the EHRs.

Dr. Boyle, observing that there seems to be a tremendous amount of activity going on in the realm of data sets and standards and codes related to the electronic transmission of health information, suggested that the Advisory Committee consider establishing a new workgroup or subcommittee that would deliberate and interact with other entities on these types of issues. Dr. Howell agreed that this was a good idea and stated that he thought Dr. Rinaldo and Dr. Boyle should be on the workgroup and that Dr. Zuckerman should be a consultant.

VI. NLM'S WORK IN STANDARDIZING NEWBORN SCREENING CODES & TERMINOLOGY FOR ELECTRONIC TRANSMISSION OF SCREENING TEST RESULTS

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Dr. Fung discussed the work of the Lister Hill Center for Biomedical Communications at the National Library of Medicine (NLM) in standardizing newborn screening codes and terminology. Dr. Fung said Dr. Clement McDonald sent his apologies for being unable to attend this Advisory Committee meeting. Dr. McDonald had made a presentation to the Advisory Committee at a previous meeting and stated that NLM would like the Advisory Committee's help in keeping newborn codes up to date.

Goals of NLM's Efforts to Develop Data Standards for Electronic Transmission of Newborn Screening Test Results. Dr. Fung and his colleagues at NLM are working to promote and facilitate use of health data standards in recording and transmitting newborn screening test results electronically. Transmitting newborn screening test results electronically has several potential benefits: (1) electronic test results can be transmitted much more quickly than paper reports; (2) when data on newborn sceening test results are transmitted electronically, it is much easier to track infants with positive newborn screening test results and to make sure that they are properly followed up; (3) standardizing the content of newborn screening test results will very much encourage and enable the pooling of results from different laboratories and centers; and (4) if enough data are collected, it is very likely that the data will give rise to some ideas to improve the newborn screening process in the future.

Coding and Terminology Framework Used by NLM in Health Data Standardization. For newborn screening test results to be able to be transmitted electronically in a standard form, two things are required: first, *standardized codes* for the contents being transmitted (e.g., test names, analytes,

conditions being screened, and other categorical answers); and second, a standard *messaging format* to convey the content electronically.

To the extent possible, NLM would like to adhere to national and international coding standards when it standardizes the content of the data being transmitted. Coding standards in use include that NLM recommends using include the following:

- **LOINC®.** LOINC, which stands for *Logical Observation Identifiers Names and Codes*, provides a set of universal codes for identifying tests (e.g., a laboratory test, an X-ray procedure, or an MRI) and other clinical measurements. The LOINC standard, which is supported by NLM and the Regenstrief Foundation (Indianapolis) is widely used in the United States and internationally (Example: glucose in different languages; one LOINC code—2349-9). There is a no-cost license that allows anyone to use for OINC in perpetuity. Everything can be downloaded from the LOINC Website at http://loinc.org/. LOINC also has a program called RELMA®, which can be used by laboratories to map test codes to LOINC.
- **SNOMED CT®**. SNOMED CT, which stands for *Systematized Nomenclature of Medicine—Clinical Terms*, has rapidly become the emergent clinical technology standard. It was originally developed by College of American Pathologists. In 2007, ownership of SNOMED transferred to the International Health Terminology Standards Development Organization (IHTSDO), which has 12 member countries, including the United States, Australia, Canada, the Netherlands, Spain, Sweden, and the United Kingdom, and is available free of charge in IHTSDO countries and in low-income countries as defined by the World Bank. SNOMED CT is very comprehensive, with more than 300,000 concepts and rich links between these concepts. Moreover, its multilingual terminology is being translated into Spanish, German, French, and even Chinese maybe) for use in EHRs and health data exchange.
- **ICD-9-CM**. ICD-9-CM, the *International Classification of Diseases, 9th Revision Clinical Modification*, is the official system of assigning codes to diagnosis associated with hospital utilization and public health reporting in the United States. In the United States, ICD-9-CM codes are used for reimbursement; moreover, ICD-9-CM is a required standard for use in administrative transactions subject to the Health Insurance Portability and Accountability Act of 1996 (HIPAA).
- **Enzyme codes.** A *List of Recommended Names for Enzymes* recommended by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB) in consultation with the IUPAC-IUBMB Joint Commission on Biochemical Nomenclature (JCBN) Enzyme Nomenclature is freely available for use.
- **OMIM® codes.** The OIMM, *Online Mendelian Inheritance in Man*, is a comprehensive, authoritative, and timely compendium of human genes and genetic phenotypes. It is now maintained by Johns Hopkins University in cooperation with the NLM.
- **UMLS®.** The UMLS, *Unified Medical Language System*, serves as a bridge between different coding standards. Developed NLM, the *UMLS Metathesaurus* incorporates over 100 biomedical terminologies, classifications, and coding systems. The contents are organized by meaning, so terms that mean the same thing are grouped together, and given a common and permanent code (Concept Unique Identifier).

Work NLM Has Done So Far. Dr. Fung said that work he and his colleagues at NLM have done so far with respect to the development of newborn screening coding and terminology data standards for

electronic reporting includes (1) standardizing content for reporting newborn screening test results electronically; (2) standardizing the messaging format for transmitting newborn screening test results; and (3) launching NLM's *Newborn Screening Coding and Terminology Guide Website* (www.newbornscreeningcodes.nlm.nih.gov).

Standardization of content. NLM staff have collected lists of newborn screening tests, analytes, conditions, and categorical answers. Some of them are already mapped to standard coding systems. For items that do not already have a standard code, NLM staff try to fill in the gaps if they can find any code in the standard coding systems that represent the concepts. They also add the UMLS Concept Unique Identifier to all the entities. Just recently, NLM has published this list on its new Website (see below).

Standardization of messaging format. To standardize the messaging format for newborn screening results, NLM would like to encourage the use of Health Level 7 (HL7) as the messaging standard. It would like to do this by facilitating the development of a standard specification for the payload part of the message that uses the codes and approaches proposed by the newborn screening workgroup of the American Health Information Community (AHIC). HL7 is an international messaging standard for the health care domain. There are two versions of HL7: version 2 (the most commonly used and universally available in large practices, laboratories, and hospitals in the United States and many other developed countries) and version 3. The U.S. Government requires HL7, version 2.5 or above for laboratory reporting. The other version of HL7 is version 3.

Dr. Fung gave a detailed explanation of the components of an HL7 message. He noted that an HL7 message is composed of segments. Each segment is usually given a three-letter acronym, and it is designed to convey a specific type of information (e.g. the MSH segment is the message header; the PID segment is the patient identifying and demographic information segment). For reporting newborn screening results, the OBR and OBX segments are the most important. OBR deals with information about observation requests like laboratory and radiology orders, and OBX is a segment used to report the results of such investigations. Apart from specifying the syntax of a message, HL7 also has predefined data types (e.g., DT is the date, which is in the form CCYYMMDD; PN is for the name, which is last name followed by first name, and then the middle mane and then the suffix). The most important data type for conveying newborn screening results is CE, which stands for coded entry. The coded data type has three parts: (1) the code (e.g., from LOINC); (2) the print text, which is a human-readable part of that code; and (3) the code system (LOINC). In the design of HL7, in a CE data type, one can send not just one code but two codes (e.g., local lab codes as well as LOINC codes).

To send newborn screening test results electronically, newborn screening labs would report both quantitative and categorical results labeled with the appropriate LOINC code from the list of codes published by NLM. They would also report the quantitative measures with agreed-upon units, as specified. The categorical results would be reported as a SNOMED CT code. Dr. Fung showed an illustration of how one might report on any one screening test result based on deidentified data collected from Georgia.

NLM's Newborn Screening Coding and Terminology Guide Website. NLM has just launched a new Website: www.newbornscreeningcodes.nlm.nih.gov. The Website includes standard codes and terminology for electronic reporting of for newborn tests and the conditions for which they screen, as well as links to other related sites. Dr. Fung showed several screenshots from the Website. The codes and vocabulary standards are provided in a series of tables that can be viewed on the Web and/or download for personal use. These tables cover conditions recommended for screening by the Advisory

Committee on Heritable Disorders in Newborns and Children or by a state within the United States. The Website is very much a work in progress.

Work Ahead. NLM is beginning to address some additional issues pertaining to the electronic transmission of newborn screening test results. One of these is developing standards for card variables—that is, additional information collected about a baby at the time of screening (e.g., birth weight, transfusion history). Some of these variables may be covered in existing HL7 segments. Variables that are not covered would be sent in OBX segment. For this to occur, however, some standard LOINC codes will be needed. Before LOINC codes can be assigned to such variables, however, NLM needs a clear indication about what the core set of data elements should be.

NLM is also exploring use of special HL7 functionalities that can be used in special-use cases (e.g., the hide function in HL7, which allows some results to be hidden from routine clinical care displays, but still to be available for management and research). Another functionality of HL7 that NLM is exploring is the delivery of a printed image of the report. Special LOINC codes will be assigned to each kind of report.

Questions & Comments

Dr. Getchell asked what process would be used to roll the coding and terminology standards out for implementation by state newborn screening programs. Dr. Fung explained that NLM is just trying to standardize codes and messaging formats for the electronic transmission of newborn screening test results and that some other entity will have to decide how they should be rolled out to facilitate adoption. Dr. Watson noted that LOINC codes are only now just being automated into the equipment in state labs, so states have a long way to go.

Dr. Howell, noting that that Dr. Fung's presentation had underscored the importance of Dr. Boyle's suggestion after Dr. Zuckerman's presentation, said he would definitely establish a workgroup or subcommittee of the Advisory Committee to stay abreast of developments related to coding and terminology and other matters related to the electronic transmission of information related to newborn screening. Dr. Rinaldo suggested that Dr. Getchell be included as a member of the new group, and Dr. Howell agreed that that was a good idea. Dr. Howell suggested that the new group should also include people from National Institutes of Health (NIH), Health Resources and Services Administration (HRSA), and the Centers for Disease Control and Prevention (CDC)

VII. PROPOSED WEB PORTAL FOR NEWBORN SCREENING

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&
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Dr. Downing, project director for the HHS Initiative on Personalized Healthcare, and Dr. Coon, a member of the Newborn Screening Development Team of the HHS Initiative on Personalized Healthcare, gave a presentation on a proposed newborn screening Web portal that would promote the exchange of information on newborn screening by states.

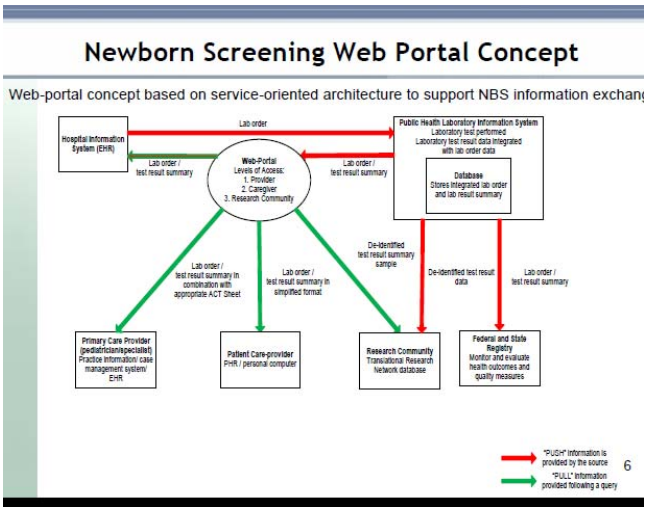
Dr. Downing thanked members of the Advisory Committee for their help. He said that a lot of foundation work has been done to support the electronic exchange of information about newborn screening, and with the work on the National Health Information Network (NHIN) beginning to unfold, he thought that we would soon start seeing some of the benefits of all of this activity in a year or so. Currently, none of the states or communities are able to move information from lab orders or results from the delivering hospital, to the lab, to the physician or other health care provider who needs that information at the time that the provider needs it. The newborn screening community is well poised to benefit from the potential ways in which all the work that has been done thus far can enable that. Dr. Downing said he would like Committee members to think about the value proposition of what they could do with information from the proposed approach to promote state information exchange through a newborn screening Web portal and to think about what service needs at the state level and in health systems a portal could serve.

Dr. Coon began her presentation by stating that the purpose of the electronic newborn screening is to improve the quality of care for newborns by enabling early detection of an intervention for heritable disorders. Special challenges and considerations in newborn screening are that there is public health screening in conjunction with primary care delivery; that it presents a case for continuity of care from the birth center to primary care and followup care; and it provides an opportunity to integrate prenatal, postnatal, and infant health care information.

The Personalized Healthcare Initiative has been busy compiling resources that help or can help to initiate electronic information exchange or develop concepts to exchange newborn screening data. One of them is the newborn screening use case that is now with the Healthcare Information Standards Panel (HITSP), the *Newborn Screening Coding and Terminology Guide* being developed by the National Library of Medicine (NLM), an information package that presents an overview of all the materials that have been developed, and a simple guide to what next steps could be taken in implementing the standards and adopting the standards. Some of these materials are available a the Website of the Health Information Technology (HIT) Policy Committee Website (http://healthit.hhs.gov), and the coding and terminology guidance is available on the new NLM Website for newborn screening coding and terminology (www.newbornscreeningcodes.nlm.nih.gov).

The current limitations for electronic information exchange in newborn screening are that public health information exchange systems such as NHIN are nascent and that the states' have only limited capability to exchange lab orders and results, although progress has been seen in some states such as Iowa, Texas, Delaware, and New York, just to mention a few. The proposed newborn screening Web portal would provide an opportunity to connect newborn screening data with data from, for example, immunization, and thus to build a comprehensive pediatric electronic health record (EHR). It also would present a case of transfer of care from the birth center to primary care providers and thus could serve as a template for other scenarios within the health care field. In addition, it would supports population health activities including research and program evaluation. Finally, it is or will be supported, as discussed by Ms. Price in her presentation, by massive federal investments in health information technology infrastructure and adoption from the Health Information Technology for Economic and Clinical Health (HITECH) Act, included as part of the 2009 American Recovery and Reinvestment Act (ARRA).

The rationale for developing a newborn screening Web portal includes the following: (1) Web portal–based information exchange addresses both the importance of newborn screening and electronic information exchange opportunities (newborn screening is an area of public health importance; it is mandated by all states and, therefore, is also at the leading edge of clinical application of genetic knowledge); (2) an effective electronic communication strategy would both improve newborn screening–based care and potentially serve as a model for health information storage and exchange to support pediatric and lifelong care, communication among various elements of the health care system, and the integration of practice and public health information; and (3) electronic storage and distribution of newborn screening data would also provide new resources for research and lay a foundation for use of genetic information in clinical care, as well as expand consumer access to information and medical decisionmaking.



Dr. Coon showed the attached slide illustrating the concept of the proposed newborn screening Web portal and asked for Advisory Committee's questions and comments. In an ideal scenario, the hospital would have a EHR system that would send an electronic lab order to the public health lab, followed by the filter paper with the actual lab blood spots on it. The lab subsequently would perform the laboratory tests and compile the lab order with the test results; then the lab would make the information available through the Web portal to the ordering physician within the hospital, as well as the primary care provider, the patient care provider, which are the parents, the guardians of the infant, and the research community. These are depicted as green arrows, basically meaning that these would be through queries rather than automatic push of data to these entities. There would also be an automatic push out of data to the federal and state registries that monitor and evaluate health outcomes and quality measures. In addition, deidentified test results would

be made available to the research community, which could be the research network, which could also be researchers looking at quality measures and so on. The Web portal would give the patient care provider and the patient a means of actually controlling and making sure that the lab test has been performed and put their mind at ease that the proposed care and followup has been completed. The primary care provider would receive the lab order information, as well as the lab test results, and then could refer this information on to specialists and other healthcare providers. The ideal state would be that data flows go through an EHR system, but the proposed Web portal would actually be accessible also through laptops, personal digital assistants, and any devices able to access the Internet. The proposed Web portal for newborn screening would have benefits for patients and parents (e.g., portability of patient record, improved coordination of care), primary care providers (e.g., actionable information, reduced time and effort entering data manually), and state health departments and public health laboratories (e.g., connect local systems into a regional network, provide a centralized data exchange).

Dr. Downing concluded the presentation by saying that the concept of the Web portal for newborn screening speaks to the need for an electronic-information supporting service through a Web portal. He and his colleagues would propose that these be open-source resources developed and made available at the state level, to health care delivery systems, and to public laboratories themselves. The Nationwide Health Information Network highways are being built, and the on-ramps and off-ramps and standards for newborn screening information need to be built, too, especially with the Section 3013 provisions of the HITECH Act.

Questions & Comments

Dr. Skeels and Dr. Rinaldo asked to what extent Dr. Downing and his colleagues at the HHS Initiative on Personalized Healthcare had studied the baseline what is already in existence and working prior to developing their idea for a newborn screening Web portal. Dr. Skeels noted that several state newborn screening programs already have Web portals and asked how what Dr. Downing and his colleagues had in mind would offer something in the way of connectivity and portability of information about newborn screening that those portals would not.

Dr. Downing replied he and his colleagues the HHS Initiative on Personalized Healthcare have spoken to many vendors and with Dr. Therrell's help have been to 10 or 15 public health laboratories, so he believes that they have a fairly good sense of what exists. He noted that the interoperability of the codes and terminologies to move unified and common data across different systems will be a challenge, so different hospital or ambulatory care systems have different EHR systems, they may not be able to accommodate the support of a message coming from a state public health laboratory now; the proposed Web portal for newborn screening might be an application for that. Dr. Downing also noted that there are many geographic and policy disparities and that he and his colleagues were particularly interested in making the proposed open-source Web portal available in areas of the country where there is no infrastructure in place already. They are just suggesting piloting an open-source system of this nature. This would provide a lot of opportunity for innovation. The problem they want to solve is a primary care physician who sees a physician for the first time and has nothing to work with.

Dr. Chen commented that the "research community" box in the slide illustrating the concept of the proposed newborn screening Web portal has two arrows. One is the deidentified one from the state lab. The other is a green arrow from the portal. He asked what the implications of mixing the research use with the clinical use consent might be and whether Dr. Downing and his colleagues had considered them. Dr. Coon replied that the proposed Web portal is still just a concept, and there are many pints that

still need to be refined and sorted out. She said she was thinking there would be automatic push out of data out from the state labs into the Newborn Screening Translational Research Network.

Dr. Boyle observed that there had been talk earlier in the day at the meeting of the Followup & Treatment Subcommittee about linking newborn screening results to electronic birth records—which would involve linking public health and vital statistics data—and she asked whether the proposed Web portal for newborn screening would allow such linking. Dr. Downing said that linking such data was in the domain of the state systems. He noted that the capacity for longitudinal data collection was not included in the proposed Web portal. In that area, some of the standards for the terminologies and measures need to be worked on.

VIII. NCQA'S EFFORTS TO IMPROVE QUALITY MEASURES IN CHILD HEALTH CARE

Sarah Hudson Scholle, Dr.P.H.
Assistant Vice President, Research
National Committee for Quality Assurance (NCQA)

Dr. Scholle described efforts by the National Committee for Quality Assurance (NCQA) to improve quality measurement in child health care. As background, she gave explained that NCQA is a private, independent, nonprofit health care quality oversight organization that unites diverse groups around the goal of improving the quality of health care. NCQA is committed to quality measurement, transparency, and accountability.

Quality measurement for NCQA means using objective measures of quality based on evidence; developing results that are comparable across organizations; impartial third-party evaluation and audit; and public reporting. NCQA's quality programs include the accreditation of health plans, the Health Care Effectiveness Data and Information Set (HEDIS), which has process and outcomes measures and is used by commercial, Medicare, and Medicaid plans to compare the quality of health plans; the measurement of quality in provider groups; and other programs. NCQA also has recognition programs for physicians. NCQA's Physician Practice Connections–Patient-Centered Medical Home Program—which assesses whether physician practices are functioning as medical homes—has been endorsed by a number of the primary care specialty societies and others for use in medical home demonstrations. This program has also been endorsed by the National Quality Forum.

In addition, NCQA has a long-term vision for developing measures to increase attention to children's health outcomes. A couple of years ago, NCQA began trying to develop measures that would link compare structural measures and process measures of children's health care quality with children's health outcomes (e.g., school readiness, workforce readiness, family productivity). Its first focus has been on the development of comprehensive well-child care measures for children. With support from the Commonwealth Fund, it has proposed comprehensive well-child care HEDIS measures for different children of different ages (i.e., 6 months, 2 years, 6 years, 13 years, and 18 years).

Among the proposed HEDIS measures for well-child care by age 6 months are newborn hearing and metabolic screening and short-term followup. For hearing and metabolic or other state-required screening, the measures are (1) a hearing screening test result and a metabolic r other screening test result; and (2) for abnormal or indeterminate results, evidence of confirmatory testing and referral in the

patient's outpatient chart In addition, NCQA is developing an individualized care plan document that outlines important health information for children with chronic conditions (e.g., current list of allergies, diagnoses, medications; treatment plan; goals for self management; other clinicians/agencies involved in the child's care; instructions for the family on when to seek urgent care; information on next scheduled appointment; evidence that the plan was discussed with the family or caregivers and was given to the family caregivers; and evidence that the plan was given to the family or caregivers). Dr. Scholle said she welcomed comments from Advisory Committee members on the individualized care plan document.

NCQA plans to complete the specifications and perform field testing of its proposed measures well-child care in up to 20 physician practices and six programs, including Medicaid and Children's Health Insurance Programs (CHIP), as well as state primary care case management programs. A report on the results of the testing will be prepared and presented to NCQA's Committee on Performance Measurement by the end of 2009, and the hope is that this committee will approve the measures for public comment in the spring of 2010. If all goes well, the new measures would be incorporated into HEDIS for 2011.

NCQA is also trying to identify an approach for the measurement of care coordination for children with or at risk of developmental delay. This may be transferable to newborn screening. NCQA wants to think about different actors in the health care system (primary care physicians, medical specialty practices, other services providers such as early intervention programs and rehabilitation programs, the community, and the state). The question is: What are the structural measures and process measures of care coordination that should be in place? Measuring the quality of care coordination is challenging, although it may be possible to measure improvement/stabilization of function and survey patients and their families regarding their perceptions. NCQA is testing some measures of care coordination in medical practices with electronic health records (EHRs), and this is one of the hardest measurement specifications she's ever done because medical practices have different staff and approaches. NCQA believes that this work is applicable to newborn screening. NCQA also plans to extend population health measurement to women's health care (pregnancy, even preconception care). In Phase 1, with support from the Health Resources and Services Administration (HRSA) and the Centers for Disease Control and Prevention (CDC), NCQA will convene a small working meeting to prioritize measurement opportunities; in Phase 2, it will develop and test measures.

Questions & Comments

Dr. Howell thanked Dr. Scholle for her presentation and said it would be helpful to have some NCQA measurement approaches applied to children and newborn screening.

Dr. Geleske asked Dr. Scholle how many of the 178 medical practices she mentioned that are certified under NCQA's Physician Practice Connections–Patient-Centered Medical Home Program are pediatric practices. Dr. Scholle replied that she thought about 20 percent were pediatric practices. Dr. Geleske asked what quality measures were used for those practices. She said the measures were process measures; the practices were asked to demonstrate that they were involved in quality improvement efforts. Dr. Geleske also said with respect to NCQA's Individualized Care Plan that it should be part of the medical record whether a care plan has been instituted.

Dr. Kus said he welcomed NCQA's efforts to develop quality measures for children with chronic conditions. He noted that research in the past indicated that children with chronic conditions were often not getting preventive health care measures. Thus, looking at that population and how well they do in terms of preventive measures might be one way of getting a sense of comprehensive care for such

children. Dr. Scholle said that was a great idea, and she would take it back to NCQA. She added that there had been a lot of concern about implementing some of the children's health measures because they require chart review, but this might be a more efficient way of getting at the issue. Finally, Dr. Kus asked: How do you identify kids at risk for developmental problems? He's not sure there is a good way. Dr. Scholle said that project is embedded in an effort already to do screening.

IX. COMMITTEE BUSINESS— NOMINATION OF ALPHA THALASSEMIA—HEMOGLOBIN H DISEASE TO THE RECOMMENDED NEWBORN SCREENING PANEL: INTERNAL REVIEW WORKGROUP REPORT

Kwaku Ohene-Frempong, M.D.
Committee Member
Professor of Pediatrics-University of Pennsylvania School of Medicine
Director-Emeritus, Sickle Cell Center
Division of Hematology
The Children's Hospital of Philadelphia
University of Pennsylvania School of Medicine

Dr. Ohene-Frempong gave a report from the Advisory Committee's Internal Nomination and Prioritization Workgroup on the nomination of alpha thalassemia—hemoglobin H (Hb H) disease as a candidate for inclusion on the recommended uniform newborn screening panel. The nomination was submitted on April 28, 2009, by Dr. Elliott Vichinsky, a pediatric hematologist at Children's Hospital in Oakland, California.

Thalassemias are the most common single gene disorders of humans, and thalassemia protects against malaria and is most prevalent where malaria is endemic. Thalassemias are due to impaired production of globin chains, creating an uneven balance between hemoglobin's alpha and beta chains. Patients with beta thalassemia do not produce enough beta globin chains and those with alpha thalassemia do not produce enough alpha chains. The deficiency of alpha globin production in alpha thalassemia is due to mutations or deletions of one or more of the four genes on chromosome 16 that make alpha globin. There are several types of alpha thalassemia with varying degrees of clinical significance. The most common form of alpha thalassemia is alpha-plus, where one of the alpha globin chains is deleted; individuals with three alpha globin genes are clinically referred to as silent carriers of alpha thalassemia, because the disorder is not hematologically apparent. There is another form of alpha thalassemia in which both of the alpha globin chains have been deleted. This type, called alpha-zero thalassemia, is the most severe type and typically leads to fetal death. About 10 percent of the cases of alpha thalassemia are nondeletional syndromes in which there are mutations that either produce a reduced amount of alpha globin, or sometimes and abnormal alpha globin, or sometimes no alpha globin at all. The most common of these types of mutations, or nondeletional forms of alpha thalassemia, is the production of a hemoglobin called Constant Springs, and there are about four or five varieties of this. Of the remaining forms of alpha thalassemia, Hb H disease, which is caused by the deletion or inactivation of three alpha globin genes and an excess gamma chain (or Hemoglobin Bart's) or beta chain (depending on the age at which an individual is tested), is the most significant clinically.

Hb H disease is a disease for which we are actually testing now, although most newborn screening programs do not recognize this. Current newborn labs can measure Hb Bart's level with little or no additional equipment. Screening for Hb H disease can be done using high performance liquid chromatography (HPLC) on dried blood spots collected during newborn screening to detect Hb Bart's in the first weeks of life. California's pilot program found that infants with Hb H disease had Hb Bart's exceeding 25 percent for DNA-based analyses. Another method is to use isoelectric focusing. We need to raise the profile of Hb H disease so labs just look for it and refer parents for care. Diagnosis is easier now because of molecular genetic techniques. State programs could include specific training for quantization and reporting of HB Bart's and referral of babies with elevated Bart's for DNA-based studies. The treatment strategy for Hb H disease would include early referral for comprehensive care and counseling before the onset of illness. Treatment would be primarily preventive and supportive (e.g., folic acid supplementation, education about signs of acute anemia, palpation of spleen, avoidance of oxidative medications; no iron therapy unless iron deficiency, etc.

Key findings of the Advisory Committee's Nomination Review and Prioritization Workgroup with respect to the nomination of alpha-thalassemia—hemoglobin H (Hb H) disease are the following:

1. *The condition is medically serious.* Hb H disease causes chronic, moderately severe hemolytic anemia in most of those affected, plus episodic attacks of acute anemia, often in response to febrile illness, with the requirement of periodic or chronic blood transfusion.

2. *Prospective pilot data (U.S. and/or international) from population- based assessment are available for this disorder.* Many states report the presence of Hb Bart's from hemoglobinopathy screening using isoelectric focusing or HPLC with no effort to determine the possible presence of alpha thalassemia. California has run a pilot screening program for Hb H disease since 1999, in which children with 25 percent Hemoglobin Bart's are identified as children with Hb H disease (although that cutoff remains to be validated). The incidence of the disease is high in California and is likely to be quite different among states depending on the mix of ethnic groups. There are no recent national data.

3. *The clinical spectrum of this disorder is well described to help predict the phenotypic range of children who will be identified via population-based screening.* The clinical spectrum of Hb H disease is very well described but it is not easily predicted. A more definitive diagnosis using DNA-based techniques allows better prediction of the clinical course of a disease that is typified by a wide range of clinical course.

4. *The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects) a low rate of false negatives).* The first level of diagnosis of Hb H disease from newborn screening is the presence of a large percentage of HB Bart's. The quantification of HB Bart's requires that HPLC methods be used in the initial screening because most isoelectric focusing techniques used in newborn screening do not quantify the Hb fractions. Molecular techniques to determine alpha gene deletions and detect nondeletional forms of Hb H disease constitute the second level of diagnostic testing. The diagnostic algorithms have been worked out in California's pilot program.

5. *If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if the treatment is onerous or risky.* The degree and onset of anemia usually determines the severity of the disease. In most case, the need for chronic transfusion therapy is apparent in late infancy.

6. *Defined treatment protocols, FDA approved drugs (if applicable), and treatment are available.* Approved therapy and drugs are available for treatment of Hb H disease. The treatment of HB H disease follows the same guidelines as those for clinically significant beta thalassemia. Transfusion dependence is the ultimate requirement of severe Hb disease, with iron overload and iron chelation therapy as issues to be addressed eventually.

7. *Internal Nomination and Prioritization Workgroup's Overall Recommendation.* While it is recognized that early diagnosis of Hb H will not lead to therapeutic intervention in infancy for most of the cases discovered and failure to detect Hb H at birth is unlikely to lead uniformly or unexpectedly to mortality or irreversibly morbidity for most of the children affected, the opportunity for definitive diagnosis provided by the transient presence of Hb Bart's in the first couple of weeks of an infant's life detectable through universal newborn screening for common hemoglobin variants is unique. …Early diagnosis will allow the education of families and primary care providers about Hb H disease, signs of acute anemia, and the importance of close monitoring during febrile illness. In addition the clinical course of each affected child can be closely monitored so that an individualized care plan can be developed before potentially life-threatening complications arise…The Advisory Committee's Internal Nomination and Prioritization Workgroup recommends that this nomination should receive a complete evidence-based review focusing on moving Hb H disease to the core recommended newborn screening panel from the secondary panel. The combination of incidence, potential severity, and available effective treatments for the most severe forms of Hb H disease make it worth considering for newborn screening.

Questions & Comments

Dr. Howell asked for recommendation from Dr.Ohene-Frempong. Dr. Ohene-Frempong said one of the questions is whether Hb H disease is a diseases for which state newborn screening programs are already testing now, so that what needs to be done is to elevate its profile, so that newborn screening programs look for it and educate their physicians to refer it along whatever channels they have so that patients can get care, or whether to consider Hb H as a new and separate disease for which newborn screening programs need to tool up. He believes that if newborn screening programs did little education and training, this would be a condition that could be reported.

Dr. Lloyd-Puryear read the last paragraph from the report submitted by the workgroup: "The Advisory Committee's Internal Nomination and Prioritization Workgroup recommends that this nomination should receive a complete evidence-based review focusing on moving Hb H disease to the core recommended newborn screening panel from the secondary panel. The combination of incidence, potential severity, and available effective treatments for the most severe forms of Hb H disease make it worth considering for newborn screening."

Dr. Skeels supported sending the nomination forward for an evidence review. He stated that like most state newborn screening labs, his lab uses isoelectric focusing for the primary screen and then HPLC to follow up. He agreed with Dr. Ohene-Frempong that state newborn screening labs are seeing babies with Hb Bart's everywhere but taking no action on them, adding that he has always felt uneasy about that. He believes that for some state newborn screening labs, screening for Hb H disease would simple be a matter of increasing their HPLC throughput and following up on these infants. For other labs, it might involve using HPLC as a primary screening method if there were a way to do this in a high throughput manner. Dr. Ohene-Frempong said that California uses HPLC as their primary screening method. He emphasized that because Hb Bart's goes down right after birth, Hb H disease cannot be

detected using a second screening sample that comes from the infant a few weeks later. The initial sample and quantitation should be based on the sample at birth. The Hb H is not going to be picked up until the child is much older.

Dr. Rinaldo also supported sending the nomination forward for a formal evidence review. The report of the original expert panel that developed the first recommended newborn screening panel, when it recommended that all variants are considered as secondary targets in newborn screening, was that all clinically significant results from newborn screening be reported. Apparently, the finding of Hb Bart's is not being reported. For that reason, he thinks adding Hb H disease to the uniform panel would be a modest incremental effort to provide better care. Dr. Rinaldo also said he would like to know more about whether the process of molecular testing to provide a confirmatory diagnosis of Hb H disease could be done regionally rather than by each newborn screening lab. Dr. Ohene-Frempong said he thought that just a few labs in the country could handle the volume of confirmatory diagnosis.

Several other Advisory Committee members—Dr. Calonge and Dr. Dougherty responding by phone, Dr. Vockley, and others—said they agreed the nomination should go for an evidence review. Dr. Vockley said he would like the Advisory Committee's external Evidence Review Workgroup chaired by Dr. James Perrin to give a more complete picture of the first year of life of affected infants and what it is that is being prevented by identifying Hb H disease through newborn screening rather than, say, at one year of age. He thought that would help cement the final recommendation. Dr. Calonge agreed, noting that if treatment for Hb H disease is initiated only when the disease becomes symptomatic, it is important to understand what the value of early detection is. Dr. Howell agreed that the Evidence Review Workgroup could consider these issues.

Dr. Vockley questioned whether who does the confirmatory molecular testing should be a major part of the Committee's decision about adding Hb H disease to the recommended uniform newborn screening panel. Dr. Watson said that Oakland Children's Hospital lab was a national referral lab that was federally supported up until about two or three years ago. It faded away, possibly because people did now know about it and it did not get enough referrals. Dr. Howell said that the Evidence Review Workgroup could be asked to look at this, too. Dr. Calonge also requested that the Evidence Review Workgroup also consider whether increasing treatment following early detection of Hb H actually improves health.

Several audience members also had questions or comments. Dr. Sara Copeland from the Iowa State Newborn Screening Program agreed that the mutation needs to be considered confirmatory testing because it is not part of the screening test. Dr. Fred Lorey from the California, said that California's newborn screening program has been screening since 1997 and has screening about 5 million babies for Hb H disease. He said screening for this condition is very easy if a lab is already using HPLC. All California had to do in the pilot screening program for Hb H disease was find the right cutoff, and now the screening works really well. Dr. Lorey said that California's program did not know of a false negative yet; and the false positive rate is extremely small. Moreover, California's newborn screening program has detected 10 cases of alpha thalassemia major. Two of the identified children were transplanted and are doing fine. Dr. Therrell said having come from state that has debated this many times, he does not think that there has been complete concurrence of the hematologists about screening for Hb H disease. Sheila Wise from the Washington State newborn screening program asked Dr. Ohene-Frempong whether it is important to distinguish between the deletional form of alpha thalassemia and Constant Spring in newborn screening. Dr. Ohene-Frempong said probably not.

Finally, Dr. Ohene-Frempong said that he believes that making the diagnosis of Hb H disease soon after birth will prevent babies from receiving treatment for iron deficiency that is not necessary.

Dr. Howell called for vote on the recommendation of its Nomination Review and Prioritization Workgroup that Hb H disease receive a formal evidence review focusing on moving the condition from the core newborn screening panel to the secondary panel. The following motion was unanimously approved by all members present or on the phone (14 yes, 0 no).

- ***MOTION #2 (PASSED): The Advisory Committee accepts the recommendation of its Nomination Review and Prioritization Workgroup that alpha thalassemia—hemoglobin H receive a formal evidence review by the External Evidence Review Workgroup. The Committee asks that the evidence review related to moving this condition from the secondary panel to the core newborn screening panel address specific questions Committee members raised at their meeting on September 24, 2009 (first year of life, the value of early detection, the value of treatment, etc.).***

X. COMMITTEE BUSINESS—FORMATION OF TWO NEW GROUPS

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

Dr. Howell welcomed participants to the second day of the meeting and then made the following brief announcements:

- **Workgroup or subcommittee of the Advisory Committee being formed to look at emerging data sets, newborn screening codes, etc., pertaining to the electronic transmission of information related to newborn screening**. Dr. Howell announced that he is forming a group of the Advisory Committee to help the Committee develop a more deliberative or interactive perspective look at information and material emerging on data sets and registries, newborn screening codes, etc. The new group will be organized with professional help from HRSA and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), as well as by other members of the Advisory Committee. Members may include Dr. Rinaldo and Dr. Boyle and Dr. Getchell, as well as individuals from the National Institutes of Health (NIH), Health Resources and Services Administration (HRSA), and the Centers for Disease Control and Prevention (CDC).Dr. Zuckerman may be asked to serve as a consultant.

- **Workgroup of the Advisory Committee established to prepare a draft response to the report of the President's Council on Bioethics.** In response to the recommendation of the previous day that the Committee draft a response to the report of the President's Council on Bioethics that would be reviewed and submitted for publication, Dr. Howell announced that he had asked Dr. Trotter to chair a small group to draft such a paper and that the group would include Dr. Burton, Dr. Fleischman, and Dr. Howell. The group expects to have a draft for the Advisory Committee's review at the meeting in January 2010.

XI. DRAFT PAPER ON STATE POLICIES REGARDING RESIDUAL BLOOD SPOTS: WORKGROUP DRAFT & COMMITTEE DISCUSSION

Harry Hannon, Ph.D.
Emeritus Branch Chief, Newborn Screening Branch
Division of Laboratory Sciences
Centers for Disease Control and Prevention (CDC)
Use and Storage of Residual Blood Spots Workgroup Co-Chair

Bradford Therrell, Jr., Ph.D.
National Newborn Screening and Genetic Resource Center (NNSGRC)
Use and Storage of Residual Blood Spots Workgroup Co-Chair

Jana Monaco
Committee Member/Parent Advocate
Organic Acidemia Association
Use and Storage of Residual Blood Spots Workgroup Member

In this session, three members of the Advisory Committee's Use and Storage of Residual Blood Spots Workgroup summarized a draft paper entitled "Considerations and Recommendations for a National Policy Regarding the Retention and Use of Dried Blood Spot Specimens After Newborn Screening." Dr. Howell noted that Committee members had had the 20-page briefing paper on state policies regarding residual dried blood spots to review for a while and suggested that the Committee make a recommendation about the paper at this meeting.

Ms. Monaco explained, as background, that at the Advisory Committee's meeting in February 2009, Dr. Hannon presented a preliminary outline of a paper on policies regarding dried blood spots from newborn screening for the Advisory Committee's review. The Advisory Committee approved the outline and recommended a workgroup. The Use and Storage of Residual Blood Spots Workgroup is co-chaired by Dr. Therrell and Dr. Hannon; other workgroup members are Dr. Don Bailey, Dr. Alan Fleischman, Ed Goldman, Jana Monaco, Dr. Bent Norgaard-Pederson, and Sharon Terry. The HRSA staff member working with the group is Alaina Harris.

To prepare the 20-page draft white paper, the members of the Use and Storage of Residual Blood Spots Workgroup performed a background literature review and then wrote and reviewed various sections of the paper, holding numerous conference calls. The workgroup co-chairs then assimilated the material into a working draft, executive summary, and recommendations. The workgroup hosted three Webinars with over 350 people to obtain input on the drafts from outside resources and community members. One Webinar was held with the Genetic Alliance (106 people), one with the Newborn Screening Regional

Collaborative Groups (38 people), and one with the Association of Public Health Laboratories (APHL) (220 people). Interest was especially great among parents and labs. The questions included technical questions, public education questions, policy questions, and general questions. Finally, the workgroup gave input to the final draft. The original 80-page paper was condensed to about 20 pages. Dr. Therrell said that it could be cut down even more but would lose some important points.

The September 2009 draft paper entitled "Considerations and Recommendations for a National Policy Regarding the Retention and Use of Dried Blood Spot Specimens After Newborn Screening" does have an executive summary that includes the following recommendations:

1. All state newborn screening programs should have a legally reviewed and accepted policy addressing the disposition of dried blood specimens remaining after newborn screening testing is complete and the screening results have been validated.
2. All state newborn screening programs should have a legally reviewed and accepted policy that specifies who may access and use dried blood specimens once they arrive at the state-designated newborn screening laboratory, including further access after newborn screening tests are completed.
3. As part of the educational process of the newborn screening system, all state newborn screening programs should maintain and distribute educationally and culturally appropriate information that includes basic information about the use or potential use of the dried blood specimens.
4. All state newborn screening programs should work proactively to ensure that all families receiving prenatal care are educated about newborn screening.
5. If residual blood specimens are to be available for any process outside of the legally required newborn screening process for which they were obtained, an indication of the parents' awareness and willingness to participate should exist in compliance with federal research requirements.
6. Newborn screening programs should assess the utility of any additional consent/dissent process implemented in order to better address issues of storage and use of residual dried blood specimens. The Federal Government is encouraged to consider this as a priority and to provide funding for utility assessment projects over the next 5 years.
7. The Federal Government is encouraged to provide administrative support and funding to develop:
    - Model consent/dissent processes for the use of residual newborn screening specimens
    - Model educational programs for the general public on the importance of newborn screening and the potential uses of residual specimens to generate population-based knowledge about health and disease
    - National data on the utility of any additional consent/dissent processes implemented relative to potential research uses of residual newborn screening specimens
    - Educational materials with facts about potential uses of residual newborn screening specimens for both consumers and prenatal healthcare providers.

During the Webinars, questions and discussions led to development of the following proposed (optional) recommendation. Since this proposed recommendation was not shared with the stakeholders in the Webinars and not unanimously embraced by all members of the workgroup, it was listed separately in the paper for the Advisory Committee's consideration:

8. *Optional recommendation (from vetting process):* Where state newborn screening programs elect to maintain a long-term newborn screening biobank of residual newborn screening specimens, a secure third-party key holder system ("honest broker"), with appropriate consent, should be used to allow for emergency linkages in de-identified specimen studies. The key holder would have the ability to reveal critical health information to a study subject should such information be discovered during the course of the research, and the ability to obtain and reveal personal information from a subject to a researcher, if such information were deemed to be of critical importance. In either case, consent from the study participant or appropriate parent or guardian would be required.

Questions & Comments

Dr. Howell asked for comments on the September 2009 white paper entitled "Considerations and Recommendations for a National Policy Regarding the Retention and Use of Dried Blood Spot Specimens After Newborn Screening" prepared by the Use and Storage of Residual Blood Spots Workgroup and suggested that the Advisory Committee come up with a recommendation regarding the paper. Several Advisory Committee members applauded the workgroup's draft paper. Some of their additional comments are summarized below.

Discussion of Recommendation #1. The first recommendation—"All state newborn screening programs should have a legally reviewed and accepted policy addressing the disposition of dried blood specimens remaining after newborn screening testing is complete and the screening results have been validated"—was a matter of some controversy among Advisory Committee members.

Dr. Rinaldo stated his belief that there should be a clear definition of what is meant by "validation" of newborn screening results in Recommendation #1. He noted that some states have very short retention periods for their newborn screening samples, which make it impossible to go back to validate their screening results. When cases are diagnosed in children at six months of age or four years of age—i.e., there are false negatives—it should be possible to go back to validate those results.

Dr. Therrell observed that the issue raised by Dr. Rinaldo is one that has been debated for years in the newborn screening community. Many of the analytes used in newborn screening do not survive over time, and there is a legal opinion in many cases, if a state newborn screening lab maintains specimens for a long time and then retests, it may have a big problem. The opinion of some states is that the specimens were collected for a specific purpose and used for that purpose, then kept for validation of that purpose for a certain length of time, and after that, they should be thrown out. Dr. Rinaldo said that was not a credible opinion, citing cases where he could retest much later and find something significantly abnormal. Dr. Therrell said the argument is, "Maybe you can, maybe you can't."

Dr. Hannon suggested that evaluating the stability of analytes used in newborn screening depends on what the end point for stability is: Is it the ability to declare a test result abnormal? Or is it the observation that an analyte has or has not declined. If the indicator is whether a specimen is abnormal or not, you can tolerate a lot of decline in the analyte.

Dr. Ned Calonge, on the phone, asked Dr. Rinaldo what the reason for validating the specimen was. Dr. Rinaldo explained that he has sometimes encountered cases where the conclusion of a normal screening was based on a questionable interpretation of the results (based on cutoffs defined in ways that would not stand scrutiny). On some occasions where it would have been easy for him to document this if the sample were still available six or seven months later, the newborn screening lab told him that it had thrown the sample away.

Dr. Calonge noted that there is a big difference for state newborn screening labs between keeping a specimen for six months and keeping a specimen for 18 years. Dr. Rinaldo suggested that perhaps the Advisory Committee could recommend that newborn screening specimens be kept for at least two years, preferably for four or five years, for verification in case a person experiences a false negative result.

Dr. Skeels, saying he thought that the last part of Recommendation #1 -- "the screening results have been validated" was confusing and unnecessary, and suggested ending that recommendation at the word complete and added that the definition of complete is different for each state. For Dr. Skeels, complete means that the state newborn screening lab has verified the analytic performance of the screening methods and that all the quality management parameters were in control and that the lab has reported the results; complete does not mean taking the results to the level of diagnosis. In Dr. Skeels' experience, the error in 80 percent to 90 percent of the cases where something goes wrong is post analytical.

Dr. Rinaldo strongly disagreed with Dr. Skeels suggestion of ending Recommendation #1 at the word complete. He said that because primary screening is really not completed and certainly not validated for a period of time, perhaps there should be a mandatory minimum period of time that a sample should be retained to permit verification of the accuracy of the results.

Dr. Skeels explained that each state has a person or group of people who are the stewards of newborn screening samples, and they bear legal responsibility and personal malpractice liability for them if they do anything beyond what is covered by state law. Thus, anything that puts state labs in too much of a box in terms of how long they should keep samples or what they should do with them is a problem because every state is different. The state of Oregon does not discard samples because quality management [to them] is more important than protecting against legal liability. That sample probably isn't even valid for that analysis anymore anyway.

Ms. Terry suggested leaving Recommendation #1 the way it is but adding a caveat that calls for administrative support and funding be provided for professional societies, the states, and laboratorians to come to some sort of consensus about the length of time that samples are retained.

Dr. Getchell said validation is up to the states, and that is never going to change. She knows exactly what is meant by validation in her laboratory because it is in her standard operating procedures; that probably is not what Dr. Rinaldo means by validation. She added that when it comes to the legal review, state attorneys general will have quite a say in how newborn screening laboratories handle residual specimens.

If what Dr. Getchell said about there being no agreed-upon definition of validation [is true], Dr. Kus stated doesn't know how to interpret Recommendation #1 or go further with it.

Comment [HHS1]: I added "to them" here to have the sentence read better. However, this is not based on transcript text. Do you think this phrase adds to much additional meaning to the statement?

Comment [HHS2]: It is not clear what the phrase "valid for that analysis" is referring to. The transcripts do not include a similar statement.

Comment [HHS3]: I've added the phrase "is true" for clarity. This is not based on specific text in the transcript.

Dr. Rinaldo said again that it should be possible to go back to a specimen to verify that things were done properly. He noted that the family of a child with false negative results has a lot of rights, which are not represented in this recommendation.

Dr. Therrell observed that there are 54 conditions that newborns are being screened for, and they all are validated at different times. The majority of specimens that would be questioned would have to do with thyroid and sickle cell, and for thyroid at least, the analytes aren't stable enough over time. The fact that some analytes are stable and some are not led to a sort of middle of the road recommendation.

Dr. Skeels objected to the use of the word "validation" in Recommendation #1, but said that if the issue was the "verification" of the screening results, he could accept that. Dr. Therrell agreed. Dr. Howell suggested changing the word "validated" in Recommendation #1 to "verified." Dr. Skeels said that change would be acceptable as long as it was understood that each state was permitted to do its own algorithm. The point was made that one reason the word "validated" was used in the document was that it also referred to validation that there was no mixup in patients at the hospital.

Dr. Kus said he was getting confused by Dr. Rinaldo's description of the validation process and screening resulting in no false negatives, because a screening test is going to have some false negatives; otherwise it is a diagnostic test. He said he was also concerned that a lack of agreement among states about verification would mean that things would be different from state to state. Dr. Rinaldo explained that the problem is that there is anecdotal evidence that some egregious mistakes have been made; and he believes that parents have the right to know what happened. As painful as it is, such knowledge would be a force for change. Dr. Rinaldo said he was not talking about a limitation of screening tests but something done wrong in the test.

Dr. Rinaldo suggested changing the last part of Recommendation #1 to read: "Disposition of dried blood spots remaining after newborn screening testing is completed and a reasonable interval of time is provided to verify, if feasible, the accuracy of the results." Dr. Skeels reiterated his suggestion that Recommendation #1 be shortened to end at the word "complete," adding that until the results have been verified, newborn screening testing is not complete. Part of the completion process is verifying the accuracy of what the lab has done and reported out. Dr. Skeels stated that the question of waiting for a period of time so that false negatives could be discovered is an issue completely different from the issue being addressed by this recommendation. Dr. Rinaldo disagreed.

At the same time, however, Dr. Skeels said, there is a fundamental moral need for quality improvement. If a child has a disorder and the state reported a false negative, it doesn't matter whether the error was clerical or analytical, the lab made an error. Perhaps the question to be wrestled with is whether a sample should be retained for some future purpose of say, long-term quality management, to inform the state newborn screening program about whether it has an underlying analytical problem.

On a somewhat different topic, Dr. Lloyd-Puryear suggested changing Recommendation #1 to eliminate the words "legally reviewed and accepted" [policy addressing the disposition of dried blood specimens]. She suggested changing the recommendation to begin as follows: "All state newborn screening programs should have a policy addressing the disposition of dried blood spot specimens remaining after newborn screening is complete…" She also suggested adding this caveat: "The state should consider review of the draft policy by legal staff prior to finalization." Dr. Lloyd-Puryear stated that this language was something she would like to consult with the National Conference of State Legislatures and people at the state level about.

Dr. Watson said he thought it would be worthwhile to make the point somewhere in the white paper that there is a difference in the perspective of state public health labs (represented by Dr. Skeels and Dr. Getchell) and the perspective of diagnostic laboratories (represented by Dr. Piero). Dr. Hannon noted that the paper has some information from ACMG as well as from the Clinical Laboratories Improvement Act, and the Clinical and Laboratory Standards Institute's molecular document on issues of retention of specimens in terms of good laboratory practice.

Dr. Vockley said that if the Committee was not going to formally accept the white paper at this meeting, he would rather that the Committee have some additional discussion to wordsmith Recommendation #1.

Discussion of Consent Issues/Recommendations #5 & 6. Dr. Buckley stated that she believed that parents' consent to the use of residual blood spots from newborn screening should be obtained at the time a blood spot is obtained because of the difficulty of going back to find the parents at a later date. Dr. Buckley also asked: Who owns residual blood spot specimens—the parents or the state lab? Can parents release a specimen?

Dr. Therrell replied that in mandated newborn screening programs, a dissent process has historically been in place. With respect to the research use of specimens, originally, that was not a big deal; over time, such use has become a big deal. A question that the Advisory Committee should probably try to answer is this: Is it necessary to have an upfront consent process for storage, use of specimens, and use of data from specimens? Ed Goldman, a workgroup member who is a lawyer, researched ownership. Legally, it appears that ownership of newborn screening specimens rests with the state. The Supreme Court of California says once you have given up medical tissue for medical reasons, and there has been an opportunity for consent/dissent, then you give it up. But even if this is technically legal, should it be done ethically? Dr. Hannon said some states have declared they own the spot, although some parents would dispute that.

Dr. Fleischman said his opinion is that would be extremely harmful to require consent prior to obtaining newborn screening specimens. Requiring parents' consent prior to newborn screening would jeopardize public health mandatory newborn screening—something that was hard won and needed.

Dr. Alexander noted that we routinely do not require special consent for routine medical practice, and there is no medical practice more routine than newborn screening that is mandated by law in virtually every state. The question the Committee needs to think about is: Where does that routine medical practice end? Does it include the retention of specimens for a certain period of time to ensure that the screening process was done correctly? He thinks it does, but each state might want to differ in where they define good medical practice starting and ending. The consent process has to come into play when the specimens are used for research that is not related to checking for false negatives, etc. If the research is for developing new tests or other things, then there should be some sort of consent process. The consent can be obtained up front at the time that specimens are obtained.

Ms. Terry, who is serving on the Health Information Technology (HIT) Standards for the HHS Secretary, urged Committee members to recognize that we are living in an age where a lot of things are going to change in the realm of how consent is going to be administered. There will be ways to consent that are much less onerous than they are today. Thus, one might imagine a time when a blood spot can be taken from a newborn for newborn screening without any consent, but then there is a system whereby a proxy for the child who is 10 or 12 years old can be contacted for their assent at a later date, and when the child turns 18 or 20, the child can be contacted for consent to additional uses of the specimen.

Discussion of Adding a New Recommendation About the Use of Specimens. Dr. Boyle asked members of the Use and Storage of Residual Blood Spots Workgroup whether they had considered a recommendation about use, capturing the idea in the first bullet of their slide under the ACMG position in the 2009 American College of Medical Genetics (ACMG) policy—something along the lines of: "Residual dried blood spots from newborn screening are a valuable national resource that can contribute significantly to the health of the nation's children and that we as a nation should put in place procedures and a process to use them in a meaningful and scientific way." Dr. Boyle noted that although the title of the paper refers to the "Retention and Use of Dried Blood Spot Specimens," the proposed recommendations seem to pertain to the retention of and access to the specimens.

Dr. Hannon replied that the use of residual specimens is very broad and generic, and the paper uses the term "research" for this. Access is an important issue, but the document extensively deals with research aspects. He further clarified that the education recommendation talks about educating the population on potential uses. And thus the document title is retention and use, not access. Dr. Boyle replied that she was hoping that as a Committee, they would get a recommendation that embodied the idea that the nation should be using the specimens as a right. Dr. Hannon said the Committee could make those changes if so desired. Dr. Therrell noted that at present, two-thirds of states get rid of the specimens and do not keep them for research.

Dr. Fleischman agreed with Dr. Boyle and suggested adding an overarching preamble that would say that the primary purpose of newborn screening specimens, whatever the Committee concludes about the good of additional uses, is a public health purpose that should be protected. Dr. Fleischman also recommended that the Committee might be able to address the controversy about the period of time that specimens are kept by specifying appropriate uses of the specimens. He thinks the main reason people want the specimens to be in the hands of the state for no more than a short period of time has to do with their distrust about future uses.

Discussion of the Optional Recommendation from the Vetting Process. Dr. Calonge generally applauded the document, but said that he had serious reservations about the optional recommendation in the document because it puts in a loophole that might raise more concerns than is worth on a national basis. Dr. Vockley agreed. He said the optional recommendation is a completely separate issue from everything else that is dealt with in the document and should not be included. He could see why it was brought up during the vetting process, but he thought that it would be virtually impossible to reconcile the rest of the document with that option in a realistic time frame.

Several other Committee members, including Dr. Chen, Dr. Getchell, Dr. Rinaldo, and Dr. Skeels, were also not comfortable with the optional recommendation in the draft document.

Ms. Terry said that she could understand that Committee members might not want to include the optional recommendation, but that it still needed to be considered. Going forward, the Committee ought to think about what the process should be when things move into the research realm and clinically relevant results emerge for people who are participating in the research. Giving back clinically relevant research results to the people participating in research is part of the standard of practice in the United States today.

Other Comments on the Draft White Paper. Dr. Chen said he appreciated the tone and tenor of all the recommendations in the draft document. He stated that in his opinion the challenge for the Advisory Committee is deciding whether or not the tone of the document is the right one to strike or whether it

was going to take on the myriad definitional issues around what validation means, who owns the samples, what consent is—and try to provide an answer to these questions, which apparently nobody else has been able to provide an answer to.

Discussion of Next Steps. Dr. Howell concluded by saying he thinks the draft paper "Considerations and Recommendations for a National Policy Regarding the Retention and Use of Dried Blood Spot Specimens After Newborn Screening" is a wonderful document. Before the Advisory Committee votes to sign off on the draft paper, however, he will ask Dr. Lloyd-Puryear (1) to contact the National Conference of State Legislatures to get input about the paper and legal issues at the state level; and (2) to work with HHS Office of the General Counsel to see how the proposed recommendations should or could be handled so as not to get involved in the issue of state responsibilities.

Dr. Skeels asked how formal an action the Advisory Committee would take with respect to the paper. Dr. Howell replied that if the Committee adopts the paper, it would be the official position of the Committee. Dr. Lloyd-Puryear indicated that after the meeting, she and her staff at HRSA would review the transcripts and portion of the meeting summaries related to the white paper. Generally, her next steps would be the following (not necessarily in this order):

- Delete the optional recommendation, but keep the other recommendations in the paper as they are and share the draft document with various organizational and legal entities that might need to be requested formally to comment and evaluate it: the HHS Office of General Counsel, the Office of Human Research Protections, the professional organizations (American College of Medical Genetics, American Academy of Pediatrics, and American Academy of Family Physicians), the National Conference of State Legislatures, Secretary's Advisory Committee on Genetics, Health, and Society, the Association of Public Health Laboratories, the March of Dimes, and any other entities that Committee members suggest to her.
- Work with Dr. Boyle to formulate a new recommendation related to the use of newborn screening specimens.
- Work with Committee members to refine Recommendation #1.

Dr. Howell suggested that HRSA should make it clear that there is a deadline for comments after which comments would not be accepted. Ms. Terry recommended that entities being asked to comment on the draft paper also be pointed to the rich discussion of the paper in the transcripts. Finally, Dr. Hannon asked whether the assignment of the workgroup was complete. Dr. Howell replied that it was, thanked the workgroup, and asked Dr. Hannon and his colleagues to move ahead with second spot study.

XII. PUBLIC COMMENTS

There were two public comment sessions at the Advisory Committee's meeting on September 25, 2009, one for general comments and one for comments related to the nomination of Krabbe disease to the recommended newborn screening panel. The full text of all public comments appears in Appendix A.

In the first session, for general comments, the following individuals made public comments:

- John W. Walsh. Alpha-1 Foundation (statement read by Natasha Bonhomme)
- Andrea Williams, Consumer Task Force on Newborn Screening

- Diane Snyder, M.D., CARES Foundation Board Member & Parent of a Child with Congenital Adrenal Hyperplasia

In the second public comment session, after the presentation of the report of the external Evidence Review Workgroup on Krabbe disease, the following individuals made comments related to the nomination of Krabbe disease to the recommended newborn screening panel:

- Jacque Waggoner, CEO, Hunter's Hope Foundation
- Jennifer Kwon, M.D., Pediatric Neurologist, University of Rochester (New York)
- Micki Gartzke, VP, Save Babies Through Screening & Parent of a Child Who Died from Krabbe Disease
- Michelle Fox, National Society of Genetic Counselors
- Rebecca Ruth, Missouri Advocate for Newborn Screening & Grandmother of a Child Who Died from Krabbe Disease
- Nicole and William Morris, Parents of a Child Who Died from Krabbe Disease

XIII. KRABBE DISEASE NOMINATION: EVIDENCE REVIEW WORKGROUP REPORT, PUBLIC COMMENTS, AND COMMITTEE DISCUSSION/ACTION

In this session, Dr. Perrin presented the Evidence Review Workgroup's final draft report on the evidence for Krabbe disease, a condition that had been nominated for inclusion on the uniform newborn screening panel in 2007. Following Dr. Perrin's presentation, members of the public were given an opportunity to make public comments pertaining to the Krabbe disease nomination and evidence review. Finally, Dr. Rinaldo summarized the key findings and led the Committee in a discussion about what to recommend with regard to Krabbe disease. Dr. Howell noted that he hoped that the Advisory Committee would reach a decision about a recommendation concerning Krabbe disease.

A. External Evidence Review Workgroup's Final Draft Report on Krabbe Disease

James Perrin, M.D.
Chair, Evidence Review Workgroup
Professor of Pediatrics, Harvard Medical School
Director, MGH Center for Child and Adolescent Health Policy, Director, Division of General Pediatrics
Vice Chair for Research MassGeneral Hospital for Children

Dr. Perrin noted that at the Committee's'18th Webcast meeting on May 12, 2009, Dr. Alex Kemper presented the external Evidence Review Workgroup's preliminary draft report on Krabbe disease—a condition nominated for inclusion on the Committee's recommended newborn screening panel in 2007. In their discussion of the draft report, Committee members had requested that the Evidence Review Workgroup provide clarification or additional information on several points in their final report.

The Evidence Review Workgroup's final draft report on Krabbe disease, which incorporates the additions and revisions requested by the Advisory Committee in May, was submitted in July 2009 (included under Tab #13 in Advisory Committee's briefing materials). The final draft was authored primarily by Alixandra Knapp, Dr. Kemper, and Dr. Perrin, with the assistance of numerous other individuals, including Dr. Florian Eichler, whom Dr. Perrin identified. The full report includes a description of methods, a summary of the evidence, tables highlighting key data from abstracted articles, materials provided to interviewees, a conflict-of-interest form, and a bibliography of all identified articles.

Dr. Perrin gave an overview of the final draft report on Krabbe disease, as described below. In addition, Dr. Perrin reported that that the Evidence Review Workgroup had completed some additional work: (1) a paper for the staff of the Maternal and Child Health Bureau of the Health Resources and Services Administration (HRSA) that describes the work that they have been doing; and (2) a paper related to the workgroup's review of the evidence pertaining to severe combined immunodeficiency disease (SCID) that has been favorably reviewed by a journal and will be published fairly soon.

Background and Methods for the Evidence Review of Krabbe Disease. Krabbe disease is an autosomal recessive, liposomal storage disease. It relates to mutations in the galactosylceramidase (GALC) gene. It is associated with progressive damage in the white matter of both the peripheral and central nervous systems. There are four main clinical subtypes: early infantile Krabbe disease (EIKD), late infantile, which is usually described with an onset after approximately six months of age; juvenile; and adult. There may also be other forms that have not been well described in the spectrum of Krabbe disease. The focus of the Evidence Review Workgroup was on the early infantile form of Krabbe disease.

The rationale for review on the Krabbe disease nomination form is that without treatment, most individuals with EIKD die within two years; that there are methods for newborn screening using a measurement of enzyme activity and gene mutation analysis; that there has been population screening in New York State begun in the middle of 2006; and that treatment with pre or early-symptomatic hematopoietic stem cell transplant (HSCT) may decrease the morbidity and mortality from EIKD.

The methods the Evidence Review Workgroup used in the evidence review for Krabbe disease, as well as in previous evidence reviews, were a fairly traditional systematic review of published literature to identify potential studies, plus an assessment of important unpublished data provided either by key investigators or advocates. Dr. Perrin noted that the final draft report submitted in July 2009 describes the methods used in the evidence review for Krabbe disease, as well as the quality assessment methods used to evaluate available published and unpublished evidence.

Findings from the July 2009 Evidence Review for Krabbe Disease. For its July 2009 final draft report, the Evidence Review Workgroup reviewed the following: (1) incidence of early infantile Krabbe disease (EIKD); (2) the natural history of the disease; (3) means of testing for EIKD, both for screening and for diagnosis of the disease; (4) evidence for treatment of EIKD; and (5) economic evaluations of EIKD (e.g., cost of screening, costs of treatment, etc.). The workgroup also identified what critical evidence does not exist and might be particularly helpful in decisionmaking in the future.

1. Incidence of EIKD. Most of the incidence data that have been published are relatively old data from limited studies. These data suggested that the incidence of EIKD is on the order of about 1 to 2 cases per 100,000. The incidence data on Krabbe disease from the pilot screening program for the disorder in New York State (discussed further below) are not included in these data.

2. Natural History of EIKD. Most infants with EIKD are diagnosed with extreme irritability, spasticity, and developmental delay typically before 6 months of age. Krabbe disease is a terrifying and very severe disorder. Infants with EIKD are in a decerebrate state in early infancy. Most affected children die before age two.

3. Screening and Diagnosis of EIKD. Screening for Krabbe disease is done by dried blood spots and initially by enzyme analysis by tandem mass spectrometry (MS/MS) for the GALC enzyme. This analysis is then followed by mutation analysis for GALC, which is done mainly by one lab in this country. The genotype/phenotype correlations have been sought in a great deal of detail, but unfortunately, the data so far suggest that while over 60 mutations have been identified in the GALC gene associated with EIKD, the only genotype that is strongly predictive of the EIKD is homozygosity for the 30-kb deletion in the GALC gene. So only one of 60 or more mutations seems to be highly predictive of Krabbe disease. Dr. Perrin gave an in-depth description of the data from New York State's pilot newborn screening program for Krabbe disease, asking Advisory Committee members to stop him if they had questions.

Experience of New York State's Newborn Screening Program for Krabbe Disease. Between August 2006, when New York began screening newborns for Krabbe disease, and June 30, 2008—as reported in a 2009 published report—New York's program had screened just over half a million newborns for Krabbe disease. In addition, the program had developed a rapid and accurate technique for assessing GALC activity and then performing DNA mutation analysis; it had developed a standardized clinical evaluation protocol based on the available literature; it had formulated criteria for transplantation; it had developed a clinical database and registry; and it had developed a systematic approach for following developmental and functional outcomes of identified children. Of the half million children screened for Krabbe disease by New York as of June 30, 2008, 4 children were identified as high risk for EIKD, six as moderate risk for EIKD, and 15 as low risk for EIKD. Diagnosis in the New York program is based on GALC activity with either supportive genetic analysis (i.e., homozygosity for the 30-kb deletion in the GALC gene) or clinical findings.

As of about June 30, 2009, New York had screened more than three-quarters of a million children for Krabbe disease. Using a complex screening and diagnostic protocol described in detail by Dr. Perrin, the New York program identified the following among the 769,853 children screened for Krabbe disease as of June 30, 2009:

- 140 newborns referred for and completed diagnostic evaluation (18.2 newborns per 100,000)
- 7 newborns considered to be at high risk for Krabbe disease (0.91 newborns per 100,000); 2 of the 7 babies considered to be at high risk referred for hematopoietic stem cell transplant (HSCT) at age 1 or 2 weeks (0.26 newborns per 100,000)
- 13 newborns (1.69 newborns per 100,000) considered to be at moderate risk for Krabbe disease (did not have the 30-kb deletion in the GALC gene)
- 36 newborns (4.69 newborns per 100,000) considered to be at low risk for Krabbe disease (did not have the 30-kb deletion in the GALC gene)

Comment [HHS4]: It seems that the laboratory definition/cut-off for moderate risk and low risk are the same? How is risk stratification determined?

Two of the seven babies whom the New York screening program considered to be at high risk for EIKD—one baby who was homozygous for the 30-kb deletion in the GALC gene; and a second baby who was compound heterozygous for the 30-kb deletion and had a novel mutation—were referred for hematopoietic stem cell transplant (HSCT). One of these two babies referred for HSCT died about 11 days after the transplant.

The New York program's recommended followup schedule for infants who screen positive for EIKD and are not referred for HSCT is as follows:

- *High-risk babies.* In the first year after screening, babies at high-risk of EIKD should come back monthly for neurological exams and come back every three months for neurodiagnostic tests (MRI, increased CSF protein, BAER, VEP, and NCS). In the second year after screening, babies at high-risk should come back every three months for neurological exams and come back every six months for neurodiagnostic tests.
- *Moderate- and low-risk babies.* In the first year after screening, babies at moderate risk of EIKD should come back every three months in the first year for neurological exams and come back annually for neurodiagnostic tests (MRI, CSF, BAER, VEP, and NCS) unless the exam is abnormal. Babies at low risk of EIKD should come back every six months for neurological exams and come back annually for neurodiagnostic tests unless the exam is abnormal. In the second year, the followup intervals for moderate- and low-risk babies lengthen.

Three of the five high-risk babies in the New York newborn screening program for Krabbe disease who were not referred for HSCT have been followed up and have been asymptomatic or assumed to be asymptomatic. Unfortunately, the remaining two high-risk babies have not been followed up. One family of a high-risk baby refused followup because they thought they had a child who was unaffected and did not want to be bothered with the followup. The other high-risk baby was not followed up because the baby's family returned to its country of origin. As of June 2009, none of the babies who had been followed up had been found to have EIKD, although full followup data on all seven of the babies the New York screening program considered to be at high risk for EIKD was not available.

4. Treatment of EIKD. The treatment for EIKD is hematopoietic stem cell transplant (HSCT) and is the only option other than palliative care. Sources of stem cells for HSCT include bone marrow and umbilical cord blood. HSCT requires that the patient be preconditioned with chemotherapy, and it seems to be clear that damage relating to the process of Krabbe disease continues post-transplant at least until there is full engraftment and new glial cell development.

Five studies of the effectiveness of HSCT to treat EIKD were included in the Evidence Workgroup's report, including two studies from one well-designed prospective cohort study with historical controls, one well-designed case control (retrospective) study, and two studies based on clinical experience from Dr. Maria Escolar and her associates in North Carolina. Dr. Perrin went through the 2005 and 2006 papers about the effectiveness of early HSCT by Escolar et al. in some detail. These studies suggest that survival is substantially higher among children with early treatment by HSCT and substantially less among children with later treatment by HSCT:

- *Early treatment with HSCT.* The 2005 Escolar et al. paper presented 11 patients who were diagnosed with Krabbe disease prenatally or at birth, mainly because of a previous family history. Their age at diagnosis was between 12 days and 44 days. These 11 patients received HSCT fairly early and had a 100 percent survival rate 36 months post-transplant, which is in the

paper the last data provided. The 2006 Escolar et al. paper presented findings for another 11 children at what they call Stage 1—that is, children who appear developmentally normal (seem asymptomatic) but may have inconclusive neurological findings. The children's age at transplant is not indicated. For these 11 Stage 1 children, there also was a 100 percent survival rate, with followup of these children between 24 months and 108 months of age.

- *Later treatment with HSCT.* The 2005 Escolar et al. paper identified 14 symptomatic children who were diagnosed with Krabbe disease between four and nine months of age—that is, much later than the children in the groups just discussed. These symptomatic children received HSCT between 142 days and 352 days of age. Among these 14 children, only 6 survived at a median time of 41 months post-transplant; the other 8 children in this late transplant group died. The 2006 Escolar et al. paper identified four symptomatic children who were Stage 2, three symptomatic children who were Stage 3, and one symptomatic child who was Stage 4. The four Stage 2 children had a 100 percent survival rate, with followup between 24 months and 108 months of age. The three Stage 3 children had a 61.5 percent survival rate. The Stage 4 child died a few weeks after that child's HSCT procedure.

Committee Members' Questions & Comments Related to the Treatment of EIKD. Dr. Calonge asked whether the death of the Stage 4 child was due to Krabbe disease or due to complications of that child's HSCT procedure. Dr. Perrin replied that he did not think that they had evidence about that. He said the death of the child who got HSCT in the New York program was reported to be due to transplant complications rather than directly from the Krabbe disease, and one might expect that the Stage 4 child who died quickly after transplant probably also died of transplant complications.

Dr. Boyle asked whether genotyping (genetic analysis) of the children with Krabbe disease who received treatment with HSCT was done. Dr. Perrin said that the Evidence Review Workgroup had gone back to figure that out and have been unable to find data on the children's genotypes. Dr. Rinaldo said that knowing the children's genotypes was critical and asked to what extent efforts had been made to obtain that information. Dr. Perrin said they could still go back and try to retrieve that information but they had asked, and the information was not accessible.

Dr. Chen noted that it was not entirely clear whether the asymptomatic children who received early treatment would have fallen into a high-risk or a moderate- or low-risk category in terms of GALC activity. Dr. Perrin said that was correct, adding that his guess would be that these children would have fallen almost entirely in the high-risk category in New York's newborn screening program for Krabbe disease.

Dr. Rinaldo said although it appears there is a strong genotype/phenotype correlation for Krabbe disease, the meaning of certain levels of residual GALC activity is not really clear. Dr. Perrin, noting that the only strong genotype/phenotype correlation is a 30-kb deletion in the GALC gene, stated that there is not a strong genotype/phenotype correlation for Krabbe disease. The New York experience is based much more on GALC activity and clinical presentation. New York does consider the genetic evidence; however, the driving force behind the decision to provide HSCT to two of the seven high-risk babies in New York was the babies' clinical state.

Dr. Skeels asked what the heterogeneity of the different genotypes was among the screen-positive babies in the New York newborn screening program for Krabbe disease. Dr. Perrin said information on the genotypes of these children is available. None of the seven babies in the high-risk category but one

had the 30-kb deletion in the GALC gene. If the Committee wants the Evidence Review Workgroup to go back and ask which of the 50 or so screen-positive babies in the New York newborn screening program had one mutation and which had two, the workgroup could do that. The workgroup does know that none of the babies but one of the two babies who had a transplant had 30-kb homozygosity.

Dr. Kus asked what the was difference between the two high-risk babies in the New York program who received HSCT and the five other high-risk babies. Dr. Perrin replied that the two babies who received a transplant had subtle indications of clinical abnormalities/neurological impairment, and one kid had the 30-kb deletion. Dr. Kemper added that his understanding from talking to Dr. Escolar and her colleagues at the University of North Carolina is that it was subtle findings on the physical exam that led the New York program to recommend HSCT for two of the babies in the high-risk category. They are working on an algorithm that could be more generalizably used, because these things would be picked up only by physicians who were experienced in evaluating babies for Krabbe disease.

Dr. Perrin stated that the New York program exercised considerable due diligence in coming up with criteria—from laboratory studies, from imaging, from examination, etc.—to develop as consistent a pattern of evaluation for EIKD as was possible in 2006-07. On the other hand, they and everyone else the workgroup members have talked with would say that it is really not clear at this point what are the characteristics of children that consistently predict EIKD. Dr. Kus, noting that the two babies from New York who received HSCT received their transplants at Duke and were evaluated by Duke, agreed that the issue related to the importance of clinical findings in diagnosing EIKD is a critical one.

Dr. Lavenstein referred people to an article on the New York newborn screening program's experience in screening for Krabbe disease in the April 2009 issue of Pediatric Neurology. He said that article gives a sense of the nuances of which high-risk babies were transplanted in New York and which ones were not transplanted and also gives a sense of the lack of correlation of diagnostic studies. Dr. Lavenstein said the lack of genotype/phenotype correlation is an enigma of Krabbe disease. He emphasized the importance of consistency in following up children who are screen-positive among people who are very well trained to evaluate neurodevelopmental outcomes.

Dr. Lavenstein said with regard to the two babies that underwent HSCT in New York, the baby at high-risk for EIKD who died after HSCT in the New York program died of sepsis, multiple organ failure, and multiple coagulopathy; the other baby who was transplanted did well. One caveat in providing HSCT to babies with EIKD is that although it is important to provide transplants as early as possible, babies who are transplanted below 28 days of age have a higher morbidity.

Dr. Buckley asked whether the babies in New York who were considered to be at low or moderate risk for EIKD have continued to be asymptomatic. Dr. Perrin replied that he thinks 70 to 80 percent of the infants have been followed up, and they continue to be asymptomatic.

Treatment of EIKD (continued). Continuing with his discussion of the Evidence Review Workgroup's findings with respect to the treatment of Krabbe disease, Dr. Perrin showed a slide comparing *mortality* among 11 asymptomatic newborns with Krabbe disease treated with HSCT (Escolar), 14 symptomatic newborns with Krabbe disease treated with HSCT (Escolar), and an untreated control group of newborns with Krabbe disease from the Hunter's Hope Registry. Mortality is clearly worse among newborns with EIKD who do not receive HSCT. As mentioned earlier, however, one of the two high-risk babies from New York who received HSCT died about 11 days after the transplant.

Next Dr. Perrin showed a slide comparing *morbidity* among children in the 2005 and 2006 Escolar et al. studies. In the children who received HSCT before they manifested symptoms of Krabbe disease—the 11 children who were diagnosed prenatally in the 2005 study and the 11 Stage 1 children in the 2006 study—HSCT maintained progressive central myelination, normal vision and hearing, and normal cognitive development, except for gross motor development. These findings for the asymptomatic children who received early HSCT are from relatively short followup—about three years maximum. In the children, who received HSCT only after they manifested symptoms of Krabbe disease, HSCT did not seem to result in neurological improvements. The later studies showed similar findings. The take-home message from the 2005 Escolar et al. paper on neurodevelopmental outcomes among asymptomatic children who received early HSCT is that the evidence suggests these children are not doing perfectly well, but they are doing relatively well as a result of their transplant. Among these children, impairments in fine motor control and gross motor delay seem to interfere with cognitive function testing. Persistent motor involvement affects expressive language in these children. During the second and third year of life, there is progressive spasticity in the lower extremities and some truncal weakness, and some significant fine motor and gross motor delay .

Moving from the published studies on the effectiveness of HSCT, Dr. Perrin turned to evidence obtained from talking with experts with experience in HSCT for Krabbe disease. The largest experience is the sample at Duke. The Evidence Review Workgroup had discussions with Dr. Joanne Kurtzberg and Dr. Escolar in the late spring and early summer of 2009, who provided longer term followup than the 2005 study by Escolar et al. Seventeen children with Krabbe disease who received HSCT at Duke University from Dr. Kurtzberg are surviving from 2 to 12 years after HSCT; the oldest is now 13 years old. One child (the baby from New York) died of sepsis following HSCT.

The views of Dr. Escolar and Dr. Kurtzberg regarding the outcomes with treatment for EIKD among children who received HSCT at Duke differ. Dr. Kurtzberg is the transplant person at Duke University that has personally transplanted all of these children. Dr. Escolar is the developmental pediatrician at the University of North Carolina who has worked closely with her.

- According to Dr. Escolar, among the 17 children with Krabbe disease who survived HSCT at Duke University Medical Center, there has been no further progress or regression in motor skill development. Two or three of the 17 children can ambulate completely independently; others need support for ambulation, and some use wheelchairs. Peripheral neuropathy in the 17 surviving children has worsened over time. Dr. Escolar has reported that neurodevelopmental outcomes among the 17 children vary. Those among the "less involved" patients have normal cognitive abilities, and the "more involved" patients have difficulty with speed of processing.
- According to Dr. Kurtzberg, who has followed the same population of children as Dr. Escolar for their first decade of life, one third of the 17 children with Krabbe disease who survived HSCT at Duke have normal motor function through the first decade of life; another third are

ambulatory; and the final third have sever spasticity and use wheelchairs. Dr. Kurtzberg reports that all 17 of the children have normal intelligence and communicate well.

Dr. Barbara Burton reports that her team has performed HSCT on two children with EIKD not reported in the literature. Both were transplanted at under one month of age. One of the children required a second HSCT because of failure to engraft, and this was performed at age two or three months of age. The child who received one transplant had symptoms at three weeks of age at the time of HSCT and is ventilator dependent now at five months of age; the patient's affected sibling died at nine months of age.

Dr. Jakub Tolar reported on his experience with HSCT among children with EIKD in Minnesota. He reported that 17 children with symptomatic Krabbe disease have received HSCT since 1986. Nine of these children are alive today, and all of them are quite delayed. He also reported experience with one child who was diagnosed with Krabbe disease early because of a family history and received HSCT at age three and a half months. At 15 months old, this child is able to sit but not walk; the child can vocalize but lacks understandable expressive speech.

Information gleaned from interviews with Krabbe disease experts indicate that there are approximately eight centers in the United States with experience in the transplantation of infants with Krabbe disease. Duke University and the University of Minnesota are the most experienced, but there are additional sites in Illinois, Ohio, Missouri, and Michigan, and Mount Sinai in New York have begun transplanting patients with metabolic disorders. The HSCT protocol for Krabbe disease is similar to the protocols for other childhood diseases, so centers that have stem cell transplant capability in general can likely deal with this HSCT for children with metabolic disorders.

5. Economic Evaluations of EIKD. The Evidence Review Workgroup could find no peer-reviewed publication relating to the cost or cost-effectiveness of screening or treatment for Krabbe disease, and the data for any serious economic evaluation are unavailable.

Summary of Key Findings Regarding EIKD. Dr. Perrin highlighted the following key findings from the Evidence Review Workgroup regarding Krabbe disease:

Key Findings: New York Newborn Screening Program for Krabbe Disease

- No cases of EIKD have been reported to be missed > Sensitivity = 100 percent.
- Observed prevalence of EIKD is less than predicted > 0.26/100,000 vs. approximately 1/100,000.
- Overall specificity of the screening is >99.9 percent if positive screen is considered the point of family and physician notification and a positive result is the identification of a high-risk newborn. Specificity is still >99.9 percent if a positive result is considered to be referral to bone marrow transplantation.

Key Findings: Treatment for Krabbe Disease

- Evidence suggests HSCT in presymptomatic or early symptomatic EIKD improves neurodevelopment outcomes.
- Motor function appears to show less improvement.

- Challenges to evaluating evidence on treatment outcomes of HSCT for EIKD are quite extraordinary due to
    - Heterogeneity in how the disorder was diagnosed (e.g., newborn screening, sibling of affected individual)
    - Differences in age at time of HSCT in children diagnosed with EIKD
    - Variability in followup with few data extending into the second decade of life following HSCT
    - Incomplete data with some loss to followup
    - Lack of standardized measures at specific time intervals

Critical Evidence Needed. Dr. Perrin concluded his presentation by identifying answers to the following questions as critical evidence related to newborn screening for Krabbe disease that is needed:

1. Are there appropriate ways to identify asymptomatic infants with low GALC levels who would benefit from bone marrow transplant? (Clinical, radiological, or other laboratory markers)
2. What are harms associated with screening, especially, in the identification of asymptomatic infants with low galactocerebrosidase levels?
3. What are the harms associated with chemotherapy used to precondition newborns with EIKD for HSCT?
4. What are long-term neurodevelopmental outcomes for children with EIKD who have received HSCT?
5. What is the cost-effectiveness of screening newborns for Krabbe disease?

Committee Members' Questions & Comments Related to the Key Findings and Critical Questions. With regard to the critical question #3 posed by the Evidence Review Workgroup, Dr. Howell asked whether there were any data that would indicate that pretransplantation chemotherapy in the first month of life that is used for HSCT is harmful. Dr. Buckley replied that she did not know; however, because of the potential long-term side effects of the full conditioning chemotherapy regimen, most people who do pretransplant chemotherapy prefer to wait until babies are older than one month unless the condition is something like Krabbe disease, where early transplantation might be better. Dr. Kemper noted that there are some recognized chemotherapeutic agents that are more harmful than others, so they are trying to not use those, but the workgroup found no data specifically related to the harms of those drugs.

Comment [HHS5]: I added the word "not" her as it seemed to more accurately reflect the previous statement. However, I was unable to verify this point in the transcript.

Dr. Alexander asked with regard to critical question #2 whether the Evidence Review Workgroup found any evidence on family functioning in babies who screened positive for Krabbe disease but stayed asymptomatic. Dr. Perrin said that they had no data for Krabbe disease, but this would be a great investigation to do with the population in New York State's newborn screening program for Krabbe disease. He added that there is anecdotal evidence that some families were annoyed with what was recommended for them in terms of followup and refused to follow the recommendations. Dr. Rinaldo asked if there was any evidence in terms of insurability of babies who screened positive for Krabbe disease but stayed asymptomatic. Dr. Perrin replied that they had not heard anything about that, but added that there was no systematic evidence. Dr. Kemper added that the New York program recognizes the potential harm of being classified at medium or low risk for Krabbe disease and is attempting to minimize that by lengthening out the followup interval for the medium- and low-risk groups. The one

thing that the people who ran the New York program emphasized is that they're still learning as they're going along, so they expect things to change in terms of what their cutoffs are.

Dr. Calonge, referring to the 99.9 percent specificity of the screening tests for EIKD, asked how many decimal points that number could be taken out because he said with 99.9 percent specificity and EIKD prevalence of about 0.25 per 100,000, there would be about 400 false positives for every true positive. In response, Dr. Kemper said that the 9s go out further than the first decimal point. It looks like the false positive rate is substantially lower than the 400:1. It's probably on the order of like 100:1 or 50:1 depending upon where you draw the threshold. Dr. Kemper said he had concerns about relying too heavily on these calculations because he was not sure what to do with the medium- and low-risk babies.

Dr. Chen, following up on the topic of false positives associated with screening newborns for Krabbe disease, observed that in the New York program, 4,000 specimens had abnormal GALC activity, and those were then retested and duplicated; they took the average of three samples, and then 230 of those samples were then DNA tested before they came up with this 140 false positives. Dr. Chen asked: Does that sound routine as part of the screening process for a public health lab or are there really 4,000 false positives? Dr. Skeels replied that that number was many more false positives than newborn screening labs usually get but would probably not be unmanageable.

Dr. Burton said the classification of children in New York's newborn screening program for Krabbe disease as being at high risk, moderate risk, or low risk is somewhat arbitrary and based on a single laboratory's experiences. Although some of the children in those categories have only one mutation, most have two mutations—and many of them are mutations that have previously been seen in some form of Krabbe disease, usually later onset Krabbe disease. In other words, many of the 56 patients identified in New York are patients that we would say, based on the biochemical and DNA evidence, are affected by Krabbe disease. We do not know what the phenotype will be in the 56 children. With Gaucher disease, for example, there are individuals who have deficient enzyme activity, two mutations, who may never manifest the disorder, while others who manifest it anywhere during the lifespan. Dr. Burton believes a similar situation applies in the case of Krabbe disease. For that reason, Dr. Burton urged Advisory Committee members not to be led astray by the categorization of low-, medium-, and high-risk for Krabbe disease invented by the New York newborn screening program and Dr. David Wenger's laboratory.

Dr. Vockley said it was enormously important that 56 babies are coming through the New York program who have been identified as having a predisposition for ultimately developing symptoms of Krabbe disease, and as far as the Evidence Review Workgroup has reported, the only way to know which of the 56 infants will develop symptoms is an exam by a pediatric neurologist who has experience in differentiating or following these babies. Dr. Vockley said he is very concerned that there is a high-risk population that we have absolutely no idea how to subsequently handle them other than to say that everybody has got to see one person or two people who know how to follow these babies and identify them. And even then, the babies are being put through a fairly invasive followup protocol that involves monthly or every three months or as needed with lumbar punctures and scans. This is an enormously difficult problem to deal with at the level of screening and public health.

Dr. Howell questioned whether it would be a good idea if newborn screening for Krabbe disease were expanded nationally if just one laboratory does quantitative, confirmatory enzyme testing. Dr. Perrin replied that the Evidence Review Workgroup had spoken to the laboratory director and asked if the laboratory could expand if screening were universal. The lab director said calculating on the basis of

the New York experience, they would be able to do this. Dr. Howell and Dr. Rinaldo agreed that relying on a single lab would not be a good idea regardless of its capability, citing problems that might arise in a national disaster and the lack of proficiency testing.

Dr. Vockley said his concern was the lack of agreement between Dr. Escolar (the developmental pediatrician) and Dr. Kurtzberg (the doctor who performed the transplants) regarding the outcomes with treatment for EIKD among children who received HSCT at Duke. Dr. Howell said he agreed.

B. Public Comments on the Nomination of Krabbe Disease

Dr. Howell noted that Dr. Rinaldo would be leading the Advisory Committee in a discussion of how to proceed with its recommendation concerning Krabbe disease after lunch and introduced the following individuals who had asked to make public comments related to the nomination of Krabbe disease to the recommended newborn screening panel:

- Jacque Waggoner, CEO, Hunter's Hope Foundation
- Jennifer Kwon, M.D., Pediatric Neurologist, University of Rochester (New York)
- Micki Gartzke, VP, Save Babies Through Screening & Parent of a Child Who Died from Krabbe Disease
- Michelle Fox, National Society of Genetic Counselors
- Rebecca Ruth, Missouri Advocate for Newborn Screening & Grandmother of a Child Who Died from Krabbe Disease
- Nicole and William Morris, Parents of a Child Who Died from Krabbe Disease

The full text of their comments appears in Appendix A.

C. Committee's Discussion and Decisions Regarding the Nomination of Krabbe Disease to the Recommended Newborn Screening Panel

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
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Dr. Rinaldo led the Advisory Committee in further discussion of the Evidence Review Group's final draft report on the evidence for Krabbe disease, which was submitted in July 2009. He noted that the Committee had reviewed the evidence for some time and that it was time for the Committee to reach a conclusion about the Advisory Committee's recommendation with respect to adding Krabbe disease to the recommended newborn screening panel, although the decision would not be an easy one. He praised the Evidence Review Workgroup for giving the Committee the tools it needed to arrive at a decision.

First, Dr. Rinaldo revisited a slide entitled "Gaps in Evidence" (slide #28), which Dr. Perrin had presented when he addressed the Advisory Committee at its May 2009 meeting. The conclusions about the gaps in the evidence were as follows: (1) the testing algorithm for early infantile Krabbe disease (EIKD) may need revisions; (2) the case definition of Krabbe disease is unresolved; (3) the benefits of hematopoietic stem cell transplant (HSCT) to treat EIKD are uncertain at this time; (4) substantial harm is possible (either from testing and/or identification; from treatment/other interventions, or both); and (5) cost-effectiveness is undetermined. Dr. Rinaldo said that he did not believe the evidence presented in the Evidence Review Group's July 2009 report had changed those conclusions and he speculated that there would not be much change in them any time soon.

Dr. Rinaldo proposed that the Advisory Committee discuss how to proceed with respect to the nomination of EIKD by focusing on three items: the condition, the test (screening and diagnosis), and the treatment:

EIKD: The Condition. Dr. Rinaldo asked for Committee members to comment on the following conclusion: EIKD, even with the uncertainty of phenotype, is a devastating disease that would benefit from early diagnosis and intervention.

> *Committee Members' Comments.* Dr. Howell, Dr. Watson, and Dr. Alexander agreed with this conclusion. Dr. Watson and Dr. Alexander emphasized, however, that were problems with the case ascertainment process for Krabbe disease. Dr. Watson noted that it was hard to tie lab components to severe EIKD. Dr. Alexander agreed, noting that because of variations in genetic phenotype and enzymatic levels associated with EIKD and extreme variations in the severity, it would be difficult to screen and find just the severe EIKD.

Noting that Dr. Watson and Dr. Alexander's comments about the screening test for EIKD and process of case ascertainment were related to the next issue, Dr. Rinaldo concluded that Committee members seemed to agree that at the better defined end of the spectrum, EIKD would benefit from early diagnosis and intervention.

The Test for EIKD (Screening and Diagnosis). Dr. Rinaldo praised New York State's newborn screening program for its pilot screening and collection of evidence related to Krabbe disease. At the same time, he noted several areas of uncertainty related to the program's screening protocol (e.g., the meaning of less than 20 percent of a daily mean, making decisions based on percents and generating absolute values, the protocol's identification of people who seem to be carriers, the lack of genotype/phenotype correlation, the uncertainty of the false positive rate with the screening protocol, depending on where the line is drawn for true positives, and the associated costs of false positives).

> *Committee Members' Comments*. Dr. Skeels indicated newborn screening labs would be using a multiplex assay system when screening for lysosomal storage disorders, which would lower the unit cost, and that false positives associated with Krabbe disease would therefore not be an overwhelming expense.

Dr. Rinaldo stated that he had heard of imminent availability of a single test for Krabbe disease but added that he was uncomfortable reaching a decision when quality and cost of test are not certain.

> *Committee Members' Comments.* Dr. Vockley said that he is personally an advocate of providing treatment to affected children, but there are a number of issues that the Advisory Committee has to consider from a public health perspective. First, the apparent incidence of

diseases that the New York newborn screening program is saying need to be treated immediately for Krabbe disease is very low, but the definition of who needs to be treated is also very nebulous. There is no test to take the 56 babies identified as being "at risk" (whether low, moderate, high) and differentiate between them. Even worse, the ultimate determination as to whether the seven babies in the high-risk category for Krabbe disease were referred for treatment with HSCT was the opinion of one individual saying: "In my experience, this mutation doesn't put them at risk." Some of the problems may or may not be solved by multiplex assays, but more information about what is being identified by screening and diagnosis and what the likely outcome with treatment is lacking. Rather than adding Krabbe disease to the recommended newborn screening panel for the entire country, it might be wise to let states such as New York that are performing pilot screening for Krabbe proceed and offer them support and funding to help provide the evidence that is needed..

Dr. Rinaldo noted that in the last few years, the United States has moved from a patchwork of different newborn screening panels in different states to a place where there is much more consistency. He thinks that consistency is a good idea and that conditions should be added to or removed from the Advisory Committee's recommended newborn screening panel on the basis of the evidence and expert review and discussion of the evidence, not on the basis of advocacy. For that reason, Dr. Rinaldo recommended that the Advisory Committee exercise restraint—that is that, it recommend not adding Krabbe disease to the recommended panel now and letting the evidence develop in New York and elsewhere over time. Once sufficient evidence to justify adding Krabbe disease to the recommended newborn screening panel had been developed, the Advisory Committee could recommend its addition and push for rapid implementation.

Committee Members' Comments. Dr. Watson observed that there is enormous variability among the states in what they can do in a pilot environment. In some states, mandated screening is required in order to do pilot screening. Pilot newborn screening for certain conditions—such as pilot screening for Krabbe disease in New York—provides an opportunity to carefully collect and analyze data over time. The process of generating and analyzing data on conditions such as Krabbe disease through pilot screening in the states has enormous potential to help inform the Advisory Committee's decisions.

Dr. Vockley agreed with Dr. Watson. He noted that the way the Advisory Committee's process of adding conditions to the recommended newborn screening panel is constituted—which involves asking proponents to nominate candidate conditions—means there will be an inevitable ebb and flow of interest in different diseases because of personal, political, and public health issues. If New York had not begun pilot screening for Krabbe disease, it would never have been nominated to the Advisory Committee as a candidate condition. Dr. Vockley stated his opinion that hybrid vigor and accumulation of data rather than uniformity in the states would enable the Advisory Committee to provide better guidance. Finally, Dr. Vockley said the question the Advisory Committee is considering is whether to add Krabbe disease to the recommended newborn screening panel. He stated his view that the available evidence does not support adding Krabbe disease to the Advisory Committee's recommended newborn screening panel. He hopes that state newborn screening programs decide to study and get more data about Krabbe disease and come back with a revised application. In his view there is no other way for the system to work, because the Advisory Committee does not drive the agenda for the diseases to be studied.

Treatment for EIKD. Dr. Vockley noted that there is a treatment for EIKD—namely, HSCT—but there is not much data on the efficacy of treatment. Some patients are surviving. Dr. Rinaldo noted that Dr. Michele Kwon had pointed out in her public comments that the prognostic meaning of various clinical "risk levels" is uncertain and complicates treatment for Krabbe disease.

Questions & Comments—Final Discussion of the Committee's Recommendation with Respect to Adding Krabbe Disease to the Core Newborn Screening Panel

At the end of Dr. Rinaldo's presentation, Dr. Howell asked Committee members to consider what they wanted to recommend about adding Krabbe disease to the Advisory Committee's recommended newborn screening panel. He also said if Committee members agreed with Dr. Vockley that the available evidence does not support adding Krabbe disease to the recommended newborn screening panel to specify the areas in which they believe the evidence is deficient.

Dr. Rinaldo noted that the Committee's recommendation when considering whether to recommend conditions for inclusion on the uniform newborn screening panel is supposed to be made on the basis of its judgment regarding the magnitude if net benefit (benefits minus harms), its judgment of the adequacy of the evidence in answering key questions, and its judgment of the certainty of net benefit. In February 2009, that the Advisory Committee decided to choose from four general categories when making recommendations about whether to add a condition to the uniform newborn screening panel:

1. **Recommend adding the condition to the core panel.** The Committee has sufficient certainty of *significant net benefit* to recommend adding the condition to the core newborn screening panel.
2. **Recommend not adding the condition to the core panel now and recommend additional studies**. The evidence is insufficient for the committee to make a recommendation to add the condition to the core panel, but the *potential for net benefit is compelling* enough to recommend *additional studies to fill in the evidence gaps*.
3. **Recommend not adding the condition to the core panel now**. There is *insufficient* evidence for the Committee to make a recommendation to add the condition to the core panel, and there is insufficient evidence of potential net benefit to lead the Committee to want to make a strong recommendation regarding pilot studies.
4. **Recommend NOT adding condition to the core panel.** The Committee has sufficient certainty or *no net benefit or of net harm.*

(*NOTE:* There was some confusion among Committee members about the order and wording and meaning of the four recommendations, and Dr. Calonge, speaking on phone, indicated that Dr. Rinaldo's slides did not reflect the precise wording of the Committee's recommendations. r. Calonge explained that Recommendations #2 and #3 both apply in the case of insufficient evidence. Recommendation #2 is one where there is insufficient evidence, but the Committee is optimistic about the evidence being gathered relatively soon in pilot or other studies (i.e., the Committee sees the light at the end of the tunnel); the Committee made this recommendation for severe combined immunodeficiency syndrome (SCID). Recommendation #3 is one where there is insufficient evidence to decide either for or against adding the condition, and the Committee does not see the light at the end of the tunnel in terms of having the evidence available. Recommendation #4 is one where the Committee has sufficient certainty that a screening test either provides zero benefit or net harm and therefore advises against adding the condition to the core newborn screening panel. The correct wording

is reflected in the recommendations above, and Committee members' comments below correspond to these recommendations.)

Dr. Rinaldo suggested that the Committee consider making the same recommendation for Krabbe disease as it had for severe combined immunodeficiency disorder (SCID)—namely *Recommendation #2. Recommend not adding the condition to the core panel now and recommend additional studies.* It set forth found conditions: detection of a case, maintenance of the performance metrics, availability of quality reference material from the Centers for Disease Control and Prevention (CDC), and the addition of at least one more program.

Dr. Vockley disagreed with Dr. Rinaldo and proposed that the Committee instead make the following recommendation for Krabbe disease—*Recommendation #3. Recommend not adding the condition to the core panel now.* Dr. Vockley said he found it difficult to believe that sufficient evidence to allow the Committee to recommend adding the condition to the core panel would be provided at any time in the near future.

Ms. Monaco asked: At what point would the Advisory Committee decide that the evidence was sufficient to recommend adding Krabbe disease to the uniform newborn screening panel? She observed that if a baby has Krabbe disease, whatever information the parents can gain about the baby's condition through newborn screening would be helpful. She also said that having a few states add Krabbe disease to their newborn screening panels and then collect information is a good way to get additional evidence.

Dr. Rinaldo emphasized that the process of getting the evidence needed for the Advisory Committee to recommend adding Krabbe disease to the recommended panel is not going to take just a few months. In a state such as Kansas, with a low number of births, it might take 10 years to get information about Krabbe disease. Moreover, the data needed to support a recommendation to add Krabbe disease to the recommended panel go way beyond the analytical validity of the screening test; clinical validation will take a long time. Dr. Rinaldo said he hoped that states would start working together to generate evidence on Krabbe disease rather than doing work independently.

Dr. Howell said that it seemed to be the sense of the Advisory Committee that they shouldn't add the condition to the core panel now. He asked the Committee members to specify deficiencies in the evidence.

Dr. Alexander said that although he agreed that the Krabbe disease should not be added to the core newborn screening panel at the present time, there were several states where pilot screening of Krabbe disease is being done—and if they pool resources, they will be able to answer the questions remaining more quickly. Dr. Alexander suggested putting the states doing pilot screening for Krabbe disease in the Newborn Screening Translational Research Network (NBSTRN) and doing systematic studies, noting that that would be similar to what was being done for SCID. Dr. Howell said Dr. Alexander seems to be supporting *Recommendation #2. Recommend not adding the condition to the core panel now and recommend additional studies.* Dr. Howell said he agreed that it would be helpful if New York and Illinois and Missouri, which are committed to screening for Krabbe disease, would combine their efforts through the NBSTRN. Dr. Watson said he believed that if there are real harms from screening, diagnosis, and treatment that cannot be managed, then that is very different from not having good enough data, which is what is suggested by Recommendation #2.

Dr. Calonge, speaking on phone, clarified what was meant by each of the various recommendations, as noted above. He said among other things that Recommendation #4 is one where the Committee has sufficient certainty that a screening test either provides zero benefit or net harm and therefore advises against adding the condition to the core newborn screening panel.

Dr. Vockley said, in light of Dr. Calonge's remarks, that he had intended to propose that the Committee's recommendation with respect to Krabbe disease be *Recommendation #4. Recommend NOT adding the condition to the core panel.* He stated that there is nothing in the nomination or evidence review for Krabbe disease to suggest that we are remotely ready to add this condition to the core newborn screening panel. Identifying seven children kids at "high risk" for Krabbe disease, as the New York pilot screening program did, might do harm if someone other than Dr. David Wenger evaluates them as candidates for HSCT. Given the potential for harm due to transplantation, the Committee should send a clear sign that Krabbe disease has a much higher hurdle to clear before the Committee can recommend adding it to the core panel.

Dr. Burton disagreed with Dr. Vockley's suggestion to adopt Recommendation #4. She stated that although evidence that suggests the possibility of harm due to screening for Krabbe disease needs to be explored, she sees nothing that really shows that harm is actually being done through the screening. Dr. Burton added that there are compelling reasons to support screening for Krabbe disease. There are clearly children with Krabbe disease alive today who would not be here had it not been for early diagnosis through a sibling. Moreover, one of the cases in New York shows that HSCT changed the natural history of the disease. There is no question that most of the children who are surviving with Krabbe disease are not normal, but they are surviving. She asked: Should the parents of affected infants have an opportunity to make a choice as to whether they get that treatment or not. There may be lab issues that need to be fine tuned, Dr. Burton said, but the benefit of screening to some children is undeniable: The benefit is that a child who otherwise would have died from Krabbe disease survives. She supports the collection of additional data about Krabbe disease.

Dr. Skeels stated that he was vacillating between *Recommendation #3. Recommend not adding the condition to the core panel now* and *Recommendation #4. Recommend NOT adding the condition to the core panel.* He said he was impressed with the data from New York, but he doesn't think that New York should be screening newborns for Krabbe disease until they are sure they can do a good job of it.

Ms. Monaco disagreed with Dr. Vockley and Dr. Skeels and agreed with Dr. Burton. She said that however small the numbers are, there are validated true cases of Krabbe disease, and children are surviving because they were screened. It does not appear that New York State is rushing to provide HSCT to everyone who screens positive. Unless there are efforts to collect and use information from this and other pilot programs, we will never get anywhere.

Dr. Howell said that it was clear to him if additional patients were studied carefully—for example, he would think that Dr. Burton's group will be using a different confirmatory diagnostic test—they will find something different.

Dr. Kus said the hard thing for the Advisory Committee is deciding what recommendation to make at the national level. The Committee should consider, among other things, how its decision will affect what states such as New York are already doing. He asked Committee members such as Dr. Vockley who were supporting Recommendation #4 to share their thinking about the harm that has been done or

could be done by screening newborns for Krabbe disease. The benefit of screening is that a child with Krabbe disease who would have died had he or she not received timely treatment would live.

Dr. Skeels said that because he is not a clinician, he would defer to others who would talk about clinical harms. He noted, however, that cost is a harm, and if tax dollars spent on screening for Krabbe disease could be spent on something else that is clearly beneficial, that is a harm. He noted that even if the Committee recommends not adding the condition to the core panel, proponents could resubmit an application at some later date.

Dr. Kus disagreed with Dr. Vockley's suggestion to adopt Recommendation #4, because he thought that would be implying that harm was being done and screening should stop and would be saying to the New York State's pilot screening program for Krabbe disease that the program should stop screening. Dr. Howell concurred with Dr. Kus.

Dr. Vockley reminded Committee members that *Recommendation #4: Recommend NOT adding the condition to the core panel* implies zero benefit or net harm. He said his concern about net harm was related to the potential harm of clinicians who are not sophisticated in the diagnosis of Krabbe making decisions about transplants. Dr. Vockley suggested that five of seven children identified as being at high risk for Krabbe disease in New York could have been referred for HSCT even though they did not need a transplant had it not been for Dr. David Wenger's judgment.

In response, Dr. Perrin clarified that the decision to perform HSCT in New York was not based solely on the decision of Dr. Wenger; New York State has a protocol for deciding which children merit HSCT and which children do not that was developed by a number of clinicians and investigators. Dr. Burton confirmed what Dr. Perrin said. In response to a question from Dr. Rinaldo, Dr. Perrin said he was not sure what the consensus on the seven children was. Dr. Rinaldo said that was important information that the Committee was missing.

Dr. Watson stated that harms from newborn screening for Krabbe disease are going to come in different forms and added that it was important for the Committee to distinguish clinical harms from cost harms. If there are clinical harms from screening for a condition, he does not think that screening for that condition should even be done in the Newborn Screening Translational Research Network (NBSTRN).

Dr. Chen said one of the babies who had undergone HSCT in New York State died. No one could say for sure whether the baby's death was from transplant complications or from the disease, but death is clear evidence of a clinical harm. Dr. Chen also suggested that the Committee should consider harms to the family; even when a child identified as being at risk for a condition is not sick, the family has to deal with uncertainty.

Dr. Burton said that she had seen no data to indicate that there had been any clinical harms from screening newborns for Krabbe disease. There may be psychological harms to parents, but these have to be balanced with benefits to affected children identified. There is at least one child in New York surviving who would not be; moreover, siblings have been identified in these early diagnosed cases, as well. There clearly are benefits from screening newborns for Krabbe disease. Dr. Burton said she had not seen any data showing net harm. Dr. Howell says he agreed with Dr. Burton. He noted that concerns had been raised about potential harm from clinicians who are not sophisticated in diagnosis of the condition recommending transplants, but no evidence that harms are occurring has been presented.

Dr. Alexander pointed out that the only reason there is as much data about Krabbe disease screening as there is today is because of the pilot screening program for Krabbe disease in New York State. He said the only way to build on that evidence is to continue pilot screening to try to fill in the evidence gaps. Maybe the application to add Krabbe disease to the uniform panel could be resubmitted in a couple of years. Dr. Alexander said he could not vote against gaining knowledge about Krabbe disease, when this looks like the best way to go in the near future.

Dr. Howell said that before the Committee voted on which recommendation to make, it would be helpful to identify the lacunae in the evidence needed to make a recommendation related to Krabbe disease. The following summarizes Committee members' comments.

- **EIKD: The Condition**
    - Dr. Rinaldo said there is no consensus about the case definition of EIKD, and a case definition of the disease is needed.
- **Test for EIKD (Screening and Diagnosis)**
    - Dr. Rinaldo said there was a need for additional information about the testing algorithm for EIKD. He also said it was important to ascertain whether testing for Krabbe disease would be a standalone test or done with multiplex testing, in part because of the cost implications.
- **Treatment for EIKD**
    - Dr. Rinaldo said important questions remain to be answered about the benefits of HSCT to treat EIKD.
    - Dr. Burton agreed that more information was needed about the specific benefits of HSCT to treat EIKD, but emphasized that she thought the evidence was unequivocal that HSCT changes the course of Krabbe disease in presymptomatic or early symptomatic children with EIKD. There is disagreement about the degree of problems, the extent, and the cause of problems in children treated for Krabbe disease with HSCT. Dr. Burton also said that there are other diseases on the core panel for which there is treatment but continued mortality and morbidity. The fact that treatment is not perfect should not be the Committee's criterion.
    - Dr. Buckley said one of the gaps in the summary of articles about treatment for EIKD using HSCT, we do not know the actual mutations of the children who received HSCT. It would be helpful to have that information.

Next Dr. Howell asked Advisory Committee members to indicate which of the four recommendations it should adopt with regard to Krabbe disease. The discussion centered on two recommendations: Recommendation #2 and Recommendation #3:

RECOMMENDATION #2: Recommend not adding the condition to the core panel now and recommend additional studies*. The evidence is insufficient for the committee to make a recommendation to add the condition to the core panel, but the potential for net benefit is compelling enough to recommend additional studies to fill in the evidence gaps.*

- Dr. Alexander indicated that he supported Recommendation #2 and putting the states doing pilot screening for Krabbe disease in the Newborn Screening Translational Research Network (NBSTRN) and doing systematic studies.
- Dr. Howell said he also supported Recommendation #2. He said he agreed with Dr. Burton. Although concerns had been raised about potential harm from clinicians who are not sophisticated in diagnosis of Krabbe disease recommending transplants, the Evidence Review Workgroup had not found any evidence of actual harms that are occurring. Dr. Kus agreed that there was a potential for harm but no evidence of it. There was just one death in New York, but in cases that have been treated that are asymptomatic and treated early, there have been no deaths. There is always a risk of harm when doing HSCT but Krabbe is a condition where the children die by age two if left untreated
- Dr. Rinaldo said he did not think the potential for net benefit was "compelling enough to recommend additional studies to fill in the evidence gaps." Dr. Howell said survival is compelling. Dr. Rinaldo said death is compelling as well. The child who died in New York would probably be alive without a transplant. Dr. Howell said the patient died of a complication of transplant, sepsis, but that was the only death of a Krabbe disease patient the New York newborn screening program has had. Dr. Buckley said she thought that there had been several deaths of transplanted Krabbe patients; at Duke, she believed there were 22 patients who were received transplants but only 17 who lived. Dr. Perrin said he wanted to verify that information. He later explained that the 17 newborns reported on from Duke were the newborns who were actually followed actively. The Evidence Review Workgroup's understanding was that of the newborns in the early transplant group, only one child had died, and that was the child who was referred from New York.
- Ms. Monaco said that the Advisory Committee did not know the cause of death in any of those patients and added that no one can predict the ultimate lifespan of children with Krabbe disease, even if their condition is detected via newborn screening. She emphasized that no one on the Committee consider children with Krabbe disease who had neurological delays after HSCT to be failed transplants.

RECOMMENDATION #3: Recommend not adding the condition to the core panel now*. There is insufficient evidence for the Committee to make a recommendation to add the condition to the core panel, and there is insufficient evidence of potential net benefit to lead the Committee to want to make a strong recommendation regarding pilot studies.*

- Dr. Calonge said he supported Recommendation #3. He noted that it is possible to get to a recommendation not to add the condition to the core panel even though people have been helped by screening for the condition. He believes that Krabbe disease is not ready for prime time yet, because there are not enough cases of either benefit or harm to be totally confident. Dr. Calonge said he had not heard enough to be optimistic enough to support Recommendation #2. Opting for Recommendation #3 for Krabbe disease, he said, would indicate that the Committee did not necessarily want to push Krabbe disease as one of the diseases that it wants to spend a lot of national and research resources on, given the uncertainties. For both

Recommendation #2 and #3, he said, there is a possibility that additional research will result in a decision not to go forward.

- Dr. Boyle said she did not disagree with Dr. Burton in terms of there being benefits of newborn screening in terms of clinical practice, but added that she was trying to evaluate net benefit in the context of newborn screening, where there are some challenging interpretations.
- Dr. Rinaldo said part of the harm from screening for Krabbe disease in New York is the lingo in which families of children are classified by the New York State pilot screening as being at moderate or low risk of Krabbe disease, as suggested by Dr. Kwan. Dr. Kus said that was anecdotal information.
- Dr. Trotter concluded by saying that he believed that there was insufficient information about Krabbe both in terms of benefits and harms. He agreed with Dr. Calonge that the Committee should choose Recommendation #3.

Following this discussion, the Committee voted down the following motion made by Dr. Alexander and seconded by Ms. Monaco (5 yes, 9 no):

- ***MOTION #3 (FAILED): Recommendation #2: The Advisory Committee recommends not adding the condition to the core panel now and recommends additional studies.***

The Committee then voted to approve the following motion made by Dr. Calonge and seconded by Dr. Trotter (10 yes, 3 no, 1 abstain):

- ***MOTION #4 (PASSED): Recommendation #3: The Advisory Committee recommends not adding the condition now.***

Dr. Howell indicated that the Advisory Committee would send a letter to the nominators of Krabbe disease about the Committee's decision to recommend not adding Krabbe disease to the recommended newborn screening panel at the present time. He noted that the letter would indicate the areas in which the evidence pertaining to Krabbe disease had been found to be deficient.

Finally, Dr. Ohene-Frempong urged the Committee, when talking about conditions for which transplants were performed, to consider transplant-related risks and mortality. He observed that much of the discussion about HSCT had been carried on as if it were a simple curative procedure. Dr. Ohene-Frempong stated that all transplants have risks. Unrelated matched donors or unrelated and not fully matched donors all carry different risks.

XIX. MANDATED REPORT FOR CONGRESS & DRAFT POLICY PAPER ON NEWBORN SCREENING AND HEALTH CARE REFORM

A. Advisory Committee's Mandated Report for Congress

Alaina M. Harris, M.S.W, M.P.H.
Health Resources and Services Administration (HRSA)

Ms. Harris noted that Section 1111 of the Newborn Screening Saves Lives Act of 2008 reauthorized and expanded the activities of the Advisory Committee on Heritable Disorders in Newborns and Children. In addition, the law specifies that not later than three years after the date of the law's enactment, and each fiscal year thereafter, the Advisory Committee shall do the following:

- Publish a report on peer-reviewed newborn screening guidelines, including follow-up and treatment, in the United States.
- Submit such report to the appropriate committees of Congress, the Secretary, the Interagency Coordinating Committee (ICC) established under Section 1114, and the state departments of health.
- Disseminate such report on as wide a basis as practicable, including through posting on the Internet clearinghouse established under section 1112.

Legislative intent indicates that the Advisory Committee's report on what it has done since the reauthorization and its plans for the future is to be published by April 28, 2011.

Ms. Harris asked Advisory Committee members what they would like for the content of the yearly report to Congress and the public on newborn screening guidelines, including follow-up and treatment, in the United States. Among the potential items for the report, she suggested, were the following: (1) revisions to the external Evidence Review Workgroup's reports; (2 updates from the subcommittees of the Advisory Committee; (3) information on the heritable conditions that states require and offer in their newborn screening programs; (4) information on the incidence and prevalence of conditions on the recommended screening panel; and (5) if available, information on the health status of individuals with these conditions.

Questions & Comments

Dr. Howell asked for comments from members of the Advisory Committee. Dr. Ohene-Frempong asked what was meant by "peer reviewed newborn screening guidelines." Ms. Harris said she thought it meant things published in journals, like evidence reviews, the paper on components of long-term follow-up after newborn screening, etc. Dr. Vockley stated his opinion that "peer reviewed publications" should include the Advisory Committee's reviews of the evidence because they are in fact peer review activities. Dr. Trotter suggested that all of the Advisory Committee members will have to help HRSA staff in preparing the report. Dr. Fleischman said he thought the Advisory Committee ought to be able to identify the number of children identified by the national newborn screening program, identify best practices of informing families and primary care providers, and linking children to long-term follow-up services after newborn screening to help Congress address future needs.

B. Draft Policy Paper: Newborn Screening and Health Care Reform

Alissa Johnson
Principal Consultant
Johnson Policy Consulting

Ms. Johnson presented for the Advisory Committee's review a 9-page draft policy paper that she had prepared with Michele Puryear entitled, "Newborn Screening and Health Care Reform: Report of the U.S. Secretary of Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children" and dated September 2009. The paper is intended to provide information to the Secretary on how the newborn screening system intersects with the current healthcare system reform debate. She explained that the basic theme of the paper is that, just as there is unequal access to health care overall in the United States, there is unequal access to newborn screening services across the country.

The reasons behind the disparities in newborn screening generally mirror problems with the broader health system and include problems in public financing, payment systems, administrative inefficiencies, and insurance coverage issues:

1. *Public financing.* The current newborn screening system relies on a combination of funding streams from fees, Maternal and Child Health Title V Block Grant funds, State appropriations, and general revenues. Existing support only provides for some education efforts, screening, diagnosis and initial confirmation of treatment in half of states. Fees do not correlate with number of mandated tests.
    - *1). Recommended reform*: Ensure stable funding for core and critical public health functions such as immunizations and screening (also a recommendation by the Trust for America's Health). (Note: developing national guidance for developing public health budgets is suggested in the paper by B Therrell, m Puryear, M Mann, and D Williams) but not as a recommendation.)
2. *Payment systems.* Features of the current newborn screening system include varying practices in billing and payment practices from state to state and a lack of financial incentives to coordinate care.
    - *2). Recommended reforms*. Convene an expert panel to examine billing and payment practices for the cost of screening services and to put forth recommendations that enhance the standardization of care.
    - *3). Recommended reforms*. Work with the Centers for Medicare and Medicaid Services (CMS) to develop and pilot a bundled payment method for providers treating the same child with a disorder diagnosed as a result of screening that can serve as a model for all children with special health care needs.
3. *Administrative inefficiencies*. Currently, there is a lack of funding in the newborn screening system to support e-health activities and promoting information exchange for State public health departments. Some entities within the U.S. Department of Health and Human Services (e.g., the Office of the National Coordinator for Health Information Technology, and the National Institute of Child Health and Human Development) are undertaking efforts to promote the electronic exchange of newborn screening information.

- *4). Recommended reforms*. Further define and adopt the meaningful use case for newborn screening for health information exchange endeavors by the U.S. Department of Health and Human Services (HHS).

4. *Insurance coverage issues.* In the current newborn screening system, state policies that require insurance coverage for medical foods vary and are not comprehensive. Gaps in coverage of necessary medical foods and foods modified to be low in protein result in a financial burden for families.

    - *5). Recommended reforms.* Close gaps in insurance coverage for medical foods and foods modified to be low in protein as recommended by the Advisory Committee in April 2009; suggest including information from the Committee's Follow and Treatment subcommittee survey of insurance coverage of medical foods.

Ms. Johnson stated that she had sent the paper out for review and received a few minor comments.

Questions & Comments

Dr. Fleischman said he thought the paper had some good recommendations, but that the paper conflated health care screening and health care delivery follow-up. He suggested defining the newborn screening system and differentiating between activities of public health newborn screening labs (screening and confirmation) and activities pertaining to health care delivery for chronically ill and complex children.

Dr. Howell asked for a sense of the Advisory Committee about whether this document should go forward or not. Dr. Ohene-Frempong said, he thought that we should have every baby screened, so government funding should support it, but he is not sure that many babies fall through the cracks in screening. He then asked: If the state takes responsibility to get a diagnosis, does the state then ensure that the child will receive care in the short and long term? Dr. van Dyck thought it would be useful to have a document like this go forward because it keeps the issue current, but he agreed with arguments on level of clarification of items discussed in concert with the recommendations. Dr. Boyle said she thought that a few more on long-term follow-up based could be added to the paper. Dr. Howell said his sense was that the Advisory Committee thought the paper was worthwhile but needed some revisions, so he asked Ms. Johnson to do additional work on the document.

XIV. COMMITTEE BUSINESS

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

In the final session of the meeting, Dr. Howell noted that calendar for the Committee's 2010 meetings would be as follows.

- January 21-22, 2010
- May 13-14, 2010
- September 16-17, 2010

Dr. Howell asked Advisory Committee members to send any suggestions for agenda items for the Committee's January 2010 meeting to Dr. Lloyd-Puryear.

Dr. Howell reported that the Advisory Committee had received a nomination for universal screening of newborns for bilirubin prior to hospital discharge and stated that the nomination would be reviewed by the Advisory Committee's Nomination Review and Prioritization Workgroup. Dr. Calonge, participating by phone, reported that the U.S. Preventive Services Task Force had new findings with respect to the benefits and harms of screening infants for hyperbilirubinemia and would release a report within the next week. Finally, with no other business at hand, Dr. Howell adjourned the meeting at 2:56 p.m. on September 25, 2009.

***

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

/s/ R. Rodney Howell

/s/ Michele A. Lloyd-Puryear, MD, PhD

R. Rodney Howell, M.D.
ACHDNC, Chair

Michele A. Lloyd-Puryear, M.D., Ph.D.
ACHDNC, 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