Summary of 20th Meeting
January 21-22, 2010
Washington, DC

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was convened for its 20th meeting at 8:30 a.m. on Thursday, January 21, 2010, at the Washington Marriott Hotel in Washington, DC. The meeting was adjourned at 2:10 p.m. on Friday, January 22, 2010. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments.

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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
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Welcome. Dr. Howell welcomed Dr. Alan Guttmacher, Acting Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), to the Advisory Committee. Dr. Duane Alexander had been appointed to a new assignment and Dr. Guttmacher has been appointed to serve on the Committee as the NIH member.

Approval of Minutes. Committee members had no comments or corrections to the minutes of the Committee's 19th meeting held on September 24-25, 2009 (under Tab #5 in Committee members' briefing books). The following motion to approve the minutes from the 19th meeting, made by Dr. Trotter, was approved by unanimous voice vote of all 12 Committee members present, with 2 members absent (Dr. Guttmacher and Dr. Skeels):

Ø MOTION #1 (PASSED, 12 yes, 2 absent): "The Advisory Committee approves the minutes of its 19th meeting held on September 24-25, 2009".

Committee Correspondence. Dr. Howell referred Committee members to several letters in their briefing materials (Tab #5).

· Two letters were from the Claire Altman Heine Foundation dated December 16, 2009 regarding supporting the establishment of a joint workgroup - between the Advisory Committee on Heritable Disorders in Newborns and Children and the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) - to consider policies regarding carrier screening for spinal muscular atrophy:

(1) a letter to the Genetic Services Branch of the Health Resources and Services Administration's (HRSA) Maternal and Child Health Bureau ; and

(2) a letter to the NIH.

· A letter from Dr. Howell to the Secretary of Health and Human Services Kathleen Sebelius urging her to facilitate adoption by all state newborn screening programs of the Committee's recommended uniform screening panel (previously the American College of Medical Genetics' (ACMG) newborn screening panel).

· A letter from HHS Secretary Sebelius, dated October 2, 2009, stating that HHS would explore the proposals in the Advisory Committee's April 2009 letter on insurance coverage for

medical foods and foods modified to be low protein for children with disorders identified via newborn screening.

Nominations.

Member Nominations:

Dr. Howell reminded Advisory Committee members that they had received a communication regarding nominations for individuals to replace current Committee members whose terms will be ending. He urged all Committee members to submit the names of individuals they thought would be good candidates.

Condition Nominations:

Finally, Dr. Howell noted that two nominations of conditions for inclusion on the Advisory Committee's recommended uniform newborn screening panel had been submitted to the Health Resources and Services Administration (HRSA):

(1) neonatal hyperbilirubinemia; and

(2) critical congenital heart disease.

II. COMMITTEE BUSINESS—INTERNAL WORKGROUP REPORT AND COMMITTEE ACTION ON TWO NEW NOMINATIONS: HYPERBILIRUBINEMIA AND CRITICAL CONGENITAL HEART DISEASE

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T. Denny Sanford Professor of Pediatrics
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Dr. Rinaldo presented the report of the Advisory Committee's internal Nomination Review and Prioritization Workgroup on two conditions nominated for inclusion on the Advisory Committee's recommended uniform newborn screening panel: (1) neonatal hyperbilirubinemia, nominated by Dr. Lois Johnson-Hamerman from Pennsylvania in July 2009; and (2) critical congenital heart disease, nominated by Robert Koppel from New York in October 2009. As detailed below, the workgroup recommended that the Advisory Committee send both conditions for an evidence review by the Evidence Review group headed by Dr. James Perrin.

A. Nomination of Extreme/Dangerous Neonatal Hyperbilirubinemia—Internal Workgroup Report and Committee Action

Dr. Rinaldo stated that the internal Nomination Review and Prioritization Workgroup had

reviewed the nomination of universal predischarge neonatal screening for extreme/dangerous hyperbilirubinemia to prevent acute bilirubin encephalopathy and kernicterus on November 2, 2009. Believing that the seriousness of acute bilirubin encephalopathy and kernicterus and the ability to prevent these conditions were compelling reasons to screen for neonatal hyperbilirubinemia, workgroup members unanimously recommended to the Advisory Committee that the nomination of neonatal hyperbilirubinemia be forwarded for an evidence review by the Evidence Review Workgroup.

Specifics of the review by the Nomination Review and Prioritization Workgroup were as follows:

1. *The nominated condition(s) is medically serious*. Both acute bilirubin encephalopathy and kernicterus are serious conditions that may cause permanent damage to the central nervous system.

2. *Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder.* Prospective studies have been conducted both in the United States and elsewhere; outcome studies suggest a lower incidence of readmissions. The University of Pennsylvania Health System (Reference # 1 in the nomination form) and hospitals in Utah (Reference #6) and in Israel (Reference #2) have adapted the practice of obtaining a predischarge bilirubin level on all infants in an effort to identify those at high risk of extreme hyperbilirubinemia and all report a lower incidence of readmissions for this problem since instituting this practice.

3. *The spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening*. Hyperbilirubinemia encompasses an extremely heterogeneous spectrum of clinical manifestations. Many newborns identified by screening will probably not require treatment. The decision about whether to treat can be made on the basis of their evaluation following a first abnormal result (the Bhutani protocol). Moreover, there is a nomogram that predicts the risk of extreme hyperbilirubinemia based on the bilirubin concentration at specified hours of age (see Figure 2 in Reference #1 in the nomination form).

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 tests to measure serum bilirubin or transcutaneous bilirubin are widely used and presumably well standardized if used in hospital labs that must pass College of American Pathologist (CAP) inspections, so they should be reasonable tests to use for newborn screening. However, it is uncertain why CAP laboratory accreditation should constitute a blanket of assurance on this matter. Reference #1 in the nomination form implies a false positive rate of approximately 2 percent. The nomogram referred to in Reference #1 is used throughout the world to calculate the predicted risk of a given bilirubin level and is considered the gold standard for plotting age of baby and bilirubin rise, along with rate of rise of serum bilirubin.

5. *If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky*. There are clearly risk factors for extreme hyperbilirubinemia (early jaundice, African American, male sex, prematurity, exclusive breast feeding, G6PD deficiency, etc.) that can alert physicians to check for elevated bilirubin levels while the infant is in the hospital. The practice of early discharge of newborns (i.e., after one or two days) makes it difficult to perceive these risk factors. Thus, the infant most likely to benefit is one whose risk factors were not perceived during the short hospital stay and who did not have a bilirubin level measured.

6. *Defined treatment protocols, FDA-approved drugs (if applicable), and treatment are all available.* These are already widely employed and include phototherapy and/or exchange transfusion—both accepted practices.

Questions & Comments

Following the internal Nomination Review and Prioritization Workgroup's report on the nomination of severe hyperbilirubinemia to the uniform newborn screening panel, Dr. Howell asked Dr. Vinod Bhutani to make a few comments at the microphone. Dr. Bhutani, from Stanford University's School of Medicine, has published extensively on newborn screening for severe hyperbilirubinemia. He explained that newborn screening for severe hyperbilirubinemia is being practiced at most academic hospital centers and regional networks, and data show that it reduces the incidence of severe hyperbilirubinemia. The evidence that has been gathered over the last few years led an the expert panel at the American Academy of Pediatrics (AAP) that included Dr. Jeffrey Maisels, Dr. Tom Newman, Dr. Ann Stark, Dr. John Watchko, and himself to recommend screening newborns for severe hyperbilirubinemia. Whether screening reduces kernicterus is too early to say. But the disease burden from kernicterus is real, with an incidence reported in *Pediatrics* last year of about 1 in 38,000 newborn infants, and this condition is also highly preventable. Dr. Bhutani said he thought that the evidence in support of screening for severe neonatal hyperbilirubinemia at this time is sound.

After Dr. Bhutani's comments, the Advisory Committee discussed the nomination package and voted to send severe neonatal hyperbilirubinemia for an evidence review by the external Evidence Review Workgroup. Dr. Dougherty, observing that the U.S. Preventive Services Task Force (USPTF) had recently reviewed the benefits and harms of screening infants for hyperbilirubinemia and did not recommend screening, asked Dr. Calonge to comment. Dr. Calonge replied that the USPTF did not recommend *against* screening infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy; rather the USPTF concluded that given the lack of direct evidence from a randomized clinical trial, the available evidence was "insufficient" to recommend for or against screening.

Dr. Calonge said at the time the USPTF reviewed the evidence for screening newborns for hyperbilirubinemia, it was difficult to develop a direct link between screening for hyperbilirubinemia and the prevention of kernicterus. The new evidence that the incidence of kernicterus is much higher than the 1 in a million previously thought is surprising, and it is important to get a better idea of what the burden of disease really is, as well as information about the links between universal screening for severe hyperbilirubinemia and a reduction of the

conditions of interest (acute bilirubin encephalopathy and kernicterus). There is kernicterus without hyperbilirubinemia and severe hyperbilirubinemia without kernicterus. Phototherapy has been shown to reduce bilirubin levels and the incidence of hyperbilirubinemia, but the link to kernicterus has not been made. This is an issue that Advisory Committee members will have to wrestle with.

Finally, Dr. Calonge made the point that the Advisory Committee on Heritable Disorders in Newborns and Children uses a process that, unlike the process of the USPTF, allows it to piece together indirect evidence on which to base its recommendations. He cautioned, however, that new evidence on hyperbilirubinemia is currently emerging, so an evidence review performed at the present time may not get the newest evidence. Dr. Calonge suggested that an evidence review for hyperbilirubinemia screening begin with the Tufts Evidence-Based Practice Center's report on the management of neonatal members of the group to consider the harms of screening.

Dr. Vockley agreed with Dr. Calonge that the Advisory Committee's process for reviewing conditions nominated to the uniform newborn screening panel differed from that used by the USPTF. He stated that he thought that it was worth proceeding with the external evidence review of the nomination. Dr. Vockley also asked how the 2.5 percent false positive rate was arrived at in the nomination. Dr. Rinaldo explained that the rate was based on the number of readmissions because of elevated measurements.

Dr. Geleske, noting that screening for neonatal hyperbilirubinemia is "bread and butter" pediatrics and seems to be the current standard of care, said he thought that a thorough evidence review was needed, regardless of what decision the Advisory Committee ultimately made with respect to the nomination. Dr. Trotter, similarly observing that screening for hyperbilirubinemia is being done now without data and that considerable new evidence has emerged in the last five years, stated that he thought it was important to perform an evidence review. Moreover, he said he was not surprised by the incidence data for kernicterus given the number of legal cases he has been involved in; he thinks the incidence could very well be 1/40,000.

Dr. Kus asked how the Advisory Committee would answer the question about whether there is an effective treatment to prevent or ameliorate the disease. Dr. Calonge said the problem is that hyperbilirubinemia (which is not a disease but a lab test result) is an intermediate outcome. The screening tests for hyperbilirubinemia are excellent and the treatment for hyperbilirubinemia is great, but the USPTF and the Tufts Evidence Based Practice found a gap between the treatment of hyperbilirubinemia and the prevention of kernicterus.

Dr. Howell indicated that he thought there were sufficient reasons to send the nomination forward for an evidence review by the external Evidence Review Workgroup and asked for a motion to that effect. The following motion, made by Dr. Trotter and seconded by Dr. Buckley, was approved unanimously by all 12 Committee members present, with 2 members absent (Dr. Guttmacher and Dr. Skeels):

Ø MOTION #2 (PASSED, 12 yes, 2 absent): The Advisory Committee accepts the recommendation of the Nomination Review and Prioritization Workgroup that severe neonatal

hyperbilirubinemia, which has been nominated for inclusion on the uniform newborn screening panel, receive a formal evidence review by the external Evidence Review Workgroup.

B. Nomination of Critical Congenital Heart Disease—Internal Workgroup Report and Committee Action

Dr. Rinaldo reported that the internal Nomination Review and Prioritization Workgroup had reviewed the nomination of critical congenital heart disease on December 30, 2009. Workgroup members recommended to the Advisory Committee that the nomination of critical congenital heart disease be forwarded for an evidence review by the Evidence Review Workgroup.

Specifics of the review by the Nomination Review and Prioritization Workgroup were as follows:

1. *The nominated condition(s) is medically serious*. The condition is very serious. Critical cyanotic congenital heart disease can be missed at birth only to have the infant be discharged and return with hypoxic encephalopathy, other organ failure, and even death. Congenital heart disease is reported to be the most common cause of death in an infant's first year.

2. *Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder*. There are large pilot studies reported in the United States.

3. *The spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening*. There are a number of serious congenital heart diseases, but they have in common the fact that they produce hypoxemia, for which the screening is aimed. Technology in most institutions can readily identify the underlying causes

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 characteristics of the screening test(s) are reasonable with a positive predictive value that is quite high, and a relatively low false positive rate. The cost of the screening test is reasonable

5. *If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky.* Yes, there are recognized plans for establishing the diagnosis of congenital heart disease, and those who will benefit from treatment can be readily identified.

6. *Defined treatment protocols, FDA approved drugs (if applicable), and treatment are all available*. Surgery or interventional cardiology will be the treatment. No drugs will be key.

Questions & Comments

After hearing the Nomination Review and Prioritization Workgroup's report on the nomination of congenital heart disease to the uniform newborn screening panel, Dr. Trotter said he thought that the nomination should go forward to the Evidence Review Workgroup. He added that the

evidence for screening newborns for congenital heart disease would be clearer than that for screening newborns for hyperbilirubinemia. Dr. Geleske, noting that his group practice had lost a baby at day 10 to this condition after having seen the baby four times, agreed that the Advisory Committee should send congenital heart disease for an evidence review and then make some recommendation.

The following motion, made by Dr. Vockley and seconded by Dr. Boyle, was approved unanimously by all 12 Committee members present, with 2 members absent (Dr. Guttmacher and Dr. Skeels):

Ø MOTION #3 (PASSED, 12 yes, 2 absent): The Advisory Committee accepts the recommendation of its Nomination Review and Prioritization Workgroup that critical congenital heart disease, which has been nominated for inclusion on the uniform newborn screening panel, receive a formal evidence review by the external Evidence Review Workgroup.

Dr. Rinaldo pointed out that the Advisory Committee needed to make a decision about the order in which the nomination of congenital heart disease and neonatal hyperbilirubinemia should be considered. Dr. Calonge agreed, adding that the Advisory Committee really needed to develop a more explicit process and criteria for prioritizing nominations given that many more nominations are going to be submitted in the not-too-distant future. Dr. Howell concurred. Dr. Dougherty asked whether bilirubin is a heritable disorder. Dr. Trotter said a substantial percentage of critical hyperbilirubinemia is heritable. Dr. Ohene-Frempong clarified that not the hyperbilirubinemia but the underlying disease that predisposes to hyperbilirubinemia is inherited.

Dr. Calonge suggested making critical congenital heart disease screening the first priority for the Evidence Review Workgroup and neonatal hyperbilirubinemia the second priority, noting that this order would make allow more time for data on the effectiveness hyperbilirubinemia screening to be published. The following motion, made by Dr. Calonge and seconded by Dr. Buckley, was approved, with 10 of the 12 Committee members present voting yes; 2 members abstaining (Dr. Ohene-Frempong and Dr. Dougherty); and 2 members absent (Dr. Guttmacher and Dr. Skeels):

Ø MOTION #4 (PASSED, 10 yes, 2 abstaining, 2 absent): The Advisory Committee directs the external Evidence Review Workgroup to review the evidence for congenital heart disease prior to reviewing the evidence for severe neonatal hyperbilirubinemia.

III. DEVELOPMENT OF A NATIONAL CLEARINGHOUSE FOR NEWBORN SCREENING INFORMATION

Sharon Terry, M.A.
President, Genetic Alliance

The Newborn Screening Saves Lives Act of 2008 called for the Health Resources and Services Administration (HRSA) to establish and maintain a clearinghouse of current materials, resources, research, and data related to newborn screening. In late 2009, HRSA awarded a five-year, $3.75 million cooperative agreement to the Genetic Alliance to develop such a clearinghouse.

Additional partners in developing the newborn screening clearinghouse (NBSC) include the National Newborn Screening Genetics Resource Center (NNSGRC), the HRSA-funded Genetics and Newborn Screening Regional Collaborative Groups, the March of Dimes, the Association of Public Health Laboratories (APHL), and others.

Ms. Terry gave an overview of the vision for the NBSC, discussed activities for Year 1 of the NBSC project, and took Advisory Committee members on a tour of the beta NBSC Website (http://www.nbsclearinghouse.org/home). She also presented a conceptual diagram that showed the foundation for the NBSC to be the Secretary of Health and Human Services and the Advisory Committee on Heritable Disorders in Newborns and Children. The diagram showed the NBSC, the Centers for Disease Control and Prevention (CDC), HRSA, the Early Hearing Detection and Intervention Program, and the National Newborn Screening Information System (NNSIS) as very closely linked. The diagram also showed interactivity between the NBSC and the HRSA-funded Genetics and Newborn Screening Regional Collaborative Groups, the Newborn Screening Translational Research Network (NBSTRN), the March of Dimes, and other entities (e.g., the Congenital Conditions Program, a HRSA-funded cooperative agreement that was awarded to the Genetic Alliance and its partners).

Ms. Terry explained that the NBSC will "live in a cloud" on the Internet. Cloud computing is a form of distributed computing composed of a cluster of networked, loosely coupled computers acting in concert to perform tasks. Unlike information for Google, which stores every Web page on its servers, information for the NBSC will generally stay in the various locations where it resides, and a cloud system will be used to link the information very quickly. The backbone for the NBSC already exists. Google Wave, for example, is an online communication and collaboration tool that allows people to discuss and work together using richly formatted text, photos, videos, maps, and more to make real-time interactions more seamless.

Vision for the NBSC. The Newborn Screening Saves Lives Act of 2008 required the Secretary of Health and Human Services, acting through HRSA to establish and maintain a central clearinghouse of current information, materials, resources, research, and data on newborn screening to increase awareness of newborn screening, and to improve the understanding and informed decisionmaking capacity of expectant and new parents, health professionals, industry representatives, and the public. The vision for the NBSC in the act is that the clearinghouse will do the following:

· Connect parents and health care providers with resources and information.

· Improve understanding and informed decisionmaking.

· Facilitate information sharing.

· Enable data transparency, integrated tools, technologies and education, and provide a basis for followup.

· Provide information on federal funding for newborn screening.

The Newborn Screening Saves Lives Act of 2008 requires that the NBSC include certain specific elements:

· Be centralized and online—The Genetic Alliance is interpreting the word centralized fairly broadly to mean that everything will be centralized in terms of the public or health care providers being able to find it.

· Provide research-based information on conditions for which newborn screening tests are available—The Genetic Alliance has another cooperative agreement with CDC called Access to Credible Genetics Resources Networks, under which it has looked at the meaning of research-based or evidence-based information, and it has set some standard that it will be applying to the NBSC.

· Include information on newborn conditions and screening services available in each state.

· Include an interactive forum—The Genetic Alliance considers cutting-edge interactive forums to be like Facebook or Amazon.

· Maintain data—The Genetic Alliance will be interpreting data fairly broadly. It has been working with HRSA about what data means and how data information and resources overlap.

· Disseminate information—Families preparing to have babies are typically young, so the Genetic Alliance believes it is important to consider the ways in which young people receive information (e.g., via texting, Facebook, or other means).

The guidance for the NBSC requires that the data, information, and resources be liquid and that the Genetic Alliance consider meaningful use, accuracy, access, information flow, and transparency. Ms. Terry gave examples of how the Genetic Alliance was addressing each of these topics. Ms. Terry sits on the Health IT Standards Committee at the U.S. Department of Health and Human Services (HHS), and she explained that meaningful use criteria for the use of health information technology that are coming out from the Office of the National Coordinator for Health Information Technology (ONC) do not include newborn screening. Ms. Terry added that it is very important for the public and perhaps the Advisory Committee to make comments on that, so that newborn screening is included.

NBSC Project Activities During Year 1. At the outset of the NSBC project, the Genetic Alliance and its partners undertook a landscape analysis of newborn screening materials, which is still ongoing. The first beta site for the NBSC (NBSC 0.9) was launched in October 2009, and successive iterations (NBSC 1.0, 2.0 and 2.x) will follow. A workshop related to the NBSC will be offered during the Association of Public Health Laboratories' (APHL) Newborn Screening and Genetic Testing Symposium in May 2010.

The Genetic Alliance presented its ideas for the NBSC to the National Advisory Council for the NBSC received feedback concerning quality filters and procedures for prioritizing information in the NBSC; the roles of consumers and primary care providers in the NBSC; public education/interactive components of the NBSC; the role of the HRSA-funded Genetics and

Newborn Screening Regional Collaborative Groups in the NBSC; and the inclusion of international perspectives/issues in the NBSC. Ms. Terry explained that Genetic Alliance is now working with HRSA to integrate this information. She explained that the question of how to prioritize information in the NBSC is a difficult one. The Genetic Alliance plans to use the iGoogle concept, which allows individuals to customize their home page the way they want to (e.g., include things such as G-mail, newspaper feeds, the quote of the day, etc.). The NBSC will be a portable information source that can be carried in mobile devices. The Genetic Alliance is still considering whether to have different portals for consumers and primary care providers or to use multiple tiers. The seven Genetics and Newborn Screening Regional Collaborative Groups are an important part of the NBSC project and have funding from the Genetic Alliance to do work in regions. Although the NBSC will start out being U.S.-centric, the Genetic Alliance will be mindful of newborn screening issues around the globe.

IV. COMMITTEE BUSINESS—DRAFT COMMITTEE PAPER ON NEWBORN SCREENING AND HEALTH CARE REFORM

Alissa Johnson
Principal Consultant
Johnson Policy Consulting

In this session, Ms. Johnson presented the second draft of the Advisory Committee white paper on newborn screening and health care reform for the Advisory Committee's review. Ms. Johnson explained that the current version of the paper incorporated Committee members' comments from September 2009 meeting, as well as additional comments from Health Resources and Services Administration (HRSA) staff and the March of Dimes.

Revised Recommendations. The revised white paper on newborn screening and health care reform presented by Ms. Johnson included the following as draft recommendations from the Advisory Committee to the Secretary of Health and Human Services:

· *Recommendation #1 (revised*): Convene an expert panel to establish a minimum recommended standard of service and care for each component of the newborn screening system—education, screening, diagnosis, followup/tracking, and evaluation services.

· *Recommendation #2 (new):* Develop national guidance on creating public health budgets for newborn screening systems in order to minimize geographical disparities and highlight budget alternatives that may better serve the needs of a particular state program.

· *Recommendation #3 (previously #2, unchanged):* Convene an expert panel to examine the billing and payment practices for the cost of screening services and to put forth recommendations that enhance the standardization of health care transactions.

· *Recommendation #4 (previously #3, modified):* Work with the Centers for Medicare and Medicaid Services (CMS) to develop and pilot a 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 needs.

· *Recommendation #5 (previously #4, unchanged*): 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.

· *Recommendation #6 (previously #5, unchanged):* 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.

Additional Changes and Comments. Ms. Johnson noted that language had been added in the summary and the text of the January 2010 version of the draft paper on newborn screening and health care reform to say that newborn screening is among first encounters where health professionals begin to compile medical information about an individual and is thus a prime area for introducing electronic health records (EHRs). Among the specific additional comments on the original September 2009 version of the paper on newborn screening and health care reform were the following:

· It was suggested that textual references that suggest all states should conform to a single design and financing methodology should be deleted. Ms. Johnson said she tried to do that in the discussion for Recommendation #2.

· It was suggested that the paper include an additional recommendation on the need for educational materials and a full national campaign to education parents and professionals about the availability and need for newborn screening.

· Regarding Recommendation #2, the comment was that the paper does not build a case for an expert panel on billing and payment. Ms. Johnson asked Advisory Committee members whether they agreed.

· Regarding Recommendation #4 (now #5), the comment was this is a good idea that may need more discussion in paper.

· Regarding Recommendation #5 (now #6), one comment was that medical foods should be discussed further in the paper. Another comment was to include in the paper a proposal to convene a working group that includes the Food and Drug Administration (FDA), CMS, and TRICARE representatives to consider expanding federal support for public program coverage of medical foods. Ms. Johnson noted that the Advisory Committee had already done quite a bit of work on medical foods and asked whether that should be referred to more in the paper.

· Concerns were raised by the Genetics and Newborn Screening Regional Collaborative Groups about creating an unfunded mandate for state programs. The point was made that recommending federal funding to support programs that are not addressing components of the newborn screening system might provide a disincentive for states that are already paying for these activities to no longer fund them if federal funding becomes available. Ms. Johnson noted that language was added to Recommendation #2 about providing additional federal funding to states for support in some areas.

· The point was made that a national coverage decision by CMS might help to resolve some of the billing and payment issues.

· The point was made that with regard to medical foods coverage, shipping is a significant portion of patient costs. Ms. Johnson said she was not sure whether to add this as she was unsure if that could be addressed at the regulatory level.

Questions & Comments

Dr. Howell asked for comments on the second draft of the proposed white paper from the Advisory Committee on newborn screening and health care reform, noting that once the Committee approved it, the document would be sent to Secretary of Health and Human Services Sebelius.

Dr. Ohene-Frempong, noting that language had been added in the summary of the draft paper about newborn screening being a prime area for developing Electronic Health Records (EHRs), asked for clarification about how EHRs would be involved given that newborn screening data are maintained by state health departments. Ms. Terry answered the Office of the National Coordinator for Health Information Technology (ONC) in the U.S. Department of Health and Human Services (HHS) and others have been thinking about how to incorporate newborn screening data into EHRs. Given that newborn screening is the first exchange of health information that begins even before birth certificates and vital statistics, the idea is that newborn screening information could be used to begin a newborn's EHR. This would provide a way to move all U.S. residents into an EHR system. Initially, the information in the EHR would be used primarily to allow the hospital to communicate with state public health lab, pediatrician, and subspecialists; eventually, parents would also be involved; and some data from EHRs could potentially be used for research. Speaking from the audience, Dr. Nancy Green suggested making it clear in the paper that an EHR is an individualized electronic medical record that is integrated with both individual and public health systems.

Dr. Watson asked with respect to the point that a national coverage determination by CMS might help to resolve some of the billing and payment issues (#7 above) whether a national decision would apply to just the newborn screening or also to diagnosis, followup, management, and treatment of infants with conditions detected via newborn screening. Ms. Johnson replied that the person who made this recommendation did not discuss that particular point. Dr. Watson said that in the absence of standards of care, it would be hard for CMS to make a national or even a local coverage decision. He said he thought focusing on the screening piece would be important to get a more uniform approach to reimbursement. Dr. Calonge observed that variations in practice pattern did not necessarily mean waste, ineffective care, and poor quality care. Dr. Dougherty suggested that Dr. Watson was talking about clinical evidence, and Dr. Calonge was talking about patterns of practice. She said that she thought EHRs would help with patterns of practice. If an infant screens positive, a health care provider should do *something* (e.g., call the lab back, make a referral) and those generic types of things can be specified without specifying the exact medical intervention.

Discussion of Recommendations #1 and #2. Dr. Boyle asked for clarification about the

Advisory Committee's role in trying to help implement the recommendations in the paper after sending the paper to the Secretary of Health and Human Services. In particular, might the Advisory Committee and the Followup & Treatment Subcommittee be involved in helping to jump start *Recommendation #1: Convene an expert panel to establish a minimum recommended standard of service and care for each component of the newborn screening system—education, screening, diagnosis, followup/tracking and evaluation services.* Dr. Howell said he saw no reason that the Advisory Committee could not be involved.

Dr. Fleischman asked why the Advisory Committee might not be the expert panel for that recommendation. Dr. Dougherty suggested deleting Recommendation #1 and saying that with additional resources, the Advisory Committee could be the expert panel for this recommendation. Ms. Terry said that rather than taking Recommendation #1 out, she would expand it to be more explicit about certain things. Dr. Vockley agreed with Ms. Terry that the recommendation should be broadened. In addition, Dr. Vockley suggested that Advisory Committee approve further changes to the paper by e-mail or a conference call rather than holding the paper up until the next meeting.

Dr. Lloyd-Puryear suggested combining Recommendation #1 and #2, noting that public health budgets should be developed to work with the recommended standard of care and service developed by the Advisory Committee. Dr. Boyle agreed that combining the recommendations was a good idea.

Discussion of Recommendation #3. Following the discussion of the Advisory Committee's role as the expert panel in Recommendation #1, Ms. Johnson asked whether the Advisory Committee should similarly be the expert panel called for in *Recommendation #3: Convene an expert panel to examine the billing and payment practices for the cost of screening services and to put forth recommendations that enhance the standardization of health care transactions*. Ms. Johnson also asked the costs of newborn screening services should be separated from other costs.

Dr. Calonge replied that he did not know how to separate the costs of newborn screening services from taking care of the newborns that test positive. Dr. Lloyd-Puryear said the words "screening services" in the recommendation should be changed to newborn screening system services (education, screening, diagnosis, etc.).

Ms. Johnson brought up the point made earlier about there being no standard of care and asked whether this recommendation should refer back to Recommendation #1. Dr. Dougherty emphasized that there is a standard of care based on work by the short-term and long-term followup workgroups of the Followup & Treatment Subcommittee. There must be education of the parents, referral, etc.

Dr. Calonge said that states were doing what was suggested in this recommendation now, and although not every state finances newborn screening services the same way, he thought states did have a sense of how much screening costs in the state. In Colorado, for example, they just average the cost of the entire program over the fee and apply it to every child that is born in a hospital in the state.

Discussion of Recommendation #4. Dr. Howell suggested wordsmithing *Recommendation #4**: Work with the Centers for Medicare and Medicaid Services (CMS) to develop and pilot a 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 needs* to say something like "multiple physicians treating a child on the same day."

Dr. Dougherty said she thought the recommendation was vague and needed additional work. Dr. Watson observed that everyone on the Advisory Committee agreed that it was important to have an organized newborn screening system that includes short-term followup and long-term followup of affected newborns. He suggested that the Advisory Committee's recommendations in the paper be stated as general principles and stay away from very specific terms like bundling payments and national coverage decisions.

Dr. Kus indicated the gist of the fourth recommendation was to provide a financial incentive to provide care to children with more complicated conditions. He noted that things get complicated when you talk about bundled payments for the same day because both managed care and fee-for-service care may be involved. He said he wanted to ensure that primary care physicians caring for children with chronic illnesses received incentives to provide the level of care that they need to provide it.

Dr. Howell said Dr. Kus and Dr. Dougherty could work on Recommendation #4, and they agreed to do so. Dr. Calonge pointed out that the recommendation just calls for working with CMS to pilot a payment method and is therefore not very threatening. Dr. Trotter stated that he thought there was value that the paper was generic and somewhat vague but outlines the points that the Advisory Committee wanted to make.

Other Comments. John Adams, the father of a son born with phenylketonuria (PKU), speaking from the audience, said that the delivery cost for medical foods is a barrier to access, and he would like to have that in the scope of the paper. Mr. Adams also stated that he would be happy to work on that language with the Advisory Committee.

Dr. Howell said he would like to move the paper on health reform and newborn screening forward. Dr. Howell asked the Advisory Committee if it would be able to vote on the white paper the morning of the following day if the changes that had been discussed were made. There was no objection, and it was agreed that the Advisory Committee would vote on a revised version of the paper the following day. .

Ø ACTION. It was agreed that Ms. Johnson and Dr. Lloyd-Puryear and others would revise the paper on health reform and newborn screening incorporating the Advisory Committee's comments, and the Advisory Committee would vote on the new language the following day.

V. COMMITTEE BUSINESS—DRAFT COMMITTEE REPORT ON THE RETENTION AND USE OF RESIDUAL DRIED BLOOD SPOTS AFTER NEWBORN SCREENING

Alissa Johnson

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In this session, Ms. Johnson presented the second draft of the Advisory Committee white paper on national policies regarding the retention and use of dried blood spots after newborn screening for the Advisory Committee's review. In his introductory remarks, Dr. Howell noted that the issue of the storage and use of residual dried blood spots is one that has received an enormous amount of attention in recent times, in part because some of the public information about their use and value is not accurate.

Ms. Johnson explained that the new version of the white paper on dried blood spots incorporated comments of Committee members made in September 2009. In preparing the paper for external review, Ms. Johnson made the following changes to paper on the basis of comments made at the Advisory Committee's September 2009 meeting:

· Added a statement at the beginning of the paper regarding the potential to advance science and clinical care.

· Added language "a policy in place that has been reviewed by the state attorney general or other appropriate legal authority" to Recommendations #1 and #2.

· Removed validation from Recommendation #1 to make it read: "The policy should specify appropriate use and storage after the completion of newborn screening testing and verification of results according to laboratory QA procedures."

· Combined Recommendations #3 and #4 concerning the educational process of the newborn screening system and educating parents.

· Kept the optional recommendation in the paper to obtain additional feedback.

The revised paper was then sent out for external review by a number of agencies. Comments on the paper were received from entities that included the Association of State and Territorial Health Officials (ASTHO) and the Secretary's Advisory Committee on Genetic Testing (SACGT), and several entities within the Department of Health and Human Services, specifically, the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Office of Civil Rights, and the Office of Human Research Protections (OHRP). The American Academy of Pediatrics (AAP) and the Centers for Medicare and Medicaid Services (CMS) said they had no comments. Several additional entities did not reply to the request for comments. These included the American Hospital Association, the Council of State Governments, the International Society of Nurses in Genetics, the Midwives Alliance of North America, the National Association of Attorneys General, the National Conference of State Legislatures, and the National Governors Association.

Ms. Johnson went through the extensive comments received from NIH and OHRP in detail. NIH comments specific to the recommendations recommended that the Advisory Committee do the following:

· Become an advocate for research use by setting forth an actual recommendation for states to consider (p. 1).

· Propose voluntary national standards, including provisions for broad research use that each state could consider for adoptions (p. 1).

· Recommend that the Secretary of Health and Human Services provide resources to facilitate a national dialogue with the relevant stakeholders across the states, perhaps through the National Conference of State Legislatures (p. 1).

· Give the critical issue of education around newborn screening a fuller treatment in the paper. Modify Recommendation #3 to lay out the currently two uninformed "audiences"—i.e., parents of newborns and health care professionals who provide them with pre- and post-natal care (bottom of p. 1).

· Consider including a statement in Recommendation #3 that the Secretary should provide federal funding to states to implement educational programs.

· Recommendation #5 calls for the development of a model consent/dissent processes for the use of residual specimens. A concerted, nationwide effort is needed to develop a national policy and best practices that could be adopted by individual states.

· Remove the optional recommendation in the paper (p. 2).

These were additional general comments from NIH:

· Add information about current state practices with regard to research use of residual specimens (p. 2).

· Add information about examples of scientific and medical discoveries made possible using residual dried blood specimens.

NIH also suggested that the following topics might warrant further discussion:

· Potential benefits and risks that screening programs should anticipate as they approach the use of residual specimens

· Anticipated scope of future uses of these resources (e.g. genetic vs. genomic; public health vs. clinical medicine oriented)

· Possible impact of increased data generation and data sharing on privacy

· Ongoing governance and oversight of future research using these specimen (oversight of distribution, including to whom, for what, and how the specimens will be distributed)

· Policies for the return of various kinds of results

· More robust discussion of (re)consent once subjects reach adulthood, which is an issue that relates back to the question of ongoing oversight and the intent to give results

· Given that residual blood spots are finite resources, consideration of the optimal approach for allocating the resources among competing uses and needs

· Consideration of whether policies for stored blood spots apply to other types of archived newborn specimens (e.g., peripheral blood, buccal swabs, urine specimens).

Ms. Johnson said that she had met with Dr. Lloyd-Puryear and Dr. Howell in a pre-meeting and they suggested the Advisory Committee move forward with the following if members of the Committee were in agreement:

· Executive Summary—Define consumers (p. iii).

· Policy, Ethical, and Legal Issues—Add international guidelines for specimen repositories (p. 4).

· Ownership—Add case law (p. 4).

· Stewardship—Define stewardship; shorten the discussion of examples in Michigan and Denmark (see appendix) and remove discussion of a global consortium (p. 6).

· Privacy Protections—Accept comments from the Office of Civil Rights about privacy protections (p. 6).

· Awareness and Education—Add a discussion of the role of prenatal care providers in educating parents and themselves and cite more published references on the subject (p. 5).

· Consent/Dissent—Work OHRP comments into the paper and add text that explains anonymized, unidentified, linked with identifiers, identifiable, completely de-identified, private unless decoded and double-coded samples (p. 5 and 6).

· Financial Considerations—Shorten the section significantly but include examples of the cost of storage and retrieval (p. 6).

Finally, Ms. Johnson noted the following points that OHRP said to consider when thinking about how HHS human subjects regulations may apply in the context of newborn screening activities:

· The collection of newborn blood spots would not involve research under HHS regulations for the protection of human subjects if the specimen collection for the newborn screening is not modified in any way for a research purpose. This is the case even if it is known the specimens will subsequently be used for research purposes (p. 1).

· If the specimens were collected for solely clinical purposes, the retention of specimens for future research studies may involve research, depending on whether the retention of the

specimens is being altered due to the plan to carry out research using the specimens. If the retention of the specimens is not altered by the future research plans, then the retention of the specimens is not a research activity (p. 2).

· If the creation or maintenance of a specimen repository is a research activity and associated individually identifiable information will be retained with the specimen, then the existence of the repository would involve non-exempt human subjects' research. In this case, the repository would require review by an institutional review board, and the informed consent of the subjects or the subjects' legally authorized representative, unless the IRB determines that informed consent may be waived. Another consideration for such studies involving newborns is that the additional regulatory protections for children involved in research will be applicable (45 CFR 46, subpart D) if the research is conducted before the subject reaches the age of majority (p. 2).

Questions & Comments

At Dr. Lloyd-Puryear's request, Dr. Geleske reported on comments on the draft paper on the retention and use of dried blood spots after newborn screening from the American Academy of Pediatrics (AAP). Dr. Geleske stated that the AAP had sent out the draft paper to the AAP Committee on Genetics and the Section on Genetics and Birth Defects. The AAP Committee on Genetics, much like the NIH, encouraged the Advisory Committee to put forth more strongly a recommendation to have a national repository for blood banking and to support the use of the samples for future consideration. Dr. Howell said his take on the NIH recommendations was that NIH was primarily interested in trying to ensure that the samples would be utilized appropriately for research and that they be preserved for that.

Dr. Howell observed that the Office of Human Research Protections (OHRP) recommendations about research were interesting and very specific. Ms. Terry said that the OHRP recommendations should be taken in context. She noted that although the OHRP recommendations are technically correct in saying that deidentified samples do not constitute human subjects research. However, the context in which the Advisory Committee is considering things involves the whole issue of public trust; this differs from the context in which OHRP typically deals.

Dr. Vockley, referring to OHRP's comments about when institutional review board (IRB) approval is required, urged the Advisory Committee to focus on the point that getting IRB approval from every hospital IRB makes any type of collaborative study using dried blood spots impossible. IRB approval cannot be handled on an institution-by-institution basis and make it work for informed consent. A better alternative would be a national IRB to approve studies at a national level through the Newborn Screening Translational Research Network (NBSTRN) or the seven Genetics and Newborn Screening Regional Collaborative Groups.

Dr. Boyle said she appreciated the inclusion at the beginning of new document of her previous comment, in line with the AAP and NIH comments, that residual dried blood spot specimens are important for research and for improving the newborn screening system, but she urged that the point be incorporated in the recommendations of the paper.

Dr. Howell asked whether Advisory Committee members thought the draft paper on residual dried blood spot specimens presented by Ms. Johnson adequately addressed the value of dried blood spots. Ms. Terry said with imminent destruction of the dried blood spots from newborn screening in Texas, the climate has changed; she suggested emphasizing that point in the introduction, crisping the paper up, and getting the paper out as fast as possible. Dr. Howell agreed with Ms. Terry that what is happening in Texas is very destructive.

Dr. Howell also noted that the Institute of Medicine (IOM) has a roundtable looking at the integration of genomics into health care and their oversight body has said it would like to see the Advisory Committee do more on newborn screening. Although the IOM Roundtable on Translating Genomic-Based Research for Health does not want to get into same area as the Advisory Committee, it has suggested sponsoring a joint public workshop with the Advisory Committee on dried blood spots. Such activities should not hold up the Advisory Committee's policy paper on dried blood spots. Ms. Terry stated that there is a role for the Advisory Committee to make recommendations, because the IOM roundtable cannot do this.

Finally, noting that the draft policy paper from the Advisory Committee on the retention and use of residual dried blood spot specimens after newborn screening paper had been in the works for quite a while, Dr. Howell asked for comments about how to move the paper along. Dr. Vockley asked whether it would be possible for Advisory Committee members to review a revised draft of the paper and then approve it via e-mail. Dr. Howell said he saw no problem with that and asked Dr. Lloyd-Puryear to comment.

Dr. Calonge asked whether public comments were required. Dr. Lloyd-Puryear explained that the plan had been to revise the document based on comments to date, send the revised paper out for formal public comments in the *Federal Register*, and then to prepare a final draft of the paper incorporating public comments from various organizations. She added that her hope was to prepare a final draft by May 2010. An IOM meeting is tentatively scheduled for May 24, 2010, and HRSA has promised the IOM that it would be part of the public comment process. Dr. Lloyd-Puryear also stated that she also wanted the Office of the General Counsel at HHS to review and give feedback on the paper.

Dr. Calonge asked Dr. Lloyd-Puryear whether HRSA staff had enough information to revise the draft paper on national policies regarding the retention and use of dried blood spots after newborn screening and start the review process rather than having the Advisory Committee go through another cycle of review. Dr. Lloyd-Puryear said they did have enough information.

Dr. Howell asked for a motion. The following motion, made by Dr. Calonge and seconded by Dr. Kus, was approved unanimously by all 12 Committee members present, with 2 members absent (Dr. Guttmacher and Dr. Skeels):

Ø MOTION #5 (PASSED, 12 yes, 2 absent): The Advisory Committee requests that HRSA staff revise the Advisory Committee's draft policy paper entitled "Considerations and Recommendations for a National Policy Regarding the Retention and Use of Residual Dried Blood Spot Specimens After Newborn Screening" incorporating suggestions and comments made at this meeting, then send the revised paper to the Federal Register for formal public

comments.

Dr. Howell asked HRSA staff to work with Ms. Johnson to proceed with the paper as directed. Ms. Johnson said it had been suggested that examples of model consent or dissent processes be included. She and Dr. Lloyd-Puryear had discussed possibly giving some examples of what states do rather than coming up with something on their own. Ms. Johnson asked if the Advisory Committee would be comfortable including such material as an appendix or something. There was no objection. Ms. Terry suggested that the paper also include examples of consent and assent processes using various technologies that have rolled out since the paper was first written.

Dr. Howell asked Ms. Johnson whether she had an adequate number of valuable uses of residual dried blood spots from newborn screening to include in the paper. Ms. Johnson noted that she and Dr. Howell had discussed adding some studies that have been done and that she also planned to talk to Dr. Watson about possibly including some unpublished information that was compiled for the National Coordinating Center of the Genetics and Newborn Screening Regional Collaborative Groups. Ms. Terry added that a workshop that the Genetic Alliance had helped put on with Dr. Watson yielded material that could be included.

Speaking from the audience, Dr. Carol Greene noted that while public comments on the dried blood spot policy paper are being sought, perhaps the Advisory Committee could pull some key elements out of the paper and write a short letter to HHS Secretary Sebelius. The letter could stress the importance of residual dried blood spots as a resource for children's health, as well as address the issue of public trust, noting that the residual specimens from newborn screening can be used as a resource safely and that OHRP says it is legal and ethical to use them. The Genetic Alliance is working on ways to do this in a way that does not violate public trust, and a short letter from the Advisory Committee could help. Dr. Howell replied the *Federal Register* public comment process would take just 45 days, so he thought the Advisory Committee could get the paper out fairly quickly. He said the situation in Texas was fairly well settled in terms of what had been legally agreed to.

Dr. Getchell said that she had concerns about Recommendation #4, which discusses the use of anonymized samples for program evaluation. She noted that states are using the samples for the purpose for which they were collected; anonymizing them would defeat the purpose. Dr. Lloyd-Puryear and Dr. Howell said the paper would be revised in accordance with OHRP's comments, and Dr. Getchell said she thought that would address her concerns. Ms. Johnson also indicated that she would correspond with Dr. Getchell to make sure she was addressing her concerns. Finally, Ms. Johnson stated that the revised paper on policies regarding the retention and use of dried blood spots would be sent out to Advisory Committee members so that they could see it again.

VI. UPDATE ON THE RESPONSE TO COUNCIL ON BIOETHICS' REPORT ON NEWBORN SCREENING

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At the Advisory Committee's meeting in September 2009, Dr. Howell announced the formation of a workgroup chaired by Dr. Trotter to prepare a draft response to the 2008 report of the President's Council on Bioethics entitled *The Changing Moral Focus of Newborn Screening.* The 2008 report expressed reservations about the American College of Medical Genetics (ACMG) uniform newborn screening panel, which the Advisory Committee endorsed in July 2005, so Advisory Committee members thought that it was important to prepare a response. The President's Committee on Bioethics that wrote the report was disbanded by President Barack Obama.

In this session, Dr. Trotter outlined a draft response from the Advisory Committee to the 2008 report of the President's Council on Bioethics for the Advisory Committee's review and comments. Dr. Trotter noted that the composition of the President's Council on Bioethics was such that its members' knowledge about newborn screening was quite limited. He stated that his goal at this meeting was to get comments from Advisory Committee members so that the workgroup could finish the document. He thanked Advisory Committee members Dr. Fleischman, Dr. Howell, Dr. Calonge, Dr. Lloyd-Puryear, as well as Dr. Alex Kemper, for their contributions to his presentation.

The purpose of President's Council on Bioethics' 2008 report *The Changing Moral Focus of Newborn Screening*, according to that report, was "to foster public awareness of the practice of newborn screening, the ethical principles that have guided it until now, and the ethical problems posed by its current and future expansion." The overarching question addressed in the 2008 report is: What ethical principles should guide the practice of newborn screening in the United States? The conclusions in that report came down to seven elements that the President's Council on Bioethics recommended be part of "an ethically sound approach to public policy in newborn screening."

Dr. Trotter went through each of the seven elements the President's Council on Bioethics recommended be part of "an ethically sound approach to public policy in newborn screening," along with the proposed comments and response from the Advisory Committee. He emphasized that the third and fourth elements particularly needed the Advisory Committee's response.

1. Reaffirm the validity and continuing relevance of the classical Wilson-Jungner screening criteria (WHO, 1968).

Proposed comments:

· The 10 criteria for population-based screening developed in a 1968 World Health Organization monograph by James Wilson and Gunnar Jungner were developed basically for adult chronic disease but have been incorporated by almost everyone in screening since. The Wilson-Jungner criteria have been summarized in an article by Dr. Fleischman as "screen only if you can treat."

· The Advisory Committee believes that implications of this recommendation of the President's Council on Bioethics are that the core newborn screening panel developed by the ACMG and endorsed by the Advisory Committee may not meet the Wilson-Jungner criteria; that evidence-based decisionmaking is lacking; that additions to the panel may not meet the criteria; and that other criteria have no bearing on newborn screening.

· Since 1968, there has been considerable progress in the field of newborn screening.

o In 1975, a report on genetic screening prepared by the National Academy of Sciences' National Research Council (NAS/NRC) broadened the concept of "benefit" from newborn screening to include not only direct medical treatment of the child (the number one concern), but also to facilitate management decisions that will benefit the child (e.g., decisions regarding supportive care), to inform subsequent reproductive decisions for families (e.g., regarding a second child), and provide knowledge regarding rare diseases.

o In 1991, the American College of Medical Genetics (ACMG) was created and gave the medical genetics world a forum. Tandem mass spectrometry (MS/MS) emerged as a newborn screening technology in the 1990s and totally changed newborn screening, leading to the creation in 2003 of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children.

o In 2005, an ACMG expert group reviewed the available evidence and recommended a uniform newborn screening panel that was subsequently endorsed and adopted by the Advisory Committee on Heritable Disorders in Newborns and Children. The ACMG said that newborn screening policy should be driven by "what is best for the affected infant." The ACMG expert group that developed the uniform newborn screening panel utilized both the Wilson-Jungner screening criteria and NAS/NRC criteria to come up with a new set of criteria for newborn screening (specific and sensitive test, sufficiently well understood natural history, available and efficacious treatment for the infant (management and support), family (inform subsequent reproductive decisions), and society (knowledge about a condition). A benefit to research studies was not one of the criteria. Finally, the ACMG expert group said that states would make the final decisions about newborn screening policies.

o In the period 2006-08, workgroups of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children have developed the "Calonge report" on criteria for and the decision process for adding conditions to the uniform panel and other reports that clarify what criteria should be used in decisions related to newborn screening.

Advisory Committee's response:

· The Advisory Committee believes that the ACMG criteria for including conditions in its recommended uniform newborn screening panel are consistent with the Wilson-Jungner and NAS/NRC principles. There is documented benefit to the affected infant from early detection. There is a reliable screening test that is feasible to use in a public health setting.

2. Insist that mandatory newborn screening be recommended to states only for those disorders

that clearly meet classical criteria.

Proposed comments:

· The Advisory Committee believes that the 29 core conditions in the ACMG's uniform newborn screening panel, which has been endorsed by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, do meet the 1968 Wilson-Jungner criteria and also meet the criteria of the NAS/NRC.

· "Secondary conditions" are conditions picked up by laboratory findings incidental to the testing procedure or as a consequence of clarifying the differential diagnosis of a core condition on the uniform newborn screening panel.

3. Endorse the view that screening for other conditions that fail to meet classical criteria may be offered by the states to parents on a voluntary basis under a research paradigm.

Proposed comments:

· "Classical criteria" are limited to the original 10 Wilson-Jungner criteria from 1968. The 2008 report of the President's Council on Bioethics Council cited the Massachusetts experience which then used 10 core mandatory conditions that the council thought met the classical criteria, but it thought that all the other conditions were optional.

Advisory Committee's response:

· The Advisory Committee believes that there is a need to move forward beyond the Wilson-Jungner criteria from 1968. Newborn screening is a far different animal than could have been imagined in 1968. In fact, newborn screening has even moved beyond the 1975 NAS/NRC report. The Advisory Committee has wrestled with and come up with a process that is appropriately robust in making this decision for criteria. When conditions do not meet the expanded criteria, there is clearly a role for research within newborn screening programs. We need that to both enhance our screening techniques and make them better and better. You need them to study disorders so that if they become candidates in the future, as is virtually certain to happen, we have data on them.

4. Affirm that when the differential diagnosis of some targeted disorders entails detection of other poorly understood conditions [that would not otherwise be suitable candidates for newborn screening], such results do not need to be transmitted to the child's physician or the parents.

Proposed comments:

· The Advisory Committee believes that the implication of this recommendation is that the detection of disorders other than the targeted disorders via differential diagnosis of the targeted disorders is a surreptitious way to advance newborn screening beyond what it should be.

· The Advisory Committee believes that another implication is that individual states may

choose to suppress incidental information about conditions that is developed as a consequence of differential diagnosis of a targeted disorder and that states may choose to require informed consent at the time newborn screening is performed.

· Laboratory findings incidental to a newborn testing procedure or as a consequence of clarifying the differential diagnosis of a core condition in the uniform newborn screening panel are an integral part of the testing process for the core conditions on the panel.

· The Advisory Committee believes that there are several reasons to reveal such incidental findings. If a state discovers that a child is affected with a rare disease, it should report that information. It is patently unfair and unreasonable to disregard these results. Such information can help families avoid a "diagnostic odyssey," help inform reproductive decisionmaking, inform decisions about early supportive intervention for the child and family, and enable families to seek out clinical research studies related to the disorder.

· Seeking informed consent at the time newborn screening is done is not appropriate for the core conditions. Informed consent is required for research studies, but would be confusing for the incidental findings.

5. Encourage the states to reach a consensus on a uniform panel of conditions clearly meriting mandatory screening.

Advisory Committee's response:

· The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children serves this purpose.

6. Urge a thorough and continuing reevaluation of disorders now recommended for inclusion in the mandatory screening panel, to ascertain whether they genuinely meet the classical criteria that would justify mandatory screening of all newborns, or whether they instead are suitable candidates for pilot screening studies.

Advisory Committee's response:

· The Advisory Committee believes that continual evaluation of the national newborn screening program is appropriate and ongoing. Organizations that perform such evaluation on a continuing basis include the National Coordinating Center (NCC) for the Genetics and Newborn Screening Regional Collaborative Groups, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, the Secretary's Advisory Committee on Genetics, Health, and Society, and the National Newborn Screening Clearinghouse.

7. Reject any simple application of the technological imperative, i.e., the view that screening for a disorder is justified by the mere fact that it is detectable via multiplex assay.

Advisory Committee's response:

· The Advisory Committee notes that if all other criteria are met, the review process looks at technology to answer three questions:

- Is there a suitable test available?
- Can it meet public health needs on a national basis?
- Is it economically reasonable or feasible?

Conclusion. Finally, Dr. Trotter presented the following conclusions:

· Newborn screening is a state-based, established, and effective public health program. In fact, it is the model for early diagnosis and treatment.

· The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children has moved well beyond the seven elements noted in the 2008 report of the President's Council on Bioethics. The Advisory Committee has created a structured, evidence-based assessment that supports a consistently rigorous, iterative, and transparent approach to making these recommendations regarding broad population-based screening for rare conditions.

Questions & Comments

Dr. Howell asked whether any Advisory Committee members had comments or questions for Dr. Trotter about the draft response from the Advisory Committee to the 2008 report of the President's Council on Bioethics he had proposed.

Comments on Element #4. Dr. Calonge noted that there is variation in the position among states and among nations with respect to the disclosure or suppression of incidental results about secondary conditions on the uniform panel obtained via differential diagnosis. He said although he understood Dr. Trotter's position with regard to not suppressing information about such results, he believes there are in-depth arguments on both sides of the issue.

Observing that the detection of an underlying condition might not fully capture the phenotypic expression of that metabolic condition, Dr. Calonge expressed concern that a condition might be detected that would never actually be expressed. Dr. Calonge went on to say that maybe there should be an attempt to find some compromise. Thus, Dr. Calonge suggested that if the Advisory Committee moves forward with a strong recommendation not to suppress incidental results, that perhaps the Advisory Committee should say not just report the results, but also recommend the development of a uniform approach to provider and parent education about the result and the lack of uncertainty that surrounds it and the need to do followup.

Dr. Trotter agreed with what Dr. Calonge had said, noting that what he had not made clear in his presentation was that he had been separating out the variance of unknown significance. Dr. Trotter agreed that criteria to help figure these issue out were needed. Dr. Howell remarked that research to follow up on these abnormalities to figure out what they mean is also needed. Dr. Trotter agreed.

Dr. Rinaldo said the distinction between target condition and other possibilities is usually made

clear only after confirmatory testing, and it is not realistic to suppress the results from newborn screening until confirmatory testing. The point that needs to be made clear is that newborn screening programs are screening for markers, not conditions. Most markers require a differential diagnosis. Dr. Trotter concurred. Dr. Fleischman, noting that a new President's Council on Bioethics is being formed by President Obama, to replace the one he disbanded, said he thought that the previous council advocated suppressing the information about secondary conditions completely, not doing confirmatory testing or anything with the information. For that reason, he said, he thought Dr. Trotter's argument came a step before what Dr. Rinaldo was talking about. Dr. Rinaldo asked Dr. Fleischman for a practical example, noting that in the vast majority of cases, it is impossible to figure out the difference between primary condition and secondary condition on the newborn screening panel until a diagnostic laboratory provides a diagnosis. He emphasized that the newborn screening laboratory should not falsify a result. Dr. Fleischman said he did not want to argue the issue.

Comments on Critical Issues to Cover. Dr. Fleischman stated that he thought there were a few critical issues that Dr. Trotter should focus in writing a report from the Advisory Committee in response to the 2008 report of the President's Council on Bioethics. Specifically, Dr. Trotter should focus on clarifying the following misconceptions in the report.

1. The President's Council on Bioethics mistakenly thought that the justification for mandatory newborn screening rests in the ability to do intervention and treatment. The Advisory Committee's report should clarify this misperception.

2. The President's Council on Bioethics mistakenly believed that the secondary conditions on the uniform newborn screening panel were not avoidable in the present technological process; they thought that the secondary conditions on the uniform newborn screening panel were just a surreptitious way for labs or pediatricians to diagnose more diseases. The Advisory Committee's report should clarify this misperception.

3. The Advisory Committee, for reasons stated by Dr. Calonge, does not believe in the suppression of information generated through the ethical process described in item #2 to families if it is information that might affect their child's and their lives. Thus, for example, Dr. Howell said, if you are doing tandem mass spectrometry (MS/MS) and see information suggesting that child could have a core condition but subsequently do some testing and learn that the child has a secondary condition, you should tell the family what you have found.

Dr. Rinaldo said that the President's Council on Bioethics had engaged in a campaign of deliberate misinformation since the publication of the ACMG's uniform newborn screening panel, which has been endorsed by the Advisory Committee. The 2008 report of the President's Council on Bioethics is a part of a campaign of disinformation. Dr. Rinaldo said that many members of the Advisory Committee had tried to explain these facts to the President's Council on Bioethics, but the council just refused to listen.

Dr. Watson suggested clarifying the issue by noting that there were 25 secondary conditions in the ACMG's newborn screening panel. Of those, 22 are conditions for which the marker identifies the patient; for 3 of the conditions, the marker may identify something totally different.

The ACMG agreed that any significant results should be reported out.

Dr. Ohene-Frempong gave an example of hemoglobin H disease (Hgb H). Although the Advisory Committee is considering Hb H disease at this meeting, the marker for this condition has been available for decades to all the newborn screening programs. Either default or by decision, however, most states do not even report the presence of hemoglobin markers. Thus, it is not a very far-fetched example of something that probably should have garnered some followup. It is not an easy marker to confirm, because it decreases after birth, so it does not lend itself to traditional confirmatory testing. Most newborn screening programs in the country do not report this marker even though it is a marker of hyperthalassemia for most of these children.

Dr. Dougherty said she did not think it was quite right to say that the ACMG expert group that developed the uniform newborn screening panel utilized did a careful review of the evidence for all of the Wilson-Jungner screening criteria. The Advisory Committee unanimously adopted that report, but agreed to use a quite different review process for the future. She said she would not sign off on something that said all those criteria were followed by the ACMG expert group.

Dr. Howell said he thought that Dr. Trotter had done a wonderful job and asked whether anyone had any concerns about Dr. Trotter and his workgroup proceeding to write a paper based on his presentation and the discussion by Committee members to clarify some of the misconceptions in the 2008 report of the President's Council on Bioethics. He indicated that the Committee would have an opportunity to review the paper before it was finished. There were no objections, and Dr. Howell indicated that he thought that Dr. Trotter had support from Advisory Committee members to proceed. Dr. Trotter requested that anyone with additional comments send them to him by e-mail.

VII. SCID NOMINATION: UPDATE ON THE EVIDENCE, PUBLIC COMMENTS, AND COMMITTEE DISCUSSION

As background, Dr. Howell explained that at its meeting on February 26-27, 2009, the Advisory Committee approved a letter to Dr. Jennifer Puck, the nominator of severe combined immunodeficiency disorder (SCID) to the uniform newborn screening panel, stating that the Committee thought that the nomination was very strong recommendation but five conditions that had to be met before the Committee would reconsider the nomination of SCID for the Committee's uniform screening panel.

Dr. Howell noted that Dr. Puck and her colleagues had submitted a revised nomination package to the Committee that also provides clarification of the definition of SCID (under Tab #10 in Committee members' briefing materials), so an important issue for the Advisory Committee at this meeting is definition of the condition being nominated for inclusion.

Dr. Howell said the Advisory Committee's deliberations on SCID offer an opportunity for the committee to consider a mechanism or a model in which the committee develops a means for approval or the addition of the uniform panel either as a primary or secondary condition that is contingent on collecting data to monitor the screening program. He suggested that the Advisory Committee consider defining a subcategory in its recommendations that would be applicable to

this situation where the condition is an important one to be nominated and the Committee requires or has as a condition of approving that nomination the acquisition of certain information or material.

A. Nomination of Severe Combined Immune Deficiency (SCID)/T- Lymphocyte Defects to the Recommended Newborn Screening Panel: Addressing Gaps in the Evidence

Jennifer Puck, M.D.
Professor of Pediatrics
Pediatric Clinical Research Center
Children's Hospital
University of California, San Francisco (UCSF)

Dr. Puck prefaced her presentation by saying that she was impressed with the Advisory Committee's process for considering nominations to the uniform screening panel. She noted that the external Evidence Review Group's report indicated that the major weakness of the nomination of severe combined immunodeficiency disorder (SCID) was "whether there are sufficient population-based data to evaluate the clinical validity of the TREC (T-cell receptor excision circles)-based screening test. The five gaps in the evidence for SCID identified by the Advisory Committee pertained to the following:

1. Prospective identification of at least one "real" SCID case through newborn screening.

2. Willingness and capacity of states beyond Wisconsin to implement newborn screening for SCID [Wisconsin and Massachusetts running pilot programs]

3. Test reproducibility, continuance of false positive rate with TREC-based screening of <0.1%

4. Standardization; laboratory proficiency testing

5. Costs and availability of resources to appropriately address the costs.

Dr. Puck addressed each of these five topics in succession, as well as the adequacy of followup and treatment of newborns found to have primary immune deficiencies.

1. Prospective Identification of "Real SCID Cases. SCID, the original primary target of TREC-based screening, encompasses a group of genetic disorders characterized by very low or absent T lymphocytes (T-cells). T cells are the conductors of the immune system, and when T cells are not present, they cannot help B lymphocytes (B cells) make antibodies. With their ability to resist infection severely compromised, infants with SCID are at a high risk of life-threatening susceptibility to infections. There exist more than a dozen known and additional unknown SCID genes.

Dr. Puck emphasized that in addition to SCID, several related conditions can have very low T

cells and similarly pose a risk of susceptibility to life-threatening infections in the individuals that have them. Such conditions include severe DiGeorge syndrome; folate receptor deficiency; and lymphangiectasia or chylothorax with T cell sequestration and loss. Moreover, Omenn syndrome and SCID with maternal T- cell engraftment are conditions where T cells exist, but they are ligoclonal T cells instead of a diverse repertoire of newly minted thymic emigrant T cells able to conduct the orchestra of the immune system.

Infants with SCID or any of the other conditions just mentioned should receive prophylactic anti-infective therapy until their condition is fully worked up and understood and addressed. Moreover, it is essential that infants with such conditions *not* receive the live, attenuated rotavirus vaccine that is currently recommended by the Centers for Disease Control and Prevention (CDC) for infants under 3 months of age. The package insert for rotavirus vaccine does say that this vaccine is not for infants with HIV/AIDS or for patients with any disease that affects the immune system, but we do not currently have a way of knowing which infants might have something wrong with their immune system. In some cases, SCID has been diagnosed when infants developed and thereby experience severe prolonged diarrhea from the vaccine.

Work done by Dr. Buckley indicates that TRECs are a good physiological correlate with a diverse T cell pool. SCID and all of the other aforementioned conditions are characterized by very low or absent TRECs that can be detected at birth. Moreover, Dr. Buckley's work indicates that the TREC assay is a good way to monitor the production of new T cells.

2. Willingness and Capacity of States Beyond Wisconsin to Implement Screening for SCID. Dr. Puck said that Wisconsin and Massachusetts are now screening newborns for SCID and that several additional states are now ready to run pilot programs. Funds for such screening initiatives were recommended by the Advisory Committee a year ago. Dr. Puck also said that she is doing a targeted trial of SCID screening among the Navajo, a population known to have a high incidence of SCID. Additional details about ongoing population-based SCID screening programs in Wisconsin and Massachusetts were provided by Dr. Jack Routes from the Children's Hospital and Health System at the Medical College of Wisconsin and Dr. Anne Marie Comeau from the New England Newborn Screening Program at the University of Massachusetts.

A. Wisconsin's Pilot Population-Based SCID Newborn Screening Program. Dr. Routes gave an update on the pilot population-based SCID screening program in Wisconsisn. As background, he explained that Wisconsin began a trial of population-based screening for T-cell lymphopenia and SCID using low TREC as the marker of SCID on January 1, 2008. In 2009, Dr. Routes and his colleagues published an article on their results in the *Journal of the American Medical Association*.

As of December 31, 2008, Wisconsin had screened 71,000 infants: 64,397 full-term infants and 6,603 premature infants (< 37 weeks gestational age). Abnormal results were defined as TREC < 25; actin normal in infants at least 37 weeks gestational age. Premature infants were rescreened until they reached the equivalent of 37 weeks of gestational age.

Dr. Routes focused on the results for the full-term infants. Seventeen of these screened in Wisconsin's pilot screening program were found to have abnormal results. As shown below,

most of the 17 infants with abnormal results in Wisconsin underwent a repeat TREC assay or flow cytometry (preferred). The findings from Wisconsin's pilot SCID screening program are summarized below.

· 71,000 infants (64,397 full-term infants and 6,603 premature infants (< 37 weeks gestational age).

· Among infants of 37 weeks gestational age, 17 had abnormal results

· 4 had normal repeat TREC assay from new dried blood spot card

· 1 died (metabolic cause)

· 1 parent refused further revaluation

· 11 had flow cytometry

- 3 "Third spacing' lymphocyte loss
- 2 DiGeorge syndrome/22A11 deletion
- 2 Idiopathic T-cell lymphopenia
- 1 Rac2 mutation (an infant who was lymphopenic and had a marked neutrophil abnormality, what might be called a "combined, combined immune deficiency"; successfully treated with bone marrow transplantation)

In summary, Dr. Routes said Wisconsin's experience with the TREC assay has been fantastic. Wisconsin is very pleased with its specificity. When the TREC assay identifies an infant with low TRECs, most of the cases are important causes of T-cell lymphopenia (low levels of white blood cells with important functions in the immune system). There are a low number of false positive results with the TREC assay. The TREC assay is cheap—about $5.50/assay—and the Wisconsin State Hygiene Lab has easily incorporated it into the state's existing newborn screening algorithm.

B. Massachusetts' Pilot Population-Based SCID Newborn Screening Program. Dr. Comeau gave an update on the pilot population-based SCID screening program in Massachusetts. She explained that when Massachusetts decided to implement the program, it first established a wide working group of transplantation specialists, immunologists, and infectious disease experts.

Massachusetts is using a multiplexed TREC assay to screen newborns for SCID, and this assay is a little different from the TREC assay being used in Wisconsin. The multiplexed assay has an internal control, so that every single baby is tested not only for TRECs, but also for a reference gene, RNaseP. Since the beginning in February of 2009, Massachusetts has tested about 77,000 specimens for about 68,000 infants. Its testing algorithm is similar to that used in Wisconsin.

The vast majority of babies with suspect TREC results in Massachusetts have been babies from neonatal intensive care. There have been 272 specimens that prompted a request for a repeat. Of the 272 specimens that prompted a request for a repeat, 51 babies had a recommendation for

flow cytometry. Nineteen of these babies who underwent flow cytometry were shown to have T-cell lymphopenia; the diagnoses of the 19 babies are still being finalized, but they have already found four partial DiGeorge, Jacobsen syndrome, and there have been many thymectomies.

The findings from Massachusetts' pilot SCID screening program since the beginning of February 2009, using a screening algorithm similar to that in Wisconsin, are summarized below.

· 77,000 specimens

· 68,000 infants, and 272 requests for repeat specimens

· 51 abnormal results

· 51 infants recommended for flow cytometry

· 19 infants found to have T-cell lymphopenia (still finalizing diagnoses), but they appear to include 4 partial DiGeorge, Jacobsen syndrome, many thymectomies

Dr. Comeau also noted that the New England Newborn Screening Program in Massachusetts was asked to train other state programs to screen for SCID using a multiplex TREC assay as a part of its grant for CDC. In mid-December 2009, the New England Screening Program gave 1 week of training to staff from the departments of health in Texas, California, and Minnesota. The newborn screening programs in these three states are now ready to perform population-based screening of newborns for SCID. There will be another training session at CDC in early March 2010. Wisconsin's program will also train additional states to use the TREC assay to screen newborns for SCID. When Massachusetts, Wisconsin, Texas, California, and Minnesota begin screening, the newborn population being screened for SCID will be between 750,000 and 1.2 million newborns each year.

3. Test Reproducibility, Continuance of False Positive Rate with TREC-based screening of <0.1 percent. Dr. Puck reported that all of the population-based screening trials of SCID screening are underway (Wisconsin, Massachusetts, Navajo Reservation in Arizona and New Mexico) are showing the reproducibility of the TREC assay screening test and the continuance of a false positive rate of < 0.1 percent.

4. Standardization; Availability of Lab Proficiency Testing. Dr. Puck presented some slides from Dr. Bob Vogt at CDC's Newborn Screening and Molecular Biology Branch pertaining to CDC laboratory support for the TREC assay used to screen newborns for SCID. By April 2010, CDC will have quality control materials to send to any newborn screening lab that needs them. These materials have been made available to Wisconsin and Massachusetts and also Dr. Puck's lab. The samples have high-range, low-range, and undetectable TRECS. The people who have run them in the different labs have had very consistent results across the states. Dr. Vogt shared a graph with a series of dried blood spot calibrators that showed very good consistency in the TREC assay being done. In addition, the laboratory training and education that the CDC has taken on as a mandate has commenced in Massachusetts, as discussed by Dr. Comeau; CDC and Wisconsin will conduct additional training and education sessions.

5. Costs and Availability of Resources to Address Costs. According to Dr. Puck, the pilot SCID newborn screening programs that that perform TREC assays on dried blood spots to screen newborns for SCID have found the TREC-based assay to be cheap: Wisconsin ($5.50); University of California, San Francisco, including California archived and Navajo ($5.00); Massachusetts (similar to other screening tests). The CDC, Newborn Screening Laboratory in Atlanta has developed an even simpler method to run the TREC assay, further lowering the per unit cost and the capital investment. Wider application of screening will drive down the cost even more. When considering costs, Dr. Puck added, it is important to think about the costs of not screening for SCID.

Dr. Puck also drew attention to the Primary Immune Deficiency Treatment Consortium (PIDTC), which was funded in September 2009 by the Office of Rare Diseases Research and the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. The PIDTC is a nationwide effort that is dedicated to the followup of all infants with lymphocyte disorders that are treated by cellular therapy—i.e., transplantation or gene therapy. The PIDTC will now enroll and follow up patients with SCID and SCID variants.

Dr. Puck concluded her presentation by saying that it is not necessarily the place of immunologists to tell the Advisory Committee to consider the narrow definition of SCID or a broader definition of T-lymphocyte defects perhaps as a secondary target. She emphasized, however, that there are several public health interests in identifying and intervening in the lives of infants with low TRECs. The public health benefits include (1) avoiding potential harm from an otherwise beneficial health program (rotavirus vaccine program) by ensuring that no live rotavirus vaccine is given to infants with low TRECs for whom it would not be safe; (2) ensuring that infants with low TRECs are evaluated by a qualified expert in immunology without delay; and (3) tracking ultimate outcomes of patients with low TRECs to measure effectiveness of screening, diagnosis, and management.

Questions & Comments

General comments. Dr. Howell asked Dr. Routes what the specific cause of the one death of the newborn with abnormal results in Wisconsin labeled due to "metabolic cause" was. Dr. Routes was not sure what the actual cause of death was, but he said the newborn had a number of abnormalities in terms of liver function tests. Dr. Routes and his colleagues are going back to all the infants that died in the first year with abnormal TRECs in Wisconsin to try to determine the cause of their deaths. He and his colleagues recently got approval from their institutional review board (IRB) to do that, and Dr. Mei Baker has obtained IRB approval at the University of Wisconsin. Dr. Howell said the Advisory Committee would be interested in hearing more about what they learn.

Noting that Massachusetts performed a significantly greater number of flow cytometrics (51 out of 68,000) than Wisconsin performed, (11 out of 71,000), Dr. Howell asked Dr. Comeau and Dr. Routes what accounted for the difference. Dr. Comeau said that she thought it was probably related to the initial screening algorithm, not so much the test as to what prompts a repeat TREC assay and then what prompts flow cytometry. In response to a question from Dr. Howell about the cost of flow cytometry, Dr. Routes stated that Wisconsin uses an abbreviated form of flow

cytometry that detects SCID and costs $100.

Dr. Rinaldo asked Dr. Puck to provide more information about her study of SCID among the Navajo. She said that the study is being run in two hospitals and currently has enrolled about 650 infants. No cases of SCID have been identified by Dr. Puck's screening study at the two hospitals, although there have been other cases of SCID diagnosed late on the reservation.. The incidence of SCID on the Navajo Reservation is about 1 in 2,000 births.

Comments About NIH/NICHD Activities Related to SCID. Dr. Howell asked Dr. Guttmacher, acting director of the National Institutes of Child Health and Human Development (NICHD), to comment on activities by the National institutes of Health (NIH) to help address gaps in information pertaining to SCID. Dr. Guttmacher first stated that as a pediatrician, medical geneticist, and former medical director of the newborn screening program in Vermont, it was a pleasure for him to be NIH's representative to the Advisory Committee.

Dr. Guttmacher then explained that NIH has a solicitation pertaining to an existing contract with Health Research, Inc, of Rensselaer, New York, regarding the addition of a SCID pilot. Dr. Kenneth Pass is the principal investigator. The basic idea is to extend the original contract to permit Health Research, Inc., and collaborators to provide evidence and feasibility of screening technologies related to SCID in the environment of newborn screening by coordinating the evaluation of a large enough screening sample to provide evidence regarding the efficacy of screening for SCID.

Among the research priorities being considered in the contract negotiations are; (1) looking at appropriate screening technologies available for SCID now or within a few months; (2) making sure there exists an ability to provide immediate confirmatory tests and procedures for presumed positive results after screening newborns for SCID; (3) making sure that there exists the capacity and resources for tracking positive cases and for arranging appropriate followup care and referral of identified newborns with presumed SCID in a timely manner; and (4) making sure that there are administrative structures conducive to prospective pilot testing of SCID, including the documentation and ability to obtain approval for human subjects research in a timely manner. The idea is to try to answer questions related to SCID screening that can only be answered with large-scale screening and to get the work done quickly and with adequate quality assurance and quality control procedures in place for accurate assessment of findings. There is also some consideration of extending or enriching the contract to a public/private partnership involving entities other than NIH that might join the initiative.

B. Public Comments in Support of Adding SCID to the Uniform Panel

There were two public comment sessions at the Advisory Committee's meeting in January 2010, one on January 21st and one on January 22nd. The full text of all public comments appears in Appendix A. In a public comment after the presentation about SCID by Dr. Puck and her colleagues (see above), the following individuals made public comments urging the Advisory Committee to add SCID to its recommended newborn screening panel:

· Fred and Vicki Modell, Jeffrey Modell Foundation

· Missy and Mike Bornheimer, Parents of a Baby Recently Born with SCID/Rac2 Mutation in Wisconsin Who Was Cured

· Stacy and James Barrett, Parents of a Baby Recently Born with SCID in Oregon Who Did Not Survive

· Barbara Ballard, SCID Family Network and Immune Deficiency Foundation

Highlights of their comments are presented below.

1. Fred and Vicki Modell, Jeffrey Modell Foundation

Mr. Modell, who along with his wife Vickie established Jeffrey Modell Foundation in memory of their son who lost life to SCID at age 15, urged the Advisory Committee to make history by recommending the inclusion of SCID and other severe T-cell lymphopenia on the uniform newborn screening panel. He noted that the evidence review had raised some important questions about newborn screening for SCID, but those questions have not been adequately addressed. Each day about 11,000 babies are born in the United States, but only about 300 to 400 of those babies are lucky enough to be born in the two states—Wisconsin and Massachusetts—that screen newborns for SCID. Babies found to have SCID or other severe T-lymphocyte defects in Wisconsin and Massachusetts will be diagnosed, treated, and often cured, but babies born with such conditions in 48 out of the 50 states that do not screen for these conditions will be sick throughout their entire lives, and their lives will be short. Mr. Modell noted that even though the Advisory Committee does not mandate the states to adopt these tests, its actions are critical in spurring progress. Once SCID is added to the recommended core newborn screening panel, states will move forward. Screening programs for SCID will be routine, and precious babies will be saved.

2. Missy and Mike Bornheimer, Parents of a Baby Recently Born with SCID/Rac2 Mutation in Wisconsin Who Was Cured

Ms. Bornheimer appeared before the Advisory Committee with her husband Mike, young son Dylan, and an adorable baby named Dawson. She explained that Dawson was born in small town in central Wisconsin on June 12, 2008, shortly after Wisconsin became the first state to screen newborns for SCID. About 12 days after Dawson's birth, the family's pediatrician notified the Bornheimers that Dawson had SCID—also known as "bubble boy disease." The family was devastated, because most babies with this condition do not make it to their fourth birthday. Dawson began to develop infections, but because his immunodeficiency had been detected early via newborn screening for SCID, he was able to be given a successful bone marrow transplant in September 2008 and be completely cured. Ms. Bornheimer said that her days are filled with joy because of Dawson and that she could not express enough thanks to those who played a role in saving her baby's life. She expressed hope that states throughout the country would adopt newborn screening for SCID, so that other young families could feel secure knowing that if any one of them gets a call from their pediatrician like they did, a program of newborn screening can turn a devastating tragedy into the kind of joy that Dawson gives their family every single day.

3. Stacy and James Barrett—Parents of a Baby Recently Born with SCID in Oregon Who Did Not Survive

Ms. Barrett explained that her son Liam was born on January 30, 2009, in Oregon, was not tested at birth for SCID, and ended up having a series of four devastating infections due to SCID that ultimately led to his death on August 17, 2009. Ms. Barrett urged the Advisory Committee to recommend adding SCID to the universal newborn screening panel, so that other children like her son Liam would not have to suffer and lose their lives. The Barrett family's journey with SCID began on June 1st when Liam was admitted to the hospital for failure to thrive; Liam did receive a bone marrow transplant from his 3-year-old sister Rylee once doctors figured out that he had SCID, but with all the infections he had, it was too late to save him. Liam died 8 months after this committee voted to delay acceptance of universal newborn screening for SCID, 10 years after the American Academy of Pediatrics (AAP) called for national newborn screening standards, 6 years after an expert on SCID, Dr. Rebecca Buckley, testified at the first meeting of this committee saying that SCID was a pediatric emergency and should be included in the uniform panel, 2 years after SCID was nominated for inclusion on the uniform newborn screening panel, and 18 months after Wisconsin began screening for SCID. If Liam had been diagnosed with SCID at birth, he might have received a bone marrow transplant before he was overcome by infections and still be alive today.

After Ms. Barrett spoke, Dr. Puck informed Advisory Committee members that the Barretts had requested that the leftover material from Liam's dried blood spot be sent to her lab and screened for TRECS. Dr. Puck performed the screening earlier in the week of the Advisory Committee's meeting and found that there were no detectable TRECs in either the nursery or the two-week blood spot. That means that Liam's condition would have been detected with a TREC test of either of those samples.

4. Barbara Ballard, SCID Family Network and Immune Deficiency Foundation

Ms. Ballard explained that she is the mother of a child with X-linked SCID (the most common type of SCID, which affects only males), runs a support network for SCID families, and is on the board of trustees for the Immune Deficiency Foundation. She criticized the Advisory Committee for not having recommended the inclusion of SCID on the uniform newborn screening panel earlier. She also urged the Committee to remember Liam Barrett, who had the misfortune of being born Oregon, a state that was not screening newborns for SCID, and to vote to recommend universal newborn screening for SCID.

C. Committee Discussion and Action Related to the SCID Nomination

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 asked Advisory Committee member Dr. Buckley, who is one of the leading experts on SCID, to offer her comments on Dr. Puck's presentation before the discussion was opened for general comments. He stated that Dr. Buckley would recuse herself from voting as a member of the Advisory Committee on the SCID nomination because of her research interests.

Dr. Buckley's Comments. Dr. Buckley said that she thought Dr. Puck's presentation was very good and she emphasized several additional points:

· The spectrum of conditions with defective T-cell production is really not known. Dr. Routes' paper shows that there are probably several additional conditions characterized by defective T-cell production that lead to death before a diagnosis is made. The babies look like the Gerber baby before they get sick, and there is no reason to suspect that anything is wrong with them. Without newborn screening, therefore, most babies' conditions go undetected, even in major teaching hospitals, acquire multiple infections like adenovirus or fulminating hepatitis and die before they get a bone marrow transplant.

· In addition to detecting T-lymphocyte deficiencies or lymphopenia, the TREC assay can detect other conditions such as Omenn syndrome, where infants may have very high T-lymphocyte counts. The TREC assay picks up Omenn syndrome, because babies with this condition do not have any recent thymic immigrants; their T cells are all memory T-cells or clonal T-cells. The TREC assay would also be effective in picking up maternal T-cells, which will persist in the fetal and newborn circulation unless the baby can reject them. The maternal T cells might confound a diagnosis based solely on lymphopenia, but the TREC assay, which picks up the memory type, the CD45RO, would still detect these babies.

· The costs of not making a timely diagnosis of a baby with SCID or other primary immune deficiency disorder are important to consider. Data from Dr. Buckley's institution (Duke University Medical Center) included in the evidence review show that if a diagnosis is made before a baby starts getting infections (usually before 3 ½ months of life), the cost of a bone marrow transplant can be $50,000. But if the diagnosis is not made until around 6 months of age, which is the mean time they come, the cost is $1-$2 million, with babies spending all of their residual days in an intensive care unit.

Other Comments. Dr. Howell observed that the issue that applies in the case of SCID—that once you start population screening, you start finding other people with related conditions—is really the story of newborn screening. Dr. Rinaldo, noting the distinction between SCID and related T-cell deficiencies, asked Dr. Puck, Dr. Buckley, Dr. Comeau, and the other experts as to what extent it would be appropriate to classify SCID as a primary target in the recommended newborn screening panel and the other conditions as secondary conditions, knowing these secondary conditions would be distinguished only after confirmatory testing is done. Dr. Rinaldo stated that he felt strongly about where the Advisory Committee should be going in light of the evidence it had heard, but emphasized that the Advisory Committee also needed to think about setting a precedent.

Dr. Buckley replied that the distinction was a matter of semantics, because two of the conditions the Committee had discussed earlier that day—hyperbilirubinemia and critical congenital heart

disease —are actually multiple conditions being considered under a single umbrella. SCID was once believed to be one condition, but now it is known that this condition is due to mutations of at least 13 different genes. Dr. Buckley said she had no problem with making SCID the primary target and other T-cell defects, but she did not think it really mattered.

Dr. Calonge said it is clear that the TREC assay identifies T-cell defects that go beyond SCID; however, the focus of the evidence review was on SCID. He said he would not object if the definition of the target were expanded beyond SCID to make T-cell defects the primary target, but he recommended that the Advisory Committee request a literature review to identify any *potential harms* from screening for T-cell defects that can be picked up by the TREC assay.

Dr. Howell said he did not think there was any problem because the case definition of SCID used for the evidence review was a broad one that went beyond classic X-linked SCID:

Case definition of SCID: For the purpose of this review, severe combined immune deficiency is defined based on the definition for the PubMed medical subheading. SCID is a group of rare congenital disorders characterized by impairment of both humeral and cell-mediated immunity, leukopenia, and low or absent antibody levels. It is inherited as X-linked or autosomal recessive defect. Children with SCID universally have extremely low or absent T-cells and may or may not have B-cells. We have included some specific subtypes, such as adenosine deaminase deficiency, reticular dysgenesis, and Omenn syndrome in the definition of SCID because they are characterized by T-cells; but we recognize that some groups consider these disorders distinct from SCID.

Dr. Calonge asked whether that case definition of SCID used in the original evidence review would capture all of the abnormalities detected in Wisconsin and Massachusetts. Dr. Howell asked Dr. Routes and Dr. Comeau whether the pilot SCID screening programs in their states had picked up any conditions other than those included in original case definition.

· Dr. Routes stated that Wisconsin had identified other conditions. One infant and her sister were identified with an atypical form of a T-cell deficiency and will be transplanted. Moreover, the baby who was given a successful bone marrow transplant (Dawson Bornheimer) had a Rac2 mutation—a "combined, combined immune deficiency" that is actually worse than SCID because it combines a neutrophil defect with a T-cell problem that is not typically considered SCID. As Dr. Buckley pointed out, this baby would have died even faster because of neutrophil problem

· Dr. Comeau said that Massachusetts was screening for SCID, but would identify infants with other primary immunodeficiencies with the TREC assay. Thus, they could help build an evidence base for other conditions and the Committee could expand the definition if that is what you choose to do. She said she did not think that the Advisory Committee needed to go backwards in the evidence review.

Dr. Vockley said he agreed with Dr. Rinaldo that the Advisory Committee had identified a primary condition—SCID as broadly defined in the original case definition used in the evidence review—and could define the other conditions detected by the TREC assay as secondary targets.

Thus, the Advisory Committee can stay to the original nomination and evidence review and not have to say it is changing the process. It just has to recognize that there is more that has to be learned.

Dr. Carol Greene representing the Society for Inherited Metabolic Disorders (SIMD) agreed with Dr. Vockley and Dr. Rinaldo, saying she thought that the evidence review for SCID would suffice for almost everything except for the deletion of a portion of chromosome 22 and that would be a secondary target. Dr. Buckley said that 22q11, if it is a complete DiGeorge, is treatable by a thymus transplantation, and it is urgent to make an early diagnosis for that condition.

Dr. Kus asked what the next step was. Dr. Howell said the decision about the next step was up to the Advisory Committee. He then asked if members thought that everything had been adequately covered.

· Dr. Dougherty observed that the evidence review for SCID had focused on the treatment by transplantation. A new article in the *New England Journal of Medicine* discussing treatment by gene therapy found some harms. She asked whether the Committee would recommend screening and then treatment by transplantation. Dr. Howell replied that the Committee to date has not had specific recommendations on a treatment, but that it would expect the treatment to be the usual treatment, and that is clearly transplantation.

· Dr. Calonge asked whether the Rac2 mutation would fall within the definition of SCID, so that the Advisory Committee could now say that at least one SCID case had been identified prospectively by testing. Dr. Buckley said yes, the Advisory Committee could now say that at least one SCID case had been identified prospectively by testing.

· Dr. Getchell asked for a clarification about whether the screening test being recommended by the Advisory Committee was the TREC assay or also included flow cytometry. Dr. Howell said that he did not think the Advisory Committee was recommending any particular assay other than a proven effective assay. The TREC assay is effective, but there may be other assays that are more specific and cheaper in the future. Flow cytometry is a type of confirmatory test that would be used only in following up babies who had an abnormal screening test. Dr. Buckley explained that flow cytometry (which tells you how many T-cells are there) is one of two types of confirmatory tests. The test that is most crucial is really one of T-cell function. Both confirmatory tests would be done before a baby was officially diagnosed with SCID or other types of T-cell defects. Dr. Skeels, participating by phone, noted that the Advisory Committee's conclusions were all built on the assumption that the TREC assay was going to be the method of SCID newborn screening. He added that from the point of view of state screening labs, the screening method is extremely important.

· Dr. Ohene-Frempong asked, given current algorithms for transplantation for SCID patients, about what percentage would one predict would be transplanted. Dr. Buckley replied that 100 percent of them would have transplantation of one form or another (about 25 percent with matched sibling donors; the rest with other types of transplants such as cord blood transplants, T-cell depleted bone marrow transplants from parents, matched unrelated donor

transplants).

· Dr. Musci asked whether anything in the TREC assay technology is proprietary or has a license associated with it. Dr. Comeau replied that there may be some small licensing with an enzyme that is used but it is otherwise free. Dr. Howell agreed that some of the enzymes used in polymerase chain reaction (PCR) assays such as the TREC assay are proprietary. Speaking from the audience, Dr. Mei Baker from the Wisconsin newborn screening laboratory, explained that for the TREC assay, the sequence is published and she does not believe that there are any licenses associated with it.

Dr. Howell, stating that one SCID case had now been identified prospectively by newborn screening and reiterating that NIH is providing funding to answer questions about SCID that can be answered only with large-scale screening, said it was the Advisory Committee's responsibility is to come up with a recommendation based on the information that has been presented. He asked for a motion.

The following motion, made by Dr. Rinaldo and seconded by Dr. Vockley was approved—after a lengthy discussion of the importance of continually monitoring the effectiveness and outcomes of screening, and amendments from Dr. Calonge and Dr. Kus—by 12 of the 13 Committee members present, with 1 member abstaining (Dr. Buckley); and 1 member absent (Dr. Guttmacher):

Ø MOTION #6 (PASSED 12 yes, 1 absent, 1 abstaining): The Advisory Committee recommends adding severe combined immunodeficiency disorder (SCID) to the uniform newborn screening panel and recommends adding other T-cell lymphocyte deficiencies to the list of secondary targets as a comprehensive entity, with the understanding that the following activities will also take place in a timely manner:

The National Institutes of Health (NIH) shall fund surveillance activities to determine health outcomes of affected newborns with any T-cell lymphocyte deficiency receiving treatment as result of prospective newborn screening.

The Health Resources and Services Administration (HRSA) shall fund the development of appropriate education and training materials for families, public health, and health care professionals relevant to the screening and treatment of SCID and related T-cell lymphocyte deficiencies.

The Centers for Disease Control and Prevention (CDC) shall develop and distribute to performing laboratories suitable dried blood spot specimens for quality control and quality assurance purposes.

Finally, Dr. Howell introduced Dr. Carla Cuthbert, a biochemical molecular geneticist who has recently joined CDC as the replacement for Dr. Harry Hannon, former chief of the Newborn Screening Branch, Division of Laboratory Sciences.

VIII. PUBLIC COMMENTS

In addition to the individuals who made public comments urging the Advisory Committee to vote to add SCID to the newborn screening panel immediately after Dr. Puck's presentation of additional evidence pertaining to SCID, the following additional individuals made public comments during the course of the January 21-21, 2010, meeting of the Advisory Committee:

o Sylvia Au, M.S., C.G.C., Newborn Metabolic Screening Program, Hawaii Department of Health

· Annamarie Saarinen, Parent of a Child with Congenital Heart Disease

· Andrea Williams, Children's Sickle Cell Foundation, Inc.

· Micki Gartzke, VP, Save Babies Through Screening & Parent of a Child Who Died from Krabbe Disease

In addition, Susan Gallagher, the parent of a child with phenylketonuria (PKU), submitted comments by e-mail. Highlights of these individuals' comments are presented below. The full text of all public comments appears in Appendix A.

1. Sylvia Au, M.S., C.G.C, Newborn Metabolic Screening Program, Hawaii Department of Health

Ms. Au urged the Advisory Committee to make sure that the HHS Secretary Sebelius understands that although state newborn screening programs work very hard to help families, they are having a very tough time trying to take on increased workloads with reduced budgets and furloughs. She also urged the Advisory Committee to be sensitive to how its recommendations may affect state programs. Given the budgetary pressures in Hawaii, for example, minimum standards may cause the state to stop paying for certain things they currently pay for, because the state administration wants to cut costs. The Advisory Committee needs to be politically sensitive to what's really happening at the state level and not dismantle what state programs have to advocate for every day.

2. Annamarie Saarinen, Parent of a Child with Congenital Heart Disease

Ms. Saarinen said she had come from Minnesota to urge the Advisory Committee to recommend adding critical congenital heart disease on the uniform newborn screening panel. Her third child Eve was diagnosed with a severe mitral valve defect and enlarged heart two days after being born and received life-saving surgery within a week of her heart stopping. One baby out of every 100 born in this country has a congenital heart defect, making this the most common of all birth defects. Less than a third of these defects are diagnosed prenatally, and routine newborn exams frequently fail to detect such defects. Pulse oximetry is a noninvasive screening method that can be used to detect silent heart defects in newborns. Many fine institutions throughout the country are already using pulse oximetry to screen newborns for this condition. The earlier children with congenital heart defects are detected and treated, the more likely they will be to survive and not have serious developmental problems.

3. Andrea Williams, Children's Sickle Cell Foundation, Inc.

Ms. Williams, who has been involved as a research assistant to Dr. Lakshmanan Krishnamurti with the followup of families with children identified as sickle cell trait carriers by a newborn screening program in western Pennsylvania since 2005, advocated that the Advisory Committee give continued attention to resources around sickle cell trait awareness, genetic counseling and education, proper screening and coordinated followup for everyone. She emphasized that there is a growing population that are in and/or entering their childbearing years that are likely to be ignorant of their sickle cell trait carrier status. To neglect to properly design and fund the education, screening and followup for everyone is to neglect the next generation of parents who will have children with sickle cell disease that will undoubtedly feel the shock that accompanies the diagnosis when one or both parents lack the knowledge of their sickle cell carrier trait status.

4. Micki Gartzke, VP, Save Babies Through Screening & Parent of a Child Who Died from Krabbe Disease

Ms. Gartzke applauded the Advisory Committee for voting to recommend that SCID be added to the uniform newborn screening panel. She also recommended that genetic counselors be considered as possible new nominees to serve on the Advisory Committee.

IX. COMMITTEE BUSINESS—SUBCOMMITTEE REPORTS

For 2½ hours on the afternoon of January 21, 2010, the Advisory Committee's Laboratory Standards & Procedures Subcommittee, Education & Training Subcommittee, and Followup & Treatment Subcommittee held meetings that were open to the public. On the morning of January 22nd, the subcommittee chairs gave reports to the full Committee on their activities, as discussed below.

Before these subcommittee chairs' presentations, Dr. Howell said that it had been suggested to him the previous day that the Advisory Committee should write to the HHS Secretary Sebelius on two areas of health insurance that will be of particular importance to individuals with conditions detected via newborn screening: (1) lifetime caps, and (2) limitations on coverage of preexisting conditions. Dr. Howell said that unless someone objected, he would ask Ms. Johnson to add these two items to the white paper from the Advisory Committee on newborn screening and health care reform that is sent to the HHS Secretary. Several committee members nodded in agreement, and no one objected.

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, said the subcommittee did some long-range planning about where to go in the next couple of years at its meeting on January 21, 2010. He also reported that the new liaison to the subcommittee from the Genetic Services Branch of Health Resources and Services Administration's (HRSA) Maternal and Child Health Bureau is Dr. Sarah Copeland.

In planning about where to go in the next couple of years, the Laboratory Standards & Procedures Subcommittee first reviewed its existing charge, specifically:

· *Charge:* Define and implement a mechanism for the periodic review and assessment of

- The conditions included in the uniform panel
- Infrastructure services needed for effective and efficient screening of the conditions included in the uniform panel
- Laboratory procedures utilized for effective and efficient testing of the conditions included in the uniform panel.

This charge encompasses far too broad a scope of work for the subcommittee to use it as a template for the next couple of years. For that reason, subcommittee members decided to narrow the scope of the subcommittee's work for the next couple of years. It seems that newborn screening applications and technology are likely to be all consuming for the Laboratory Standards & Procedures Subcommittee in the near future. For that reason, the subcommittee will not have time to deal with the issue of other age windows for screening children in the immediate future. Eventually, though, subcommittee will have to address these issues.

Three members of the Laboratory Standards & Procedures Subcommittee serve on the Advisory Committee's internal Nomination & Review Workgroup, and subcommittee members agreed that there is adequate input from the subcommittee with this arrangement. Experience with the conditions nominated to date suggests that technology rarely drives the Advisory Committee's decision about moving a nomination forward. The Advisory Committee is probably going to be focusing almost exclusively on newborn screening in the near future, so the subcommittee recommends that the Nomination & Review Workgroup continue to include a laboratorian, especially one with experience in the implementation of newborn screening.

Two other ideas for the Laboratory Standards & Procedures Subcommittee's work in the near future were proposed at the meeting were reviewing new technologies that are on the horizon and mediating state-to-state interactions in the realm of newborn screening:

· Reviewing new technologies for newborn screening on the horizon

o Get an overview of new enabling/disruptive technologies that will change landscape in big way (e.g., microfluidics technologies) like tandem mass spectrometry changed newborn screening.

o Provide guidance for states making decisions about implementing new screening tests if there are various technologies available, especially early in the implementation phase.. The subcommittee could collect comparative metrics on those and make data available to states. Mike Watson said a lot of committees and consortia involved in this are already collecting this information.

o Consider replacement technologies for existing members of the newborn screening panel if something better arises.

· Mediating state-to-state interactions in the realm of newborn screening

o Review existing interactions and agreements between states.

o Consider backup for minor disruptions outside of a formal declaration of emergency.

o Analyze state lab capacity and regionalization.

o Help disseminate technical information to the states.

Other future projects for the Laboratory Standards & Procedures Subcommittee discussed were the following:

· Finish routine second-tier testing study (report from this study will be ready for presentation at the May 2010 meeting).

· Consider second test expansion.

· Should we suggest tests for removal from the newborn screening panel?

· Compare technologies for hemoglobinopathies (not much done on this yet).

· Delineate technical demands required for TREC assays.

· Survey states for needs related to the subcommittee.

Questions & Comments

Dr. Howell said he was happy to hear that there would be a report from Laboratory Standards & Procedures Subcommittee at the May 2010 meeting on the study of routine second specimens in newborn screening congenital hypothyroidism (CH) and congenital adrenal hyperplasia (CAH). This study is being conducted by the National Newborn Screening and Genetic Resource Center (NNSGRC) and Association of Public Health Laboratories (APHL). *Jelili Ojodu from* APHL confirmed that he would provide an update on the routine second specimen study at the Advisory Committee's May 2010 meeting, Dr. Howell said he looks forward to the presentation of the

results from the study, which will help answer the question of whether all states should be doing the second screens or no states should be doing them.

Dr. Howell, noting that Dr. Vockley had mentioned regionalization of newborn screening, said that regionalization of some of the more complex tests and confirmatory tests seemed to make sense. Is regionalization within the purview of the Advisory Committee? Is it a part of the Genetics and Newborn Screening Regional Collaborative Groups? Is it part of the Laboratory Standards & Procedures Subcommittee? Dr. Vockley said he thinks the answer is yes to all those questions. All of these entities can play a role in raising awareness and putting the possibility of regionalization on the radar screen in a way that individuals cannot.

Dr. Howell said he had attended the last part of the meeting of the subcommittee and found a side discussion brought up by Dr. Rinaldo about the increasing number of situations where the number of an analyte you are looking at is low (rather than high) although labs have been looking for the number to be elevated Dr. Vockley said that as someone who is not a laboratorian, he had thought that abnormal included both high and low levels, so he was surprised to hear that people have not been looking at the low levels. Dr. Rinaldo said mining all the data would probably lead to some interesting findings. Dr. Howell said it would not be necessary to add any tests; it would just require mining the data that already exists.

Dr. Fleischman asked whether the Laboratory Standards & Procedures Subcommittee might be interested in taking up the definition of standards for quality assurance in newborn screening labs. He noted that although the Advisory Committee had argued that quality assurance is a key element of a newborn screening lab program, it was hard to find a clear and crisp definition of what quality assurance means, and there is some disagreement. Dr. Fleischman suggested that perhaps the subcommittee could develop a white paper on quality assurance and quality improvement, saying that these are integral to a newborn screening program and issuing some standards in that regard. Such a paper might be helpful to state when they are considering their residual specimens and length of storage and use.

Dr. Vockley said he thought that having the Laboratory Standards & Procedures Subcommittee develop a white paper on quality assurance and quality improvement was a great idea that could have an important impact. Moreover, he said, the subcommittee could probably do this with minimal work just by looking at current standards in the literature, etc., and acknowledging that these are part and parcel of newborn screening lab activities in the current environment. Dr. Howell said he thought that it would be valuable for the Advisory Committee to publish a document such as the one Dr. Fleischman had suggested.

Dr. Carol Greene said she thought it would be good to make it clear to newborn screening labs that there are legal requirements to save samples and to do quality assurance. She stated that the Centers for Disease Control and Prevention (CDC) person staffing a workgroup on good lab practices that she chairs has looked over all that information. Dr. Greene will be presenting on this topic to the Clinical Laboratory Improvement Advisory Committee (CLIAC) on February 8, 2010, . There will be an opportunity for comment when the document becomes publicly available on February 8th, and if that workgroup has not made it strong enough, that would be a good place to bring it up. Dr. Greene said that Association of Public Health Laboratories (APHL)

documents will have something to say about these topics as well. She said that the workgroup's document on good laboratory practices would be publicly available on February 8, 2010. CLIAC will probably accept it with some modifications, and then publish it in an issue of *Morbidity and Mortality Weekly Report.* In the meantime, she agreed to communicate with Dr. Vockley about this document and state laws (e.g., in New York) that have a role in laboratory quality assurance.

B. Education & Training Subcommittee Report

Tracy L. Trotter, M.D., F.A.A.P.
Senior Partner
Pediatric and Adolescent Medicine
San Ramon Valley Primary Care Medical Group
Committee Member
Jana Monaco
Organic Acidemia Association
Committee Member/Parent Advocate

Dr. Trotter, who chairs the Education & Training Subcommittee with Jana Monaco, reported that two new members of the subcommittee are Deborah Rodriguez, from the New York state newborn screening program, and Jaimie Higgs, a genetic counselor in the Washington, D.C., area who is employed with GeneDX. Other subcommittee members are Natasha Bonhomme, Colleen Buechner, Dr. Frederick Chen, Dr. Alan Fleischman, Dr. Timothy Geleske, Joyce Hooker, Dr. Thomas Musci, and Andrea Williams.

Dr. Trotter stated that the Education & Training Subcommittee heard updates from several entities at its meeting on January 21, 2010. Natasha Bonhomme from the Genetic Alliance gave a report to the subcommittee on progress that has been made in creating the nation's first Newborn Screening Clearinghouse (NBSC). The goal of the NBSC 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. The development of the Web-based NBSC is a project being undertaken by the Genetic Alliance, the National Newborn Screening and Genetics Resource Center (NNSGRC), and other collaborators with funding from the Genetics Services Branch of HRSA's Maternal and Child Health Bureau, and the NBSC project is off to an impressive start. The NBSC will take advantage of newly established and promising communications technologies that allow just-in-time and point-of-service access for parents and providers. It will integrate electronic health technologies, data standards, data collection and consumer-focused educational materials all in one coordinated system. As reported by Ms. Terry in her presentation, the NBSC website is now active.

In addition to hearing a presentation on the NBSC, the Education & Training Subcommittee heard presentations from the following at its meeting:

· Congenital Conditions Program (Genetic Alliance/HRSA/ National Coalition for Health Professional Education in Genetics)

· Perinatal Family Health History (National Coalition for Health Professional Education in Genetics/Harvard Partners/Genetic Alliance/March of Dimes)—a report by Joe McInerney and Emily Edelman about a very fascinating, point-of care, interactive, tablet-PC-based family genetic history with immediate feedback

· American College of Medical Genetics Foundation—a report by Dave Cotter about a summer internship plan for intense genetic immersion as many as 30 second-year medical students for the summer of 2011

· Educational Task Force of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS)—a report by Kathy Camp and Sylvia Au on a report from the Educational Task Force that will be published later this year

· Genetics in Primary Care Training Institute—a report on a program the subcommittee has been shepherding along for the last year

· Genetics and Newborn Screening Regional Collaborative Groups

· National Newborn Screening and Genetics Resource Center (NNSGRC)

· March of Dimes Foundation

· American Academy of Pediatrics (AAP)—a report on an AAP project with ACMG looking at ACT sheets in which Dr. Geleske is involved.

Dr. Trotter said that the Education & Training Subcommittee did not have time to do anything else but looks forward to broadening the consumer representation in its presentations to the committee in May 2010, as well as to continually try to stay in touch with consumers about how they want to receive information. Now that the Advisory Committee has voted to recommend adding SCID to the uniform newborn screening panel, there will be one more disorder about which to convey information.

C. Followup & Treatment Subcommittee Report

Coleen 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, thanked members Dr. Alan Hinman, Jill Levy-Fisch, Dr. Celia Kaye, Dr. Susan Berry, Dr. James Figge, Dr. Ohene-Frempong,, Dr. Fred Lorey, Dr. Denise Dougherty, Dr. Christopher Kus, Dr. Alex Kemper, Dr. Brad Therrell, and Jill Shuger from HRSA for all of their contributions.

Dr. Boyle noted that the Followup & Treatment Subcommittee's meeting on January 21, 2010, had been a very productive meeting with several presentations. Highlights of the meeting

presented by Dr. Boyle included the following.

1. Activities Related to Long-Term Followup (LTFU) After Newborn Screening. Dr. Boyle explained that for some time now, the Followup & Treatment Subcommittee has been trying to look at issues of LTFU after newborn screening and trying to frame LTFU—identifying the components of LTFU and how to measure them, identifying the roles and responsibilities of the major sectors involved in LTFU, and developing core questions and how to best measure the issue to obtain information needed to ensure optimal LTFU of infants with conditions detected via newborn screening.

· *Progress in developing overarching questions related to LTFU.* Dr. Kus and others are taking the lead in developing a white paper on the overarching questions related to the components of LTFU (care coordination, evidence-based treatment, continuous quality improvement, new knowledge discovery) that can be used to collect data. In September, the subcommittee convened a workshop of experts from those sectors to identify primary questions to be addressed. Since then, Dr. Kus and a subgroup of the subcommittee have tried to move forward in developing those questions. Dr. Kus gave a presentation to the subcommittee on January 21, 2010, and there was a very interesting discussion about the concepts and how to expand and operationalize those.

· *Assistance from the National Committee for Quality Assurance (NCQA*) in *developing measures related to LTFU.* Dr. Lloyd-Puryear and Dr. Boyle, after a presentation on NCQA to the Committee by Dr. Sarah Scholle, asked NCQA to help the Followup & Treatment Subcommittee in developing quality measures in LTFU. They agreed, and HRSA has a contract now with NCQA to help the subcommittee frame overarching questions in LTFU and develop quality measures to help answer those questions.

· *Update on LTFU projects funded by CDC, HRSA, or NIH.* Dr. Sue Berry updated the subcommittee on the status of HRSA and NIH-NICHD NBSTRSB funded LTFU projects, and Dr. Cindy Hinton updated the subcommittee on CDC-funded projects. Recognizing the need for common data elements across all systems, Dr. Boyle and Dr. Lloyd-Puryear have been trying to make sure that the grants they fund complement each other with regard to data elements.

2. The Subcommittee's Medical Foods Survey. Dr. Boyle reported that Dr. Mary Kay Kenney, a statistician with the HRSA's Maternal and Child Health Bureau, who was going to report on the Followup & Treatment Subcommittee's three-state medical foods survey, was not able to attend the meeting because of illness in her family, but work related to that survey has been progressing, and Dr. Kenney has submitted an abstract to present at the upcoming Association of Public Health Laboratories (APHL) meeting. The hope is that Dr. Kenney will provide a full report on the survey at the subcommittee's meeting in May 2010.

3. Short-Term Followup (STFU) Issues After Newborn Screening. At its meeting in September 2009, Dr. Boyle explained that the Followup & Treatment Subcommittee had discussed two potential mechanisms to improve the STFU of infants who undergo newborn screening: (1) state-mandated reporting of abnormal findings from newborn screening; and (2) timely and routine linking of newborn screening information with birth certificates. A subgroup

of the subcommittee consisting of Dr. Deborah Freedenberg, Dr. Brad Therrell, and Dr. Celia Kaye was appointed to make recommendations about what the subcommittee and the Advisory Committee could do to improve STFU after newborn screening.

At the subcommittee meeting on January 21, 2010, Dr. Therrell made a presentation on behalf of that workgroup. The workgroup dismissed state-mandated reporting of abnormal findings from newborn screening as a bad idea (Dr. Boyle is not sure she agrees with that) and focused on improving STFU via the linking of newborn screening information with birth certificates. The workgroup also surveyed states by e-mail and learned that several states include the newborn screening serial number as a field on the birth certificate.

A unique newborn serial number as part of a birth certificate can be used to ensure that every newborn gets screened. It would also make possible the linkage of data between newborn screening and vital statistics programs. Currently, the standard U.S. birth certificate does not contain a field for the newborn screening serial number. The subcommittee thought that such a field should exist. For that reason, the Followup & Treatment Subcommittee offers the following recommendation to the Advisory Committee:

Recommendation: "Newborn screening is an essential core public health activity required in every state. In order to facilitate verification that every child has received screening, the ACHDNC requests that the U.S. *model birth certificate* include a field for capturing the serial number of the initial newborn screening blood collection form [using the format described in the Clinical Laboratory Standards Institute LA4-A5]."

—Send this recommendation to the National Committee on Vital and Health Statistics (NCVHS).

—CDC/HRSA or the Followup & Treatment Subcommittee will work with NCVHS to develop field specifications.

Questions & Comments

Dr. Howell said he wasn't aware that there was a U.S. model birth certificate. Dr. Boyle and Dr. Calonge explained that each state has a different birth certificate, but all states are supposed to use certain core elements.

Dr. Therrell, reporting on results of the e-mail survey conducted by the workgroup appointed by Dr. Boyle, indicated that all but a few states have electronic birth certificates; of the states with electronic birth certificates, 10 states have a field for the newborn screening serial number on the certificate (previously, 11 states had such a field, but Texas removed it); moreover, 4 additional states are adding such a field in the next couple of years. Most states commented that it is hard to get states to add such a field, because their birth certificate is already full of fields and there has to be a good reason to add a new field. Dr. Therrell pointed out that newborn screening is now considered a core element in public health by the Association of State and Territorial Health Officials (ASTHO) and stated that the subgroup recommended putting the field for the newborn screening serial number on the U.S. model birth certificate, so that it would be possible to

validate that every new baby is screened. The Clinical and Laboratory Standards Institute (CLSI) has a standard for state birth certificates (LA4-A5) that includes a format for a newborn screening serial number, and it would be good if states would use that.

Dr. Ohene-Frempong asked for more elaboration from Dr. Therrell about why the field for the newborn screening serial number in Texas was removed. Dr. Therrell said Texas had a field for the newborn screening serial number for about six of seven years after he had pushed for it. The problem was that filling out that field was not required, so hospitals ignored it. Eventually, the field was removed.

Dr. Boyle said she thought it sounded like maybe there were two issues: (1) getting a field for the newborn screening serial number on the U.S. model birth certificate; and (2) getting states to require that the field be filled out. Dr. Calonge stated that getting the U.S. model birth certificate changed is a major undertaking that happens only about every 15 years. Although getting a field for the newborn screening serial number on the model birth certificate is a worthwhile endeavor, Advisory Committee members should recognize that the national standard will not be changed overnight. Still, it is a good thing to set it up in the queue.

Dr. Watson and Dr. Therrell have been in communication with the Joint Commission on Hospital Accreditation about hospital standards related to newborn screening, and the Joint Commission has a critical results requirement that if a critical result comes back, hospitals have to be able to communicate that. If the problem is that there is no standard for filling out the field for the newborn screening serial number on birth certificates, Dr. Watson said he would be happy to work with someone from the Followup & Treatment Subcommittee to help get the Joint Commission to set up standards for newborn screening that would improve the ability to find a baby after screening results came back. Dr. Watson thinks a direct communication pathway is better through the Advisory Committee.

Speaking from the audience, Dr. Nancy Green said she thought that the proposed recommendation from the subcommittee was a good one and suggested expanding it to include the results of newborn screening. Also, Dr. Carol Greene said she thought adding a field for the newborn screening serial number to the birth certificate was a good idea but that she did not think that newborn screening results should be included. Noting that all but one state allow babies to decline newborn screening, and not all babies are born in hospitals, she said that if there is a required field for the newborn screening serial number, there also should be field for "family declined screening' or "woman had baby at home."

Dr. Calonge explained birth certificates vary from state to state, but a huge number of fields and data are collected on birth certificates that do not show on the printed birth certificate. Thus, it would be possible to include newborn screening results on the birth certificate and suppress those results when printing the birth certificate used for identity verification. Two choices are to put the newborn results in the birth certificate data set or to build a permanent link from the birth certificate to newborn screening data and never delete the screening data. Dr. Calonge said he thought it was a good idea for the Advisory Committee to set up the expectation for including newborn screening information on the U.S. model birth certificate, but added that the Advisory Committee should also understand how this idea would actually play out.

Dr. Fleischman said he thought that the Followup & Treatment Subcommittee's proposed recommendation was an extremely important recommendation that the Advisory Committee should move forward. He noted that there is a lack of uniformity of national vital statistics and problems in ascertainment due to that lack of uniformity, and many national organizations and meetings, including the Surgeon General's Conference and the Institute of Medicine (IOM), have recommended strengthening vital statistics starting with the birth certificate, and that such a recommendation should be in the queue.

Dr. Kus, who noted that there is great variation in birth certificates between New York State and New York City as well as among states, suggested the possibility of working directly with states to make changes in birth certificates more rapidly. Dr. Howell said he wondered what was taking the states so long, noting that Florida had just linked its birth certificates to newborn screening information.

Finally, Dr. Howell noted that it seemed to be the sense of the Advisory Committee that it was interested in pursuing the Followup & Treatment Subcommittee's proposal and asked Dr. van Dyck and Dr. Lloyd-Puryear to share their thoughts about what the next step should be. Dr. van Dyck recommended that the subcommittee first develop a short white paper on recommended changes to birth certificates to ensure that all newborns are screened at birth; then work with Dr. Watson to mine everything that has been done; and then come forward as a recommendation through the Advisory Committee to the HHS Secretary. The HHS Secretary oversees the nation's vital statistics program. Dr. Boyle agreed to proceed in the manner Dr. van Dyck suggested. She said that rather than seek the Committee's endorsement of the proposed recommendation, the Followup & Treatment Subcommittee would develop a white paper with recommended changes to birth certificates to present to the Advisory Committee at its meeting in May 2010.

Ø ACTION: The Followup & Treatment Subcommittee will develop a short white paper on recommended changes to birth certificates to ensure that all newborns are screened at birth for presentation to the Advisory Committee at its meeting in May 2010.

X. CARRIER SCREENING FOR SICKLE CELL DISEASE AND OTHER CONDITIONS

As background, Dr. Howell explained that the National Collegiate Athletic Association (NCAA) recommended in 2009 that all student-athletes undergo screening for sickle cell trait (carrier) status. subsequently, the Sickle Cell Disease Association of America (SCDAA), in collaboration with the Health Resources and Services Administration (HRSA), the Centers for Disease Control and Prevention (CDC), and the National Heart, Lung, and Blood Institute (NHLBI), held a meeting in December 2009 to review the level of evidence for sickle cell carrier screening and current prenatal and newborn screening practices.

In this session, Dr. Howell explained, SCDAA chief medical officer Dr. Lanetta Jordan would give a presentation on these developments and SCDAA's recommendations. After her presentation, Dr. Ohene-Frempong, a member of the Advisory Committee who is an expert in sickle cell disease and other hemoglobinopathies, would be the first Committee member to offer

comments. Finally, after the discussion of carrier screening for sickle cell disease, the Advisory Committee would have a broader discussion of carrier screening.

A. Report from the Sickle Cell Disease Association of America's (SCDAA) Workshop on Carrier Screening

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Chief Medical Officer
Sickle Cell Disease Association of America (SCDAA)

Sickle cell disease is a serious inherited blood disorder that can cause pain, serious infections, organ damage, and even death. The condition occurs in individuals who inherit two copies of the sickle cell gene—one from each parent. Dr. Jordan explained that sickle cell trait occurs in individuals who inherit one copy of the sickle cell gene. Historically, sickle cell trait (SCT) has not usually been regarded as a disease state because associated complications have been thought to be either uncommon or mild; however, it has been recognized that individuals with SCT (i.e., those with Hb AS, Hb AC, or Hb AD hemoglobinopathy) do have the potential to pass a sickle gene along to one or more of their children. Dr. Jordan reported that 300 million people have SCT worldwide and 3 million have SCT in the United States.

In June of 2007, the National Athletic Trainers' Association posted a consensus statement promoting screening for SCT. That consensus statement did not receive the support of the Sickle Cell Disease Association of America (SCDAA). In June of 2009, secondary to litigation, the National Collegiate Athletic Association (NCAA) recommended that its member colleges and universities athletic departments confirm SCT status in all student athletes during their required medical examinations. A news release from the American Academy of Pediatrics (AAP) issued in October of 2009 did not support testing for SCT but did emphasize taking common-sense precautions for safe training.

After the NCAA's June 2009 statement, the SCDAA began receiving calls from around the United States seeking the SCDAA's recommendations with respect to the NCAA statement. The SCDAA sought the assistance of the Health Resources and Services Administration (HRSA), the Centers for Disease Control and Prevention (CDC), and the National Heart, Lung, and Blood Institute (NHLBI), and these entities convened a meeting entitled "Scientific and Public Health Implications of Sickle Cell Trait" on December 17, 2009. Dr. Jordan discussed the following four topics in her presentation: (1) the state of evidence on health outcome with SCT; (2) screening, followup, and health education for SCT; (3) ethics, stigma, and discrimination related to SCT; and (4) SCDAA draft recommendations regarding testing for SCT. Highlights of her presentation are summarized below.

1. State of Evidence on Health Outcome with SCT. In 2009, an article by Amoateng-Adjepong and others in the *Journal of the American Medical Association* suggested that physicians should be aware of some possible and probable associations of SCT status with a number of other conditions, although it noted that the average life span of individuals with SCT is similar to that of the general population. The article said that two of the conditions with the most convincing cumulative evidence for an association with SCT were exertional

rhabdomyolysis (rapid breakdown of muscle tissue) and exercise-related sudden death. These are two conditions on which the NCAA has focused its attention.

Dr. John Kark, performing a retrospective analysis using data from 2 million military recruits who experienced nontraumatic death from 1977 to 1981, found that recruits who had SCT (specifically, Hb AS hemoglobinopathy) had a relative risk of 30 vs. a relative risk of 3 for recruits without it. This finding was alarming enough for the military to decide to gather more information and make a determination whether there was an absolute risk for recruits with SCT that the military needed to be concerned about.

For that reason, an interventional trial among 1.8 million basic training recruits was conducted between 1982 and 1991 with a strict protocol to prevent exercise-induced heat illness or illness. The hypothesis was that the prevention of exertional heat illness or injury would reduce mortality for all recruits and significantly so for the recruits with SCT. When the strict protocol to prevent exercise-induced heat illness or illness was followed, not 1 of the 13 predicted deaths occurred. The conclusions of this interventional study were (1) that the prevention of exercise-related death did not require the identification of SCT, because the prevention, diagnosis, and treatment of such illness and injury were unrelated to hemoglobin type; and (2) that exertional heat illness is a preventable factor contributing to sudden exercise-related death in persons with SCT.

The U.S. military's policy has been evolving since 1960. The military now says that evidence supports SCT as a risk factor for exertional health illness or injury, but likely with contribution from still unidentified genetic polymorphisms. The military also says that SCT does not exclude individuals from military duty, although it does preclude their participation in certain military occupations (e.g., diving or flying). Finally, the military says that preventive measures can reduce exertional heat illness or injury.

2. Screening, Followup, and Health Education for SCT. Universal hemoglobinopathy screening has existed in the United States since 2006. For the 90 percent of newborns screened since 1993, the primary purpose of screening was primarily to identify babies with sickle cell disease so that appropriate medical care could be initiated and parents could be educated about the children's health risks.

Clinically significant results are reported to physicians in every state, but there is considerable variation in the reporting by states of newborns' carrier/trait status. SCT was once thought to be completely benign, although we now know that it is not, and there is considerable variation among the states in screening, followup, and health education for SCT: 48 states report carrier/trait status to primary care physicians (exceptions being Florida, Georgia, Louisiana, and New Jersey); 27 report it to birthing hospitals; 17 report it directly to families; 12 report it to sickle cell community-based organizations; and 6 notify hematologists. Moreover, the lack of agreed-upon clinical evidence defining health risks associated with carrier status makes it more challenging to develop protocols that will be adopted across the states for followup and education of individuals with SCT and their families.

Dr. Jordan noted that the costs of rescreening athletes in secondary schools for SCT could be very costly and stated that the funds could be better spent elsewhere. She also raised concerns

that the rescreening would primarily affect African Americans and African American males. SCDAA would want the stigmatization of that group to be minimized. Dr. Jordan also raised several additional concerns related to the proposed carrier/trait rescreening in secondary school athletic programs, including the adequacy of the referral process for the screening, the adequacy of consent mechanisms, the adequacy of mechanisms to protect individuals' privacy, and the adequacy of long-term followup of individuals identified through rescreening.

3. Ethics, Stigma, and Discrimination Surrounding SCT. Dr. Jordan cited a long history of past discrimination related to sickle cell disease and urged everyone to keep this in mind when recommending screening for SCT. The Genetic Information Nondiscrimination Act of 2008 (GINA) has a section related to sickle cell testing:

This form of discrimination was evident in the 1970s, which saw the advent of programs to screen and identify carriers of sickle cell anemia, a disease which afflicts African Americans. Once again state legislatures began to enact discriminatory laws in the area, and in the early 1970s began mandating genetic screening of all African Americans for sickle cell anemia, leading to discrimination and unnecessary fear. To alleviate some of the stigma, Congress in 1972 passed the National Sickle Cell Anemia Control Act, which withholds federal funding from states unless sickle cell testing is voluntary.

Dr. Jordan emphasized that GINA does not apply to members of U.S. military, veterans obtaining health care through the Veterans Administration, or the Indian Health Service; GINA also does not prohibit discrimination in life insurance, disability insurance, and long-term care insurance. For that reason, as the SCDAA continues to educate its client population, it would like to make that population aware of what GINA will and will not do.

4. SCDAA Recommendations Regarding Testing for SCT. SCDAA has 10 recommendations related to testing for sickle cell carrier status:

1. Screening for sickle cell hemoglobinopathy should be part of established universal newborn screening legislation.

2. Genetic information should be protected by Health Insurance Portability and Accountability Act (HIPAA) privacy laws.

3. Hemoglobin testing should be done using hemoglobin high-pressure liquid chromatography (HPLC).

4. The referral process should have experienced professionals who are culturally competent, and professional resources to carriers should also be available.

5. Consent (informed and voluntary) should be obtained.

6. Potential benefits and risks of carrier testing should be communicated.

7. Stigmatization of the carrier by the community should be minimized.

8. Universal precautions should be implemented to prevent exercise-related illness/injury.

9. There should be ongoing continuing professional education and awareness in all disciplines (medicine, sports, education, public health).

10. An appropriate carrier research agenda that complements sickle cell disease research should be pursued. (Sickle cell disease is a major disorder, and research funds should not be shifted from that to research on carrier screening.)

The next step for SCDAA is to take about 10 community-based organization executive directors to a meeting on blood disorders that CDC is holding in March. CDC will have a workgroup with those individuals to help put in place a process of understanding how community-based organizations can work with the states and physicians and CDC, HRSA, and NIH to develop a unified message related to sickle cell disease and also to carrier testing. SCDAA will also be participating in a meeting that the National Institutes of Health is holding on June 3-4, 2010, to set a research agenda related to SCT.

Questions & Comments

Dr. Ohene-Frempong's Comments. Dr. Ohene-Frempong offered his comments about SCT first, saying he was somewhat biased on the subject of SCT because he has SCT. He first learned that he had it just before he was supposed to represent Ghana as a high hurdler in the 1968 Olympics. He played soccer and ran track at a very high level all his life, so he found it hard to believe that SCT could affect him physically in any way.

Dr. Ohene-Frempong emphasized that the post mortem discovery of the sickling of red blood cells in an individual with SCT who has died (e.g., a boxer named Francisco Rodriguez in New York who had heart failure) does not mean that the individual died from SCT. In anyone with SCT who dies (unless death is due to carbon monoxide poisoning), the blood cells will become sickle. Many pathologists do not seem to recognize this.

Dr. Ohene-Frempong stated that he did not think blanket screening of student athletes for SCT is necessary or desirable. He observed that most of the injuries in the United States seem to have been among football players rather than among basketball or track or soccer players. Football players are not the best-conditioned athletes, and some physicians associated with NCAA suggest that the training methods used in football are "insane," but the NCAA does not want to look there. The U.S. military looked at its training practices and made recommendations on how to hydrate recruits, and in the 10-year prospective study, after changing hydration practices, the military wiped out increased mortality completely by just monitoring body temperature and enforcing water drinking at frequent intervals.

Given that the retrospective analysis using data from 2 million military recruits cited by Dr. Jordan showed a very small risk of increased mortality among untrained military recruits with SCT, however, it does appears that there might be link between SCT and something else that we have not been able to find. It may be that people with SCT are at higher risk for heat-related injury because they have a higher risk of getting dehydrated due to hyposthenuria (production by

the kidneys of less concentrated urine). There is something, and the NCAA has the opportunity to work with trainers and pathologists to study this very carefully.

The NCAA could draw lessons from the military by implementing universal precautions to prevent exercise-related illness/injury. Moreover, given that 300 million people in the world have SCT, any health implications of SCT have major public health implications. The United States has led much of the sickle cell disease research in the world and now has an opportunity to do some studies to make recommendations regarding SCT.

Finally, Dr. Ohene-Frempong noted that even though SCT may not confer much or any benefit for people in the United States, it is important to bear in mind SCT offers 90 percent protection against severe malaria, which is a significant benefit for individuals in Africa.

Dr. Howell asked Dr. Ohene-Frempong what suggestions he had for the Advisory Committee regarding the NCAA's recommendations regarding SCT. Dr. Ohene-Frempong said he thought athletic programs in high schools and colleges should follow the example of the military and change their protocols to ensure that student athletes get adequate hydration, rest, etc. He also referred Committee members to something he had written for SCDAA about this that was included under Tab #11 in their briefing materials. In addition, Dr. Ohene-Frempong recommended that since most young people in high school and college in the United States have been screened for sickle cell disease at birth, it would be a good idea to have some linkage between the newborn screening results and counseling of individuals with SCT when they reach the age of reproduction so that they know what the odds of their having children with SCT or sickle cell disease are.

Dr. Howell proposed that a writing group including include Dr. Ohene-Frempong, Dr. Jordan, and others to prepare a draft white paper with comments about SCT and the Advisory Committee's recommendations to the HHS Secretary Sebelius. Dr. Ohene-Frempong agreed to serve on the group.

Ø ACTION: Dr. Ohene-Frempong, Dr. Jordan, and others will develop a draft white paper discussing sickle cell trait issues related to young athletes with the Advisory Committee's recommendations to the Secretary of Health and Human Services for to review by the Advisory Committee at its meeting in May 2010.

Other Comments. Dr. Rinaldo, referring to SCDAA's fifth recommendation regarding SCT, asked Dr. Jordan to clarify whether SCDAA was recommending informed consent for newborn screening. Dr. Jordan said that the fifth recommendation applied only to adolescents and young adults. Dr. Carol Greene from the Society for Inherited Metabolic Disorders (SIMD), said she was going to ask the same question as Dr. Rinaldo and asked whether the SCDAA's recommendations could be changed to make this point clear. Dr. Jordan said that the recommendations had not yet been distributed and could be revised as needed.

Dr. Kus said he thought that SCDAA's eighth recommendation calling for universal precautions was something the Advisory Committee should recommend. He asked Dr. Jordan whether there was a definition of universal precautions implemented to prevent exercise-related illness and

injury. She said that the National Athletic Trainers' Association had posted them on its website (http://nata.org/statements/consensus/heatillness.pdf); however, the National Athletic Trainers' Association suggests that it is challenging to get coaches to comply with the precautions, and the precautions are not followed strictly. Dr. Kus and Dr. Howell agreed that the document the Advisory Committee sends forth should be clear about what the universal precautions are and state that people should follow reasonable precautions when dealing with athletes.

Dr. van Dyck asked Dr. Jordan whether SCDAA in recommending that there be universal newborn screening for sickle cell hemoglobinopathy was recommending that newborns' sickle cell disease and carrier status be communicated to parents. Dr. Jordan said yes, adding that greater uniformity in carrier status reporting among the states would be beneficial because it would allow for followup with carriers (i.e., individuals with SCT) to let them know that they may bear children born with sickle cell disease. Speaking from the audience, Dr. Kathy Hassell, medical director of the University of Colorado's Sickle Cell Center, agreed that standardizing notification of sickle cell disease status and of carrier status among the states would be desirable.

Dr. Hassell urged that the Advisory Committee act promptly to provide guidance regarding screening of student athletes for SCT, noting that the Arizona Department of Health, had convened athletic associations to tell them what to do about this, wrongly making the assumption that the information is vetted, understood, and codified.

Another member of the audience, Dr. Ellen Werner from NHLBI, stated that as part of the Healthy People 2020 initiative, CDC, HRSA, and NIH had proposed and gained approval for a new focus area in blood safety. One of the approved objectives in this focus area is to increase awareness among carriers of their trait status. The federal government will have an obligation to measure progress in this area. Part of the implementation strategy will address the issue not only of informing parents but also of providing health education through critical milestones in the development process so that affected individuals can be aware of their trait status when they go to school, participate in athletics, and reach reproductive age, etc. Dr. Howell encouraged Dr. Werner to work with Dr. Ohene-Frempong, Dr. Jordan, and others in developing the draft white paper discussed earlier.

B. Committee's General Discussion and Action Regarding Carrier Screening

Dr. Howell stated that he thought that carrier screening would become a huge issue in the future as newborn screening technology became more inexpensive, because there are a number of untreatable conditions that would benefit at this point in time from carrier identification (not unlike what has been suggested for cystic fibrosis).

Dr. Howell reminded Advisory Committee members that the Claire Altman Heine Foundation was supporting the establishment of a joint workgroup between the Advisory Committee on Heritable Disorders in Newborns and Children and the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) to consider policies regarding carrier screening for spinal muscular atrophy (SMA). He added that the American College of Medical Genetics (ACMG) has issued a recommendation about carrier screening for SMA, and several NIH institutes recently held a meeting to discuss this issue. At the NIH meeting, several important

issues arose. One is that professional societies would have to deal with implementing prenatal testing; another concern among some groups is that implementing carrier screening might undercut interest and attention to identifying effective treatments.

Ms. Terry said she was at the NIH meeting on SMA carrier screening, and it was a very rich meeting, but she thought that the place for the ongoing heavy lifting to be done in terms of developing policies for carrier screening for SMA and other conditions is a committee such as the Advisory Committee on Heritable Disorders in Newborns and Children. Dr. Guttmacher, who also attended the NIH meeting, agreed with Ms. Terry that the Advisory Committee would be a very good group to look at the complex issue of carrier screening, which has many nuances that need to be considered. He noted that with new technologies making it possible to sequence everyone's DNA, a tidal wave is about to engulf us. Ms. Terry recommended that the Advisory Committee obtain the proceedings from that meeting as the basis for its own work in the area. Dr. Howell said that Dr. Guttmacher was working on a summary and he would try to get the document when it was finished.

Dr. Vockley observed that the conventional wisdom to date has been not to provide carrier screening unless it has immediate applicability to individuals who are not of an age to consent. Giving a child's SMA or other carrier screening result to the child's family eliminates the child's ability to make a decision later in life about whether to receive that information. This observation is relevant to a point that Dr. Vockley made earlier in the meeting—specifically, that although the Advisory Committee will probably be focused on newborn screening for the immediate future, age-appropriate screening is also needed for children at other ages as they mature.

Dr. Howell observed that a lot of heavy lifting is needed on ethical, legal, and social issues related to carrier screening. He has been contacted by the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) about having some joint conversations about overlapping interests and said that if Advisory Committee members do not object, Dr. Howell could contact the SACGHS Executive Secretary Sarah Carr and pursue this idea.

Dr. Fleischman emphasized that dealing with issues related to carrier screening should be not be done merely on a disease-by-disease basis but would require some hard and complex conceptual thinking and advice to the HHS Secretary about the future of preconception and prenatal testing in America. He said that he thought the Advisory Committee on Heritable Disorders in Newborns and Children would be a good group to work on carrier screening issues if it were expanded to include some specific expertise relevant to the topic or collaborated with the SACGHS.

Ø ACTION: Dr. Howell will contact the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) about possibly collaborating on some work in developing recommendations pertaining to ethical, legal, and social issues related to carrier screening.

XI. NEWBORN SCREENING INTEROPERABILITY SPECIFICATION — HITSP/IS92

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Dr. Zuckerman, a consultant to the Initiative on Personalized Healthcare at the U.S. Department of Health and Human Services (HHS), had previously given several 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." AHIC was a federal advisory body chartered in 2005 to make recommendations to the Secretary of Health and Human Services on how to accelerate the development and adoption of health information technology. AHIC successfully concluded its operations in November 2008 and was transitioned from a federal advisory committee to a private-public organization, the National eHealth Collaborative.

Sharing information requires interoperability. Dr. Zuckerman explained that the Healthcare Information Technology Standards Panel (HITSP) has been awarded contracts by the HHS Office of the National Coordinator for Health Information Technology (ONC) to identify interoperability standards to facilitate the exchange of health information using electronic health records (EHRs) and other health information technology products. HITSP is currently charged with harmonizing interoperability standards based on AHIC use cases such as the use case on newborn screening. HITSP's completion of the Newborn Screening Interoperability Specification (HITSP/IS92) represents the culmination of several years of work on the Newborn Screening Use Case. At the most basic level HITSP's interoperability specifications define the necessary business and technical actors, the transactions between them, including the message, content, and terminology standards for information exchange. The standards do not specify any particular system architecture.

The Certification Commission for Healthcare Information Technology (CCHIT) has been awarded a contract by ONC to create an efficient, credible, and sustainable product certification program that certifies that health information products meet specified standards. Other entities have been awarded contracts from ONC to develop a series of prototypes to establish the requirements of a Nationwide Health Information Network (NHIN).

HITSP's Newborn Screening Interoperability Specification (HITSP/IS92). Dr. Zuckerman explained that HITSP's Newborn Screening Interoperability Specification focuses on electronic transfer of results from the newborn screening laboratory to the EHR, building on capabilities that will be required in every certified EHR. The Newborn Screening Interoperability Specification uses the following:

· Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT®) codes for conditions

· Logical Observation Identifiers Names and Codes (LOINC®) codes for tests and quantitative results

· LOINC codes for fields on the filter paper

· Existing HL7 message segments and codes for demographics.

All events and actions in the use case now have proposed standards, including consents and the delivery of policies and educational materials. Both summary and detailed reporting by category or specific condition are possible.

Next Steps Related to Ensuring the Interoperability of Newborn Screening Information.

· Interoperability specifications are evaluated by inspection testers and reviewed by HITSP members prior to HITSP approval. Inspection testing has determined that the Newborn Screening Interoperability Specification (HITSP/IS92) will meet the needs of individual states and will be an ongoing process as revisions are requested.

· The coordination of all newborn screening datasets and codes through the National Library of Medicine and the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children is where the real use case work will continue to take place, and close coordination with HRSA is needed. Although public comments on the HITSP Newborn Screening Interoperability Specification are closed, the National Library of Medicine will continue to accept comments and make necessary changes to messages and codes with the help of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. The Newborn Screening Interoperability Specification (HITSP/IS92) should become the foundation for gathering followup data related to newborn screening, and the Advisory Committee's Laboratory Standards & Procedures Subcommittee and the new workgroup or subcommittee of the Advisory Committee being formed to look at data sets pertaining to the electronic transmission of information on newborn screening should coordinate their needs with the National Library of Medicine's maintenance of the messages and codes.

· Encouraging vendors' participation in the Integrating the Healthcare Enterprise (IHE) Connectathon in January 2011 will help demonstrate interoperability of newborn screening. IHE is a voluntary organization that tests health information technology systems to foster compliance with standards, electronic health record system connectivity, and interoperable exchange of patient health information. IHE runs the Connectathon at the Healthcare Information and Management Systems Society (HIMSS) and has selected Newborn Screening and a Newborn Discharge summary for its next cycle, which will culminate in the IHE Connectathon in January 2011. Adding newborn screening results to a Hospital Newborn Screening Discharge Summary will assist hospitals in making data on these results available automatically after newborns leave the hospital.

· The exploration of new approaches to the Nationwide Health Information Network (NHIN) is underway at the NHIN Workgroup of the HHS Health IT Policy Committee and should ensure that the NHIN will include newborn screening. The Health IT Policy Committee is a federal advisory committee established by the American Recovery and Reinvestment Act of 2009 to make recommendations to HHS Office of the National Coordinator for Health Information Technology (ONC) on a policy framework for the development and adoption of a nationwide

health information infrastructure, including standards for the exchange of patient medical information. The Health IT Policy Committee is chaired by the HHS National Coordinator for Health Information Technology David Blumenthal, and the NHIN Workgroup is one of six workgroups of the committee. The NHIN Workgroup's work on new approaches to the NHIN is exploring the use directories to assist in the delivery of medical information, so that secure electronic mail of medical information is as easy to use as U.S. Postal Service mail is today, with the addition of appropriate security constraints.

· Encouraging the Centers for Medicare and Medicaid Services (CMS) to include newborn screening in future regulations on "meaningful use" of certified EHR technology will help speed adoption the adoption of the electronic specifications for newborn screening. The American Recovery and Reinvestment Act of 2009 authorizes CMS to provide reimbursement incentives for eligible professionals and hospitals who are successful in becoming "meaningful users" of certified EHR technology. It is important to get newborn screening into this equation.

Encouraging the Implementation and Use of Health Information Technology in the Realm of Newborn Screening. The Advisory Committee on Heritable Disorders in Newborns and Children will be an important user of interoperable newborn screening data. The interoperability of electronic health information will improve the efficiency and accuracy of gathering evidence on newborn screening through long-term followup. There will now be opportunities to look not just at reported cases of conditions detected via newborn screening but also at entire populations. Dr. Zuckerman suggested that the Advisory Committee can help drive state-level implementation of interoperable health information technology in the area of newborn screening in several ways:

· Encourage all states to continue preparation for electronic messaging by inspection testing of the standards and developing a plan for how each state will use the standards. The Advisory Committee should consider a letter to the states.

· Explore opportunities to assist states with implementation and encourage collaboration.

· Provide comments to ONC on the Interim Final Rule on Standards and to CMS on "meaningful use" and EHR incentives. On December 30, 2009, CMS announced a notice of proposed rulemaking to implement provisions of the American Recovery and Reinvestment Act of 2009 that provide incentive payments for the "meaningful use" of certified EHR technology. CMS's proposed rule would phase in more robust criteria for demonstrating meaningful use over time.

- In Phase I, which is beginning now, meaningful use will be the use of EHRs to move data.
- In Phase II, meaningful use will require measuring and reporting on health care quality.
- In Phase III, the focus will be on demonstrating improvement in health care quality.

In order to get payments, a health care provider has to be an eligible provider under Medicare or Medicaid; has to be using an EHR product that meets certification criteria; and has to demonstrate use of the EHR in a meaningful way to change health care. An interim final regulation issued by ONC sets initial standards, implementation specifications, and certification

criteria for EHR technology. Both the CMS regulations on incentives and the ONC regulations on certification criteria and standards are open to public comment, and these regulations will control a significant amount of the funds disbursed beginning in October. It is important to get newborn screening into this equation. We are now in the middle of a 60-day window of opportunity to comment on regulations released by ONC and CMS. Although newborn screening did not make it into Phase I, there is a short window of opportunity (perhaps 18 months) to get it into Phase II quality measures and requirements of Medicaid programs. Comments to ONC on the Interim Final Rule on Standards and to CMS on "meaningful use" and EHR incentives could introduce newborn screening into Phase II Medicaid quality measures.

· Encourage CMS to have state programs report on screening by 2013. The Newborn Screening Interoperability Specification (HITSP/IS92) is an important opportunity for all states to review their data reporting practices and to select the codes and methods they will use when opportunities for system change become available. Vendors need the states to specify their requirements in terms of the codes and messages of the specification. Every state needs a plan that identifies the data it will process and how the data will be coded.

Questions & Comments

Dr. Howell noted that there was a 6-page letter from him as the chair of the Advisory Committee dated January 22, 2010, that addressed a number of things that Dr. Zuckerman had mentioned in his presentation. The letter, entitled "Committee Comments on the Specification, Certification, and Stage 1 Criteria for Meaningful Use and Newborn Screening," recommended among other things that the Newborn Screening Use Case be incorporated into the framework for meaningful use of health information technology proposed by on June 16, 2009, by the HHS Health IT Policy Committee.

Dr. Howell asked for comments on the 6-page letter, saying that if Advisory Committee members approved, it could be sent to the Secretary of Health and Human Services, to ONC, and to CMS. Dr. Howell also asked Jelili Ojodu from the Association of Public Health Laboratories (APHL) whether the proposed letter was consistent with comments from APHL. Mr. Ojodu confirmed that APHL was still developing its comments and planned to submit them prior to the deadline but said the comments were not yet public. Ms. Terry stated that the Genetic Alliance would be providing comments, and its comments would be consistent with the proposed letter from Dr. Howell.

Dr. Dougherty said she thought the proposed letter from Dr. Howell was very good but asked that a couple of things be clarified. First, she said she was a little confused by the letter saying "a measure of newborn screening" because the Advisory Committee often talks about the newborn screening system. What would the measure be and where would that measure be collected?

Dr. Zuckerman explained that the measures would have to come from users of EHRs as measures of meaningful use. One of those measures is sending information back to a public health department. Thus, one of the things that medical practices can be asked to count is whether they have sent back information to public health on the outcome of a repeat hearing screening in infants who left the hospital with their last screening saying that they were referred.

Dr. Dougherty said that efforts were being made to get away from measurements that merely required physicians to check something off in a box, because checking something off does not necessarily mean that something happened.

Dr. Zuckerman said if we define a cohort of infants seen in a practice less than 30 days of age, one could go through and determine whether the practice obtained a copy of the infants' newborn screening report and whether that report is part of the infants' EHR. Moreover, performance criteria can be set for what percentage of children reach 30 days of age without having there newborn screening results filed in their charts. Dr. Zuckerman added that the first step in quality measures is the ability to report the data, to report back on how many children with various metabolic or hearing conditions are in a given practice and whether that condition is reported on their problem list. Dr. Zuckerman said that he and his colleagues had worked toward a getting a comprehensive list of SNOMED codes and other codes to enter on the problem list, making it possible to audit records for the number of children with conditions detected by newborn screening that are known to the practice.

Dr. Dougherty said that approach seemed very feasible, but she still had trouble figuring out how to measure whether a health care provider actually reported something to the public health department. Dr. Zuckerman said that is very easy. Every time a health care provider sends something out of a patient's electronic record, the provider is required to keep a privacy log of whom the information is sent to. Thus, it is very feasible to find out how many children have had newborn screening done, how many had referrals for testing, and how many were referred to public health. Dr. Kus said with immunization registries, medical practices already do this. The idea is that if a physician gives an immunization, it must report it back to the registry. Dr. Dougherty suggested giving examples such as this in the letter from Dr. Howell to show that what is being proposed is not entirely novel.

Dr. Howell said the inclusion of newborn screening in the electronic revolution seems to him to be a very important effort. He said that the 6-page letter at Advisory Committee members' desks had been worked on by HRSA staff with input from Dr. Zuckerman. He asked for a motion to send the letter forward.

Dr. Boyle said it was not clear to her from the first two pages of the letter what was missing from newborns, what still needed to be done. Dr. Zuckerman one thing that is needed is validated and nationally recognized performance measures that can be used by health care providers to get federal financial incentives for meaningful use of health information technology. There is no agreement yet on what the performance measures should be, and part of what the Advisory Committee needs to do is to make sure that there are evidence-based performance measures that have been validated and are nationally recognized in 18 to 24 months. Dr. Zuckerman said that a second thing needed is proof of industry readiness. The question that needs to be answered is how many states are able to send their newborn screening reports to EHRs.

Dr. Howell asked Dr. Getchell and Dr. Calonge to comment on states' readiness to send newborn screening reports to EHRs. Dr. Getchell replied that states' readiness varies by state. Delaware is working toward being able to do this in 2013. Dr. Zuckerman said that the 2011 federal regulations will be out in June 2010, sand that is why he is talking about 18 to 24 months. He

added that his hope is that the seven states that are already participating with HRSA and a number of states like Delaware that will benefit from the early adopters are going to make it feasible to reach some level. The Advisory Committee has role in making people aware we are playing catch-up to get ready. Dr. Getchell said labs are working on interoperability in many areas (e.g., infectious disease) and she can't say that they will all be ready by 2013.

Dr. Greene asked if the changes are tied to financial incentives for the meaningful use of health technology, would it be possible that pediatricians may not be able to qualify for the incentives if they are from a state that does not have a system for pediatrician to participate. Dr. Zuckerman said many pediatricians are worried about that for immunizations and will be worried about it for newborn screening when they hear about it; on the other hand, each state Medicaid program sets its own rules, and there is CMS guidance saying do not ask for something in your state that is not widely available or that would represent a barriers to providers getting incentives.

Dr. Getchell asked whether there are financial incentives for states as well as for health care providers. Dr. Zuckerman said there are pools of money for health information exchange, but they are not tied to meaningful use objectives. Dr. Kus said he thought there was some incentive money available through Medicaid for state programs to build data systems, and there has always been some discussion about how that applies to people who are not on Medicaid. But in New York, state programs are being told that there are some dollars available if you work with your Medicaid agency closely as they put their plan together. Dr. Zuckerman noted that, unlike Medicare, Medicaid is a revolving door, and people go in and out. At the State Alliance for e-Health at the National Governors Association, there was recognition that certain state programs in health information technology have to be applied to everyone because transfer in and out of Medicaid and transfer between some state programs is so widespread. Private practices are eligible for incentives for meaningful use of health information technology only if a minimum of 20 percent of patients in the practice are Medicaid patients or 30 percent of the patients are Medicare patients.

Speaking from the audience, Dr. Kathy Hassell, medical director of the University of Colorado's Sickle Cell Center, stated that the terms outlined by Dr. Zuckerman would not be implementable as written in Colorado and Wyoming based on the testing those states do for hemoglobinopathy. She asked if there would be opportunities to change them. Dr. Zuckerman said yes, absolutely. The comment field is always open on the National Library of Medicine website, and efforts are being made to make the changes states request even if a change is requested by only one state.

Dr. Howell asked if there was any opposition to sending the letter forward, and Dr. Dougherty suggested the letter be edited a bit more. Dr. Howell agreed. The following motion, made by Dr. van Dyck and seconded by Dr. Vockley, was approved unanimously by the 13 Committee members present, with 1 member absent (Dr. Skeels):

Ø MOTION #7 (13 yes, 1 absent): The Advisory Committee approves sending Dr. Howell's January 22, 2010, 6-page letter "Committee Comments on the Specification, Certification, and Stage 1 Criteria for Meaningful Use and Newborn Screening" to the Secretary of Health and Human Services, to the Office of the National Coordinator on Health Information Technology (ONC), and to the Centers for Medicare and Medicaid Services (CMS) for public comments,

with the understanding that the document may be edited first.

Dr. Zuckerman thanked Advisory Committee members for their support and cooperation over the last few years and said that he was hopeful that they could look forward to seeing an impact in 2013.

XII. COMMITTEE BUSINESS—CALENDAR AND AGENDA ITEMS FOR MAY 2010 MEETING

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

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

- 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 future meetings to Dr. Lloyd-Puryear.

Workgroup on Electronic Data Issues Related to Newborn Screening. At the meeting in September 2009, Dr. Howell announced the formation of a new workgroup of the Advisory Committee chaired by Dr. Boyle and Dr. Rinaldo 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. Dr. Boyle and Dr. Rinaldo had discussions with the staff at the Health Resources and Services Administration (HRSA), and decided they needed more data expertise on the Committee. For that reason, Dr. Howell has appointed several additional individuals to the workgroup: Dr. Watson, Dr. Alan Hinman, Dr. Alan Zuckerman, and John Eichwald. The workgroup will report at the Committee's May 2010 meeting.

Evaluation of Logistics. Committee members were asked to complete an evaluation form after the meeting to offer feedback regarding the logistics services provided at this meeting by Altarum.

New Committee Members. A Federal Registry Notice has been published in the *Federal Register* calling for nominations of three new members of the Advisory Committee to replace departing members. Moreover, the Committee's Reauthorization Act called for the addition of a medical ethicist and an infectious disease specialist as members of the Committee. Two individuals have been nominated for these positions, and the hope is that they will be approved in the near future.

XIII. EVIDENCE REVIEW WORKGROUP: PRELIMINARY REPORT ON THE LITERATURE REVIEW FOR ALPHA THALASSEMIA/HEMOGLOBIN H DISEASE

Alex Kemper, M.D., M.P.H., M.S.
Associate Professor
Department of Pediatrics
Duke University

In April 2009, Dr. Elliott Vichinsky, a pediatric hematologist at Children's Hospital in Oakland, California, nominated alpha thalassemia/hemoglobin H (Hb H) disease for inclusion on the uniform newborn screening panel. In September 2009, the Advisory Committee's internal Nomination and Prioritization Workgroup recommended sending the nomination of alpha thalassemia/Hb H disease as a candidate for inclusion on the recommended uniform newborn screening panel, and the Advisory Committee asked the external Evidence Review Workgroup chaired by Dr. James Perrin to prepare a review of the evidence for this condition.

In this session, Dr. Kemper gave a preliminary report from the external Evidence Review Workgroup on alpha thalassemia/Hb H disease based on a review of the peer-reviewed published literature. The preliminary report, included in Committee members' briefing materials under Tab #15, contains a detailed description of the literature review methods, summary of evidence from literature review, tables highlighting key data from abstracted articles, a table of studies excluded because they are based on four or fewer cases, and a bibliography. Dr. Kemper explained that the plan is to use this literature review as a springboard to talk with experts in Hb H disease, including investigators, advocates, and clinicians. Thus, the Evidence Review Group's final evidence review for Hb H disease would incorporate additional information obtained from experts and advocates, as well as from assessments of unpublished data.

As an aside, Dr. Kemper noted that the Evidence Review Workgroup had revised its report on Krabbe disease and was planning to submit it to Genetics in Medicine for publication. He also said that the workgroup had prepared an overview paper describing the Evidence Review Workgroup's process that is in press, along with brief summaries from the final reports that the workgroup has completed, in *Genetics in Medicine.*

Overview of Alpha Thalassemia and Hb H Disease. Thalassemia is an inherited blood disorder in which the body makes an abnormal form of hemoglobin, the protein in red blood cells that carries oxygen, resulting in excessive destruction of red blood cells and anemia. Alpha thalassemia occurs when one or more of four gene or genes related to the alpha globin protein are missing or changed (mutated).

· *Normal*. If you are normal, you have four functional alpha-globin (α-globin) genes, and your genotype is αα/αα.

· *Silent carrier.* If you are a silent carrier, you have one deletion, so your genotype would be something like -α/αα.

· *Alpha thalassemia trait*. If you have alpha thalassemia trait, you have two deletions (which can both be on one gene or the other), and your genotype would be something like -α/-α/ or --/αα.

· *Hemoglobin H (Hb H) disease.* Hb H disease is caused by deletions and/or nondeletional mutations of three of the four alpha globlin genes on Chromosome 16.

- If you have Hb H disease in the deletional form, you have three deletions, and your genotype would be --/-α.
- If you have Hb H disease in the nondeletional form and you have
- two deletions and one mutation (T), your genotype would be --/αT α.
- two deletions and the Constant Spring mutation, your genotype would be --/αCSα.

· *Hb Bart's hydrops fetalis*. If you have Hb Bart's hydrops fetalis, you have deletions of all four alpha globlin genes on Chromosome 16, and your genotype would be --/--.

Alpha thalassemia in which all four alpha genes are deleted (Hb Bart's hydrops fetalis) typically leads to fetal death. Of the remaining forms of alpha thalassemia, Hb H disease is the most significant clinically. Hb H disease has a variable clinical course but symptoms include chronic or acute anemia in most of those affected, hepatosplenomegaly, cholelithiasis, or growth retardations. Certain mutations in Hb H disease, including the Constant Spring mutation which is one of the most common, are associated with worse health outcomes than the simple deletional form of Hb H disease.

Rationale for Review. The rationale for the evidence review of Hb H disease as a potential candidate for inclusion on the recommended uniform newborn screening panel is as follows:

· Individuals with Hb H disease may experience significant anemia and growth retardation.

· Presymptomatic identification of infants with Hb H disease may improve health outcomes

· Newborn screening is possible using dried blood spots:

- California has screened since October 1999.
- Newborn screening occurs in critical window for Hb Bart's detection (characterized by tetramers of beta chains) before newborns switch over to the adult form of hemoglobin (characterized by tetramers of gamma chains).
- Current-state hemoglobinopathy screening technologies could be used for Hb H disease.

Overview of the Preliminary Report. For their preliminary review of the evidence on Hb H disease, the key topics addressed by the Evidence Review Workgroup were the incidence of Hb H disease, natural history of the disease, testing (screening and diagnostic) for the disease, treatment for the disease, economic evaluation, and critical evidence needed. Of the 1,362 abstracts selected for preliminary review, 88 articles were selected for in-depth review. Kemper performed a systematic review of articles on Hb H published from January 1989 to October 2009 that met their review criteria. Only 19 articles met the review criteria—12 case series, 6 cross-

sectional studies, and 1 case-control study. The Evidence Review Workgroup evaluated the quality of all of these studies in terms of study design and study goal.

Summary of Findings from the Preliminary Report. Dr. Kemper presented the following findings from the literature review.

1. Incidence. The overall birth incidence of Hb H disease as reported from two studies on California's newborn screening experience ranges from 1/15,000 in one study to 9/100,000 in another study, which also found an incidence of 0.6/100,000 for Hb H with Constant Spring.

2. Natural History. Case-series reports indicate that newborns with Hb H disease can develop anemia, jaundice, and hepatosplenomegaly (especially with the Constant Spring mutation). There are reports of babies being born with Hb hydrops fetalis, which was somewhat surprising to Dr. Kemper because it is usually thought babies with that condition die. In infancy and childhood, individuals with Hb H disease can develop significant pallor, growth retardation, and anemia, as well as pulmonary defects, mild cardiac anomalies, and hepatosplenomegaly. There were numerous reports in adults of significant iron overload and cholelithiasis. It is clear that children with nondeletional Hb H disease are diagnosed at younger ages because of the worse course that they have; these children have high rates of anemia and require more transfusion and more often are at risk for hepatosplenomegaly.

3. Tests for Hb H Disease

- *Screening.* Three articles on screening indicate that the first-tier screening method is the detection of elevated Hb Bart's levels in newborns.
- *Diagnosis.* The second tier is confirmatory diagnostic testing via alpha-globin genotyping for newborns with elevated Hb Bart's. Multiple strategies are used for confirmatory diagnosis (e.g., multiplexed gap-PCR assay to detect deletional and nondeletional alpha thalassemia mutations).

3. Effectiveness of treatment. The Evidence Review Workgroup had some problems finding evidence on the effectiveness of treatment. There were no peer-reviewed publications regarding the effectiveness of presymptomatic treatment of newborns with Hb Bart's among the studies the workgroup reviewed. This does not mean that there is no evidence of the effectiveness of treatment. Discussions with people in California have led the Evidence Review Workgroup to believe that there may be evidence on the effectiveness of treatment that has not been published. The workgroup's next step, therefore, will be to go gather that evidence.

4. Economic evidence. No peer-review publications regarding presymptomatic treatment were identified. There is insufficient evidence to perform an economic evaluation.

In conclusion, Dr. Kemper said the key findings from the literature review of the evidence on Hb H disease were the following:

In comparison with children with deletional Hb H, children with nondeletional Hb H more often had jaundice, hepatosplenomegaly, growth retardation, and blood transfusions.

Most published natural history evidence is from studies on clinically identified populations in older children and adults.

California data suggest that high-performance liquid chromatography (HPLC) for elevated Hb Bart's is a feasible newborn screening method for Hb H disease.

Validated methods for the diagnosis of Hb H disease by confirmatory genotyping exist.

Critical Evidence Needed for Hb H Disease. Dr. Kemper asked the Advisory Committee for guidance about the critical evidence needed for Hb Bart's. He suggested that there were two key questions that the Evidence Review Workgroup planned to go back to try to evaluate:

1. What is natural history during newborn period and first 5 years of life

2. What are the benefits of early diagnosis?

    - What treatment methods are available?
    - What is effectiveness of treatment?

Dr. Kemper noted that Hawaii and states other than California are using a screening process to identify Hb Bart's and thinks that a systematic evaluation of what other states are doing is needed. Dr. Kemper said he recently learned that the Centers for Disease Control and Prevention (CDC) is planning to collect data on this topic.

Finally, Dr. Kemper provided a list of Hb H disease and newborn screening experts that the Evidence Review Workgroup plans to consult. He added that the list will expand to include state public health labs that are actively screening for Hb H disease to see what their experience has been.

Questions & Comments

Before asking for comments from Advisory Committee members, Dr. Howell asked Dr. Vichinsky to make some brief comments on Dr. Kemper's presentation. Dr. Vichinsky said the presentation was very clear and the data were largely accurate in his opinion. He noted, however, that because of the way the literature review was done, some key and important information that has been published in mainstream journals was not included. Dr. Kemper said that the Evidence Review Workgroup had identified some of the papers Dr. Vichinsky was referring to and found them helpful even though they did not meet the specific criteria of the evidence review. Dr. Vichinsky said the papers would not change the analysis but would expand on outcome points, and he would share them with the workgroup. He also offered to share additional data from someone who has a database that shows natural history of patients with Hb H who have the Constant Spring mutation over 25 years with Dr. Kemper; that database shows that all of the individuals with that mutation end up being transfused by age 25. Dr. Howell said that Dr. Vichinsky would certainly be on the Evidence Review Workgroup's interview list.

Dr. Ohene-Frempong asked how many babies had transfusions in the first year of life. Dr.

Vichinsky said judging from data from the database on 23 Hb H patients with the Constant Spring mutation, about 20 percent of patients with the Constant Spring mutation get transfusions in first 2 years; by 5 years, it is 45 percent, and by 20 years, it is 100 percent. Many of transfusions were precipitated by a viral illness. Only about 22 percent of them are major transfusion patients; the rest are intermittently transfused.

Dr. Calonge said he has two big areas of concern with the evidence pertaining to Hb H disease. One is that he does not feel there is any evidence about the natural history of children who have been screened for diseases and followed over time. The children that have come to the attention of a center and been followed over time may not be an accurate representation of children identified via newborn screening. All we know is the extreme phenotypic expression; we want screening-detected Hb H disease, not center-detected Hb H disease.

Dr. Vichinksy said that hemoglobinopathies such as Hb H disease have a higher prevalence among immigrant populations that are growing dramatically over time in the United States. Census data underscore that the epidemiology of the country is going to change. The only easy time to diagnose Hb H disease in the neonatal period. After that, the tetramers are unstable and are not picked up. Dr. Vichinsky also noted that splenectomy is very effective in changing transfusion needs, but it carries a substantial risk of thrombosis.

Dr. Calonge said his second concern about the evidence for Hb H disease was the need for evidence of effectiveness of treatment over time in preventing complications and a lack of clarity about which complications treatment should prevent. Early detection of Hb H disease in the neonatal period does open an opportunity for early treatment. If the treatment intervention is or could be splenectomy, however, that is something to think about. What percentage of the children who are found to have Hb H disease via newborn screening could be expected to have all of the problems that are associated with the cohorts of children that have gone to referral centers? It is important to ensure that screening yields a substantial net health benefit.

Dr. Watson said the Advisory Committee's discussion about Hb H reminded him of the discussion of screening on the previous day, when it was noted that there were different kinds of secondary targets identified as part of a differential diagnosis with an analyte. Dr. Watson stated that ACT sheets are done and will be on the American College of Medical Genetics (ACMG) website in the next few weeks for nine of the non-S allele-related hemoglobinopathies. Since the conditions are being reported out, it thought that the ACT sheets needed to be posted. Dr. Kemper noted that newborn screening reports in North Carolina indicate the presence of Hb Bart's when the reports are looked up in the computer, but there is no guidance about the next step when this is found; there also is no quantification of the amount of Hb Bart's.

Dr. Howell asked Dr. Kemper whether he had enough feedback to assist in the deliberations of the Evidence Review Workgroup. Dr. Kemper said the feedback had been very helpful. Dr. Calonge urged the workgroup not to regard the lack of peer-reviewed articles on the effectiveness of treatment for Hb H disease to be a problem in the evidence review. He said that the Evidence Review Workgroup could serve as a peer review group for the quality of unpublished data on treatment, or ask other people to review the quality so that the Evidence Review Workgroup is not both the reviewer of the information and the incorporator of the

information into the evidence review. Dr. Kemper agreed.

Dr. Ohene-Frempong said that one of the concepts that the Advisory Committee may have problems with is a clear presymptomatic plan for the patients. Transfusion and splenectomy have been discussed as if they are the things to prevent some symptom, but it is not clear what the symptom being prevented is supposed to be.

Dr. Getchell said that many state newborn screening programs may still be using isoelectric focusing and be unable to report the percentage of Hb Bart's. Dr. Kemper said the Evidence Review Workgroup was gathering data on that topic. Dr. Ohene-Frempong said that isoelectric focusing cannot be used to quantitate; if states want to know the percentage of Hb Bart's, they should use high-performance liquid chromatography (HPLC).

Dr. Calonge said that the changing demographics increasing the amount of Hb H mentioned by Dr. Vichinsky suggests that there is an identifiable risk factor. He stated that he did not know that anyone had looked at newborn screening or screening at any age based on risk factors and suggested that this was something the Evidence Review Workgroup might investigate.

Dr. Watson suggested that the Advisory Committee might want to step back and look at the hemoglobinopathies separately because they are very disparate from the conditions detected via tandem mass spectrometry. Dr. Howell concluded the discussion by saying that the Advisory Committee would look forward to the Evidence Review Workgroup's final report on Hb H disease at the May 2010 meeting.

XV. FINAL COMMENTS

Dr. Howell thanked the Advisory Committee for an excellent and very productive two days. He asked Advisory Committee members to think about how to handle conditions that they have previously reviewed and have not recommended be added to the uniform newborn screening panel at this time but have been asked to produce additional information. In the case of severe combined immunodeficiency syndrome (SCID), Dr. Puck and her colleagues did an excellent job. For the future, however, Dr. Howell would like to hear Advisory Committee members' ideas about how to ensure that proponents who are addressing gaps in the information about nominated conditions that the Committee has identified do so in a systematic way. Dr. Rinaldo mentioned that it would be nice to have the original evidence review before Advisory Committee members when proponents come back with evidence related to previously identified gaps.

Dr. Kus said that he and Dr. Dougherty proposed the following wording for Recommendation #4 in the white paper on newborn screening and health care reform presented by Ms. Johnson.

· *Recommendation #4:* Work with the Centers for Medicare and Medicaid Services (CMS) to develop and pilot a payment method for an integrated system of care coordinated through the medical home for children diagnosed through screening.

Finally, with no other business at hand, Dr. Howell adjourned the meeting at 2:10 p.m. on January 22, 2010.

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, M.D.
SACHDNC, Chair

/s/_____
Michele A. Lloyd-Puryear, M.D., Ph.D.
SACHDNC, Executive Secretary

The Committee at its next meeting will formally consider these minutes, and any corrections or notations will be incorporated in the minutes of that meeting.