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

Summary of 18th Meeting
May 12, 2009

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children met by Webcast for its 18th meeting at 1 p.m. on Tuesday, May 12, 2009. The meeting was adjourned at 4:40 p.m. 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

R. 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

New Secretary of HHS. Dr. R. Rodney Howell opened the meeting by reporting that Kathleen Sibelius, the former governor of Kansas, had been sworn in as the new Secretary of the Department of Health and Human Services (HHS) on April 20, 2009. Secretary Sibelius expanded the state of Kansas newborn screening program and put a renewed emphasis on childhood immunization and increased eligibility for children's health coverage. Dr. Howell said the Advisory Committee looks forward to working with her.

New Organizational Representative. Dr. Howell welcomed Mary Willis, M.D., Ph.D., as a new organizational representative member to the Committee from the U.S. Department of Defense. He also explained that, contrary to what had been reported at the previous meeting; Dr. Rinaldo would be staying on as a member of the Advisory Committee. Finally, Dr. Howell noted that the Committee was accepting nominations for two individuals with expertise in bioethics and infectious diseases to serve on the Committee. For each nominee, a letter of nomination, contact information, and CV must be submitted by May 18, 2009. More information is available at the Advisory Committee's Web site: http://www.hrsa.gov/heritabledisorderscommittee/.

Approval of Minutes. Dr. Tracy L. Trotter moved that the Minutes of the Committee's 17th meeting on February 26-27, 2009 (under Tab #5) be approved, and Dr. Gerard Vockley seconded the motion. By voice vote, the Committee unanimously approved the Minutes.

Committee Correspondence. Dr. Howell reported that Dr. Elliott Vichinsky from the Children's Hospital in Oakland, California, had submitted a form nominating thalassemia as a condition for addition to the Committee's recommended newborn screening panel. Health Resources and Services Administration (HRSA) staff will conduct an administrative review.

Dr. Howell drew attention to several items of Committee correspondence (under Tab #5 of Committee members' briefing materials). First, the Committee's letter dated April 7, 2009, to then-Acting HHS Secretary Charles Johnson regarding insurance coverage of medical foods for the treatment of conditions identified through newborn screening.

Second, the Committee's letter dated April 9, 2009, to Dr. Jennifer Puck, the nominator of severe combined immunodeficiency disorder (SCID) for inclusion in the recommended screening panel, in which the Committee stated that it had voted to recommend not adding SCID to the recommended panel at the present time and to recommend that additional studies be done to fill the following five evidence gaps: (1) prospective identification of at least one confirmed case of SCID through a population-based newborn screening program; (2) demonstrated willingness and capacity of additional states to implement newborn screening for SCID; (3) reproducibility of the screening test and continuance of a false positive rate of < 0.1%; (4) absence of laboratory proficiency testing; and (5) an accounting of costs accrued in implementing newborn screening for SCID and the availability of resources to appropriately address the costs.

Third, an e-mail from Dr. Edward Bartlett following-up on comments at the February 2009 Committee meeting about a *Federal Register* notice from the Office for Human Research Protections (OHRP) seeking comments from the public by June 3, 2009, on whether OHRP should make a regulatory change to hold institutional review boards (IRBs) and the institutions or organizations operating IRBs directly accountable for meeting certain regulatory requirements of 45 CFR Part 6.

II. SCID NOMINATION: PROGRESS IN ADDRESSING GAPS IN THE EVIDENCE

In February 2009, as noted in the letter to the nominator, the Committee recommended not adding SCID to the uniform newborn screening panel and also recommended that five critical evidence gaps related to SCID be addressed quickly. In this session, Dr. Robert Vogt from the Centers for Disease Control and Prevention (CDC) and Dr. Duane Alexander from the National Institutes of Health updated Committee members on progress that has been made in addressing two of those evidence gaps—namely, the development of laboratory proficiency materials for SCID testing and the prospective identification of at least one confirmed case of SCID through a population-based newborn screening program.

A. Update from CDC on Laboratory Proficiency Testing Samples for SCID

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

One of the five critical evidence gaps for SCID noted by the Committee was the development by CDC of laboratory proficiency materials for SCID. Dr. Vogt explained that CDC had made awards to Wisconsin and Massachusetts for pilot SCID newborn screening programs. All newborns in those two states are now being screened for SCID and other immune deficiencies that result in a severe decrease in T-cells. The SCID screening test being used in the two states quantitates TREC (T-cell receptor excision circles) in newborns' DNA extracted from blood spots. The tests used in the two states are in principle the same, although there are some differences with the reagents.

CDC is required by virtue of its cooperative agreements with the newborn screening programs in Massachusetts and Wisconsin to provide SCID reference materials to those programs. In March 2009, CDC conducted the first inter-laboratory proficiency testing and quality control evaluations of candidate materials for proficiency testing and quality control to four laboratories, one in Massachusetts, one in Wisconsin, one in California, and one at CDC. In general, the TREC assays appear to be comparable between the four laboratories and seem to perform well. The reference materials developed by CDC for SCID will be available to any state newborn screening program that wants to engage in pilot screening for SCID and other T-cell immune deficiencies.

Questions & Comments

Dr. Howell asked whether CDC had funding for additional pilots of newborn screening for SCID in states other than Wisconsin and Massachusetts. Dr. Vogt said CDC had no immediate plans for pilots in other states. Dr. Howell also asked when the proficiency materials for SCID would be available from CDC. Dr. Vogt said he anticipated that they would be available in late June or mid-July 2009.

Dr. Howell asked whether CDC was evaluating any screening or diagnostic technologies other than TREC assays to detect T-cell deficiencies. Dr. Vogt said yes, CDC had been working with Dr. Kenneth Pass on an approach that would measure CD3 and interleukin 7. The plan is to use these methods on the same samples as the TREC assays, as well as on reference spots of children known to have SCID that Dr. Pass obtained in Denmark. In response to Dr. Rebecca Buckley, Dr. Vogt stated that the dried blood spots from Denmark would be for both control and SCID babies.

Dr. Vogt also mentioned a new platform called the Sequinome mass array system. The machine is not expected to be in newborn screening labs soon at a half a million dollars to install, although the running cost of the machine is relatively low compared to using fluorescent probes; the license fee cost is also low. At the moment, Dr. Vogt anticipates that the Sequinome will be used to assigning values to CDC's reference materials. CDC looks forward to working with the SCIDs researchers to determine the correct values for reference materials.

B. Update from NIH on Additional State Pilots of SCID Newborn Screening

Duane Alexander, M.D.
Director
***Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)**
National Institutes of Health (NIH)
Committee Member

The need for prospective identification of at least one confirmed case of SCID through a population-based newborn screening program was another of the five evidence gaps noted in the Committee's April 2009 letter to the nominator of SCID. The incidence of SCID is believed to be about 1 in 100,000. As of February 2009, no cases of SCID had been found in the pilot SCID newborn screening programs in Wisconsin or Massachusetts; a total of approximately 60,000 newborns had been screened.

Dr. Alexander reported that the Newborn Screening Translational Research Network (NBSTRN) funded by NICHD and coordinated by the American College of Medical Genetics (ACMG) was going to make pilot screening of newborns for SCID in additional states one of its first projects. Dr. Alexander stated that the Jeffrey Modell Foundation has offered to provide some extensive cofunding to augment federal dollars for SCID pilot screening. Funding mechanisms for the projects are still being determined. It is expected that NIH will report on the status of the pilot projects by the time of the Committee's September 2009 meeting.

Questions & Comments

Dr. Howell said he was glad to hear that progress was being made on additional pilots of newborn screening for SCID and would look forward to hearing more on the subject from Dr. Alexander soon. Dr. Vogt mentioned that that he was under the impression that the Modell Foundation thought that a pilot screening program for SCID would take funding of half a million dollars, as it did in Wisconsin; in a large state like California or New York, Dr. Vogt said, the cost would actually be much more. Dr. Alexander agreed, adding that federal money would have to be added to get the SCID pilot to the size needed. He also stated that a decision about whether to pilot the SCID screening in one large state or several smaller states had not yet been made.

Dr. Howell asked the Committee to give some consideration to the question of what role the Committee should play after identifying gaps in the evidence related to a nominated condition in providing assistance to people working on filling those gaps. Dr. Lloyd-Puryear asked whether the Committee might want to develop a monitoring workplan for a nominated condition after considering a condition and finding evidence gaps. Dr. Mike Skeels opposed this idea, saying he thought doing this would increase the Committee's work exponentially. Dr. Vockley similarly opposed the idea, saying he did not think it was a good idea for the Committee to get into micromanaging. Dr. Howell said that even if the Committee did not develop a workplan, individual Committee members have already come forward with ideas for addressing evidence gaps and could continue to help as individuals.

Next Dr. Howell asked whether the Newborn Screening Saves Lives Act had any funding mechanisms that the Health Resources and Services Administration (HRSA) might use to address gaps in the evidence for conditions nominated for inclusion on the recommended newborn screening panel. Dr. Peter van Dyck replied that there is some money in the Newborn Screening Saves Lives Act, but it is generally educational and service or infrastructure money that would not be available for research. Funding for newborn screening research would have to be sought from CDC, NIH, or private funding.

III. STATE POLICIES GOVERNING RESIDUAL DRIED BLOOD SPOTS: PROPOSED WHITE PAPER

Jana Monaco
Committee Member
Bradford Therrell, Jr., Ph.D.
Director
National Newborn Screening and Genetic Resource Center (NNSGRC)

Ms. Jana Monaco introduced this session by noting that Dr. Howell had asked Dr. Brad Therrell, Dr. Harry Hannon, Dr. Don Bailey (a parent advocate), Alaina Harris from HRSA, and Ms. Monaco herself to develop a draft outline for a white paper on state policies pertaining to the retention, storage, and use of residual dried blood spots from newborn screening. As presentations at the Committee's meeting in February 2009 made clear, state policies for the use and storage of residual dried blood spots vary widely and several individuals and entities have called for the improvement in the state policies. Media attention to the existence of the residual blood spots and the policies governing them was acknowledged.

Dr. Therrell reviewed a draft outline of the proposed white paper on dried blood spots from newborn screening and asked for Committee members' comments. He explained that the proposed white paper from the Committee would support the development of a national guidance policy for retaining and using dried blood spot specimens that remain after newborn screening. As background, he noted that publications in recent years about the stability of DNA in stored dried blood spot specimens from newborn screening suggest that DNA can be detected from blood spots for at least 11 years and possibly 25 years. The biggest area of controversy, given that most newborn screening programs do not require consent for screening, pertains to educating and obtaining informed consent from parents for the retention and use of residual blood spots for research.

The thesis of the proposed white paper would be that dried blood specimens that remain after newborn screening is completed are valuable resources that should be carefully and thoughtfully preserved and used for public health benefit. Dr. Therrell pointed out that some states save residual dried blood spots forever (54% save them more than 18 years); most of the rest save them for only 3 years (46% save for 3 years). Currently, only 12 newborn screening programs mention storage of dried blood spots in their educational materials.

The proposed white paper from the Committee would cover four major topics:

- **Scientific issues** would include *physical limitations* (blood volume; specimen quality, biomarker stability); the *retention process* (including permission and consent or dissent process for parents; retention conditions, retention duration, space requirements, accessibility, and disposal); and the *usage process* (program use for quality improvement, method validation; parental request process and evaluation; research with identified samples requiring institutional review board review and deidentified samples; accountability; and legal requests).
- **Policy issues** would include *general interest issues* (policymakers' responsibilities and privacy protections), *state responsibilities, federal responsibilities* (responsibilities of federal agencies and the Advisory Committee); and *policy guidance (*including published guidance from entities such as the American College of Medical Genetics (ACMG) and the Association of Public Health Laboratories (APHL) and examples of model working repositories (e.g., in Michigan and South Carolina).
- **Financial issues** (cost and value) would include *education* (value, process); *blood spot collection kit modifications* (retention and use); *storage* (program, research); *access* (including computerized access if appropriate, shipping (research uses), and *storage* (researcher – confidentiality).
- **Legal and ethical issues** would include ownership; stewardship, privacy protections; awareness and education (parents and public); consent/dissent communication; and legal backup.

In addition, the white paper would present the Committee's recommendations for national policies pertaining to matters such as parent education materials (models for state use); the consent/dissent process (models of forms and procedures for state use); public/private partnerships involving public health departments, advocacy groups, researchers, companies; and national repositories (virtual and/or real; state, multistate, regional, national). Finally, the paper would include an extensive list of references.

Questions & Comments

Dr. Howell said there were few issues of greater importance to the Committee than state policies pertaining to dried blood spots from newborn screening because a failure to assure the public of the value of such specimens or to address storage and privacy issues could very well undermine newborn screening programs. He asked Committee members to voice their opinions about whether they would like to proceed with the white paper as outlined by Ms. Monaco and Dr. Therrell.

Several Committee members expressed their support for proceeding with the proposed white paper. Dr. Ned Calonge expressed his support and asked whether the state newborn screening programs that are retaining residual dried blood spots from newborn screening keep identifying information. Dr. Therrell replied that all the screening programs he knows of keep the specimens linked to identifying information at the beginning (typically using a serial number on a form that is the link and keeping the information that connects to the serial number elsewhere). Dr. Calonge also asked whether states that have put consent or assent processes into place have established procedures enabling them to retain some specimens and throw others out. Dr. Therrell said they would do some research on this to find out.

Dr. Piero Rinaldo said that an essential part of the white paper should be to underscore the importance of developing and validating assays so that there are no surprises when newborn screening tests are used in high throughput mode. Referring to the slide under Scientific Issues labeled "3. Usage Process," which includes method validation, Dr. Rinaldo suggested that the paper detail the distinction between what people perceive as research uses vs. method development and validation issues, noting that in Minnesota anything labeled with the term "research" seemed to have a negative connotation. Dr. Therrell agreed to incorporate Dr. Rinaldo's suggestions.

Dr. Coleen Boyle said she thought that the Committee should proceed with the white paper. She also asked whether the paper would define in its thesis what the public health benefits are from a programmatic standpoint as well as a research standpoint. Dr. Therrell said he was thinking they would probably include the public health program point of view rather than just research. Dr. Boyle suggested going further and actually providing some guidance about what the public health benefit is.

Dr. Skeels said he supported the idea of the white paper, because some states do not retain dried blood specimens from newborn screening because they are unable to deal with all the associated issues, and the paper might help. However, he thought the Committee would need to better define the concept of public health benefit and cautioned against using this concept to justify proposed policies.

Dr. Jane Getchell asked whether the white paper would address the issue of informed consent, which was a topic discussed extensively at the Committee's February 2009 meeting. Dr. Therrell replied that the paper would address that issue, but the Committee would have to make a decision about what position it wants to take with respect to that issue. In response to a question from Dr. Buckley about how many state newborn screening programs obtain informed consent, Dr. Therrell said three programs claim to get informed consent—Maryland, Wyoming, and the District of Columbia; in practice, though, things don't work much differently in those states than in others. In response to a question about which, if any, programs obtained informed consent to

store residual specimens, Dr. Therrell said South Carolina serves as a model. Dr. Rinaldo said he believes that in Minnesota, some people want the results of newborn screening tests to be thrown out after with the samples after 2 years.

Noting that Dr. Rinaldo's comment underscored the need for the Committee to develop the white paper to improve public understanding of dried blood spots from newborn screening, Dr. Howell states that it seemed the Committee has reached a consensus that Dr. Therrell and the other members of the group should continue to develop the paper. He also asked whether the group had thought about a national site where families might request that a newborn screening specimen be kept in perpetuity. Dr. Therrell said they had discussed that. Dr. Chris Kus asked whether the group would look at international experience in the area, and Dr. Howell said he hoped it would.

Ms. Sharon Terry said she would like to see the proposed white paper developed by a broader coalition of entities, including some consumer groups. Dr. Howell stated that the paper would be a report of the Committee.

Dr. Howell identified the group that he had asked to develop a draft outline for the proposed white paper as the "Dried Blood Spot Workgroup." He named Dr. Alan Fleischman and Dr. Bent Nørgaard Pedersen to the workgroup to help address ethical issues related to dried blood spots. In addition, Dr. Howell suggested adding as a member of the workgroup a person with international experience and an attorney with experience in the area, possibly Lynn Fleisher. He said he would discuss this matter with Dr. Michele Lloyd-Puryear. Ms. Terry offered to serve as a member of the Dried Blood Spot Workgroup, and Dr. Howell accepted her offer.

Dr. Howell asked the Dried Blood Spot Workgroup to develop a draft white paper fairly soon and then present it at a Webinar in the summer of 2009 to get input from groups such as the Genetic Alliance, the press, screening programs, pediatricians, and others. He asked the workgroup to have a final draft of the Committee's white paper ready to present at the Committee's meeting on September 24-25, 2009.

Dr. Lloyd-Puryear noted that the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) had expressed an interest in working with the Committee on this issue and asked whether she should invite SACGHS to the Committee's September 2009 meeting along with the Office of Human Research Protections (OHRP). Dr. Howell said he had spoken to the SACGHS chair Dr. Steven Teutsch about this and agreed that both SACGHS and OHRP should be invited to the Committee's September meeting.

Finally, Dr. Skeels noted that since there have been no examples of state newborn screening programs using the spots in an unlawful or unethical manner, that it would be important to include that information in the Committee's white paper. Dr. Howell agreed. He concluded the session by saying that the goal is to have a document that will be widely publicized and will help to improve understanding of the process.

IV. STATE NEWBORN SCREENING PROGRAMS: IMPACTS OF THE CURRENT ECONOMY

Jane Getchell, Dr. PH.
Director
Delaware Public Health Laboratory
Committee Representative

Dr. Getchell discussed the findings of a survey that she, Dr. Therrell, Jelili Ojodu, and Dr. Kus conducted recently to determine the impact of the downturn in the U.S. economy on state newborn screening programs. As background, she showed a U.S. map indicating that the number of conditions for which newborns are screened in the states has greatly increased in the past 3 or 4 years, although the number of conditions for which screening is mandated varies, ranging from 24 conditions in New Jersey to 54 conditions in South Dakota.

Financing systems for newborn screening vary by state. Many states rely on multiple sources of funds (state appropriations, program fees, Title V) for newborn screening. State fee collection mechanisms usually include the sale of "kits," but some states also bill insurance, Medicaid, or hospitals. Medicaid reimbursement varies widely from state to state. The use of newborn screening fees varies from state to state. Newborn screening fees usually cover lab costs, and some of the follow-up costs, but they may not cover all of the follow-up costs or education costs or treatment or special foods. In states with second screening tests, the fee usually covers both screening tests but not always. Three states and the District of Columbia charge no fees. There is no correlation between the fees charged for newborn screening and the number of mandated screening tests. South Dakota, for example, has one of the lower fees.

To obtain information about the impact of the poor U.S. economy on state newborn screening programs, Dr. Getchell and her colleagues developed a set of survey questions asking whether the current economic climate has affected the following, and if so, how: (1) travel to meetings, workshops, seminars; (2) personnel (hiring freeze, staff reduction, etc.); (3) newborn screening panels (addition of new conditions, subtraction of conditions from existing panel, etc.); (4) number of operational days; and (5) other. They piloted the questions and then modified them on the basis of the results of the pilot. Then they e-mailed the questions to newborn screening lab managers, follow-up coordinators and state lab directors. At end of a week, they had received responses from 35 state newborn screening programs; after a follow-up e-mail, they got responses from 47 programs.

The results of the survey suggest that the economic climate is presenting many challenges for state newborn screening programs:

1. Travel is severely curtailed (37 state programs said yes; 9 said no; 7 states have no out-of-state travel; most states have restrictions on number of people who can travel, process for getting approval for travel, etc., regardless of funding source).
2. Personnel are decreased (35 state programs said yes; 12 said no; several state programs have experienced hiring freezes, furloughs, and pay cuts, resulting in understaffing; some states have stopped weekend work).
3. Expanding newborn screening panels is a challenge (8 state programs said newborn screening panels had been affected; 36 said they had not; several states reported

challenges in adding new tests; second screening requirements are under increased scrutiny).

4. Training is restricted, and other system improvements (e.g., upgrades to computers and software and courier service) have been delayed.

Dr. Getchell and her colleagues want to make the Committee aware of the challenges being faced by newborn screening programs in the current economic climate. They recommend that the Committee continue to review the U.S. economy's impacts on state newborn screening programs periodically; consider the economic impact of the Committee's core panel recommendations to states by requesting an economic impact statement in evidence reviews; and work to raise awareness within health systems of the critical nature and need for the prioritization of newborn screening as an essential public health program.

Questions & Comments

Dr. Kwaku Ohene-Frempong questioned the accuracy of the number of newborn screening tests mandated in Pennsylvania that was shown on one of Dr. Getchell's slides. Dr. Therrell explained that the number of tests shown on the slide is the number the state's newborn screening program reported as being mandated. Dr. Getchell added that what is mandated in a state is not always what is done.

Dr. Rinaldo asked whether state newborn screening programs would be willing to consider improving their newborn screening practices—for example, eliminating routine second tests for certain conditions—to survive in the current economy. He noted that if newborn screening programs have high false positive rates, improving performance and getting lower false positive rates could result in substantial savings. Dr. Getchell replied she did not think states should eliminate routine second screens until the results of the Laboratory Standards & Procedures Subcommittee's study to assess the utility of the routine second screens of newborns were available. She added that some state programs have been doing two screens for years, and eliminating second screens is not something that can be done precipitously. Dr. Skeels said he completely agreed with Dr. Getchell, adding that many states are operating high-throughput, extremely efficient programs and can do two tests for the same price that many states are charging for one test.

Dr. Howell asked Dr. Hannon when the study of the utility of routine second screens for congenital hypothyroidism (CH) and congenital adrenal hyperplasia (CAH) might be done. Dr. Hannon promised to report on the study (but not to provide a resolution or answer) at the Committee's next meeting in September 2009.

V. KRABBE DISEASE NOMINATION: PRELIMINARY EVIDENCE REVIEW AND COMMITTEE DISCUSSION

Krabbe disease was nominated for inclusion on the uniform newborn screening panel in 2007, and the Committee asked the external Evidence Review Workgroup, chaired by Dr. James Perrin, to prepare a review of the evidence for this condition. The Evidence Review Workgroup's preliminary draft report on Krabbe disease dated April 27, 2009, by Alixandra Knapp, Dr. Alex Kemper, and Dr. James Perrin, was included in Committee members' virtual briefing materials under Tab #9.

In this session, Dr. Kemper gave an overview of the preliminary draft report on the evidence for screening for Krabbe disease, explaining that the report was still undergoing revisions. He also noted that that the Evidence Review Workgroup's final report on the evidence for severe combined immunodeficiency disorder (SCID) had been submitted to HRSA in April 2009. After Dr. Kemper's presentation, Dr. Rinaldo summarized the key findings and led the Committee in a discussion of the evidence review. Dr. Howell stated that the Committee would not vote on its recommendations with respect to the inclusion of Krabbe disease on the uniform newborn screening panel until its next face-to-face meeting in September 2009.

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

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

Dr. Kemper explained that Krabbe disease is a disorder that affects the nervous system caused by an inborn error of lipid metabolism associated with mutations in the galactocerebrosidase (GALC) gene. Krabbe disease has been nominated for possible inclusion in the uniform newborn screening panel recommended by the Committee for the following reasons. First, most infants afflicted with Krabbe disease who are left untreated die by age 2. Second, hematopoietic stem cell transplant (HSCT) before the onset of symptoms may decrease the morbidity and mortality associated with infantile Krabbe disease. Third, methods to screen infants for Krabbe disease by measuring the enzymatic activity of GALC in dried blood spots have been developed. Fourth, New York State began population screening of newborns for Krabbe disease in August 2006.

Summary of the Preliminary Evidence Review for Krabbe Disease. More than 60 disease-causing mutations that severely reduce the enzymatic activity of GALC have been identified in connection with Krabbe disease, leading to four main clinical subtypes of the disease. Because of the Advisory Committee's interest in newborn screening, the Evidence Review Workgroup's review of the evidence focused on the early infantile form of Krabbe disease.

The Evidence Review Workgroup's preliminary report on the evidence for early infantile Krabbe disease (EIKD), based on a systematic review of the literature, January 1988-March 2009, and an assessment of critical unpublished data from key investigators, addresses the following questions:

1. **Incidence/prevalence of EIKD**. The incidence of EIKD is thought to be 1 per 100,000 newborns in the United States. Population case ascertainment in European and Asian studies ranges from about 0.6 per 100,000 to 1.35 per 100,000**.** The case ascertainment rate in New York's newborn screening program for EIKD (whose case definition is based on a combination of laboratory and clinical findings and requires frequent follow-up examination and testing over 2 years) is just 0.28 per 100,000 newborns screened based on those who proceeded to HSCT.
2. **Natural history of EIKD.** Most infants with EIKD are diagnosed with extreme irritability, spasticity, and developmental delay typically before 6 months of age.

3. Tests for EIKD

a. Screening: Screening newborns for EIKD is performed using a combination of enzyme assay and tandem mass spectrometry (MS/MS) to find enzyme products (GALC enzyme activity) in newborns' dried blood spots. There are relatively few studies of the characteristics of the Krabbe screening test. Explaining that the Krabbe screening experience of New York seems most pertinent to the Committee's deliberations, Dr. Kemper reviewed the algorithm for screening for Krabbe disease in New York in the evidence review as published in a recent review by Duffner et al (Figure 2: New York State pilot screening program diagram of management guidelines).

In the first stage of screening newborns for Krabbe disease in New York, GALC activity in newborns is determined by enzyme assay and MS/MS. If newborns' screens exceed 10% of the daily mean activity, they are considered screen negative. If newborns' screens are less than or equal to 8% of the daily mean activity, they are considered screen positive. Newborns whose screens are 8% to 10% of the daily mean are considered indeterminate, and newborns in this group undergo genotyping; if they are found to have at least one of the genotypes, they move on as if they had tested screen positive. In the second stage, there is notification to the families and inherited metabolic disease physicians of newborns who screen positive, and these newborns return to a clinic for further studies. This second sample is used to repeat the initial assay, determine GALC activity, and confirm the initial result. In the third stage, newborns whose second assays are screen positive are sent to a child neurologist for evaluation. The screen positive newborns are categorized into three groups depending on their level of GALC enzyme activity—low risk (enzyme activity 0.30 - 0.50 nmol/h/mg white blood cell protein), moderate risk (enzyme activity 0.16 - <0.30 nmol/h/mg white blood cell protein), and high risk (enzyme activity ≤ 0.15 nmol/h/mg white blood cell protein)—and then proceed through diagnosis based on their risk stratification.

So far, New York's newborn screening program has screened about 727,000 newborns for EIKD. Of these, 128 newborns (17.6 per 100,000) have screened positive and were referred to the child neurologist for evaluation. Of the 128, 36 were characterized as low risk (4.95 per 100,000), 11 as moderate risk (1.51 per 100,000), and 7 as high risk (0.96 per 100,000). Two of the 7 high risk newborns (0.28 per 100,000) were referred on for cord blood transplants: one infant who was homozygous for the 30-kb deletion and one infant who was compound heterozygous for the 30-kb deletion and novel mutation.

b. Diagnosis. In New York, newborns who screen positive and are characterized as high risk for EIKD are followed monthly and receive neurodiagnostic studies every 3 months for a year; the following year, they are followed every 3 months and receive neurodiagnostic tests every 6 months. Newborns that screen positive and are placed in the moderate risk group are followed every 3 months and receive neurodiagnostic studies annually for 2 years unless an abnormal exam is found; those in the low risk group are followed every 6 months for 2 years and receive neurodiagnostic studies only if their exam is abnormal.

4. **Treatment of EIKD.** Without treatment, EIKD is a devastating illness. Treatment for EIKD consists of allogeneic hematopoietic stem cell transplant (HSCT), with sources for stem cells being either umbilical cord blood or bone marrow. Unlike treatment for SCID, treatment for EIKD requires preconditioning and therefore exposes children to that potential risk. HSCT carries some risk of mortality.

   The Evidence Review Workgroup identified five studies evaluating treatment for Krabbe disease, and divided the children within each study into two groups: one treated before they were symptomatic and others when they became symptomatic. The study that provides the most comprehensive data for the Committee's purposes is a study by Escolar et al. (2005 & 2006). Dr. Kemper showed a graph based on data from the Escolar study in which 11 asymptomatic infants and 14 symptomatic newborns receive umbilical cord transplants. The 11 infants with EIKD who were treated when they were asymptomatic survived the process of transplantation and up to 72 months of life or so, which is the period following; however, the 14 infants with EIKD who were treated after developing symptoms had a much greater risk of mortality. Infants with EIKD in an untreated control group had the highest mortality of all. Under the algorithm in New York, newborns that are treated for EIKD are treated when they are in the early stages of becoming symptomatic. Both newborns received cord blood transplants before 28 days of life, and one baby died of complications of transplantation (vaso-occlusive disease and multisystem organ failure).

   Dr. Kemper said the Escolar study cited in the evidence review also provides information about morbidity and developmental outcomes in infants treated for EIKD. The results are somewhat complicated, and there are changes over time. Among the 11 newborns treated before they became symptomatic, the Escolar study (2005) found that fine motor control interfered with cognitive function testing; motor involvement affected expressive language; during the 2nd and 3rd year of life, there was progressive spasticity in lower extremities and truncal weakness in 2 of 6 children; and two of the children suffered severe delays in motor function. In summary, after early treatment for EIKD, infants' cognitive development may be normal, some infants may have persistent fine motor delay, and some infants may develop gross motor delay. There are no long-term outcome data after early treatment.

   With respect to the availability of treatment for EIKD, interviews with Krabbe disease experts indicate that Duke University and University of Minnesota have been the main sites for treating affected infants but about eight centers in the US are experienced in transplantation of infants with EIKD. Transplants for both EIKD and LOKD are performed at: Northwestern University (Chicago, IL); Nationwide Children's Hospital (Columbus, OH); St. Louis University (St. Louis, MO); BC Children's Hospital (Montreal and Vancouver, Canada); and Devos Children's Hospital (Grand Rapids, MI). Mt. Sinai Hospital (New York, NY) has started to perform transplants in metabolic patients.

5. **Evidence of cost-effectiveness of screening for EIKD.** Experts identified costs associated with newborn screening in terms of the costs of setting up a program or the cost of reagents, but there are insufficient data for a complete economic evaluation.

Critical Evidence Needed to Inform the Committee's Screening Recommendations for Krabbe Disease. The Evidence Review Workgroup believes that several critical pieces of

information are needed to inform the Committee's screening recommendations for Krabbe disease:

- *Accuracy of screening.* There are limited data regarding the sensitivity and specificity of screening. New York's early screening experience underscores the challenge of establishing whether an infant who screens positive for Krabbe disease needs treatment. There exist no data regarding the accuracy of other screening methods in population-based protocols.
- *Feasibility of screening.* New York's experience suggests that screening newborns for Krabbe disease is feasible. Illinois has mandated newborn screening for five lysosomal storage disorders, including Krabbe disease (projected to begin in late 2010). There is no data regarding the ability of other NBS programs to offer Krabbe Disease screening.
- *Acceptability of screening and diagnosis.* There are no systematically collected data regarding consumer attitudes toward Krabbe disease. The current strategy for diagnosing infants with EIKD may impose harm to children and families (e.g., frequent followup, uncertainty, invasive testing).
- *Value or harm of early treatment.* Treatment of EIKD may prolong survival and significantly improve developmental outcomes. Current evidence is limited, especially regarding the risk of HSCT and long-term developmental outcomes.
- *Cost effectiveness of screening and treatment.* Cost-effectiveness analyses utilizing measured costs and utilities, as well as applicable sensitivity analyses, are needed.
- *Adequacy of available treatment centers*. No current data address variation in treatment and outcomes or the number of centers and their capacity to provide treatment for EIKD. Future data from the registry of the Pediatric Bone Marrow Transplantation Consortium may provide evidence of treatment availability and variation.

B. Committee's Discussion of the Preliminary Evidence Report on Krabbe Disease

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

Dr. Rinaldo led the Committee's discussion of the Evidence Review Group's preliminary report on the evidence for Krabbe disease, reminding everyone that the report would be undergoing additional revisions. To get the discussion started, Dr. Rinaldo went through each of the six key questions in the basic analytic framework adopted by the Committee and provided answers to each question:

- **Key Question #1 (overarching question)**: Is there *direct evidence* that screening for the condition at birth leads to improved health outcomes for the infant or child to be screened, or for the child's family? Answer: Dr. Rinaldo said there is no direct evidence from randomized clinical trials of newborn screening for Krabbe disease vs. not screening.

- **Key Question #2:** Is there a *case definition* that can be uniformly and reliably applied? What are the clinical history and spectrum of disease of the condition, including the impact of recognition and treatment? Answer: Dr. Rinaldo said the preliminary evidence report underscores that we are relying on a single source for a case definition of Krabbe disease. Dr. Rinaldo said at this time the Committee has no alternative but following the case definition of high risk early infantile onset Krabbe disease used by the newborn screening program in New York (GALC enzyme activity <0.15 nmol/h/mg protein, homozygosity for 30-kb deletion, and early clinical signs of neurological disease).
- **Key Question #3**: Is there a *screening test* or screening test algorithm for the condition with *sufficient analytic validity*? Answer: Dr. Rinaldo said clarification of the New York's Krabbe disease screening algorithm for newborns is needed. Noting that the draft report said that 220 cases were sequenced in New York, and only 128 were deemed abnormal, Dr. Rinaldo said it would be informative for the Committee to know what the outcomes for the other infants were. It would be useful to know not only how the algorithm works but also to get a sense of the case load at each stage. Dr. Rinaldo also questioned why the classification of newborns' Krabbe screening results in New York was based on a daily mean rather than an absolute value.
- **Key Question #4:** Has the *clinical validity of the screening test or screening algorithm* in combination with the diagnostic test or algorithm been determined and is that validity adequate? Answer: Dr. Rinaldo estimated on the basis of extrapolations from data presented in the evidence review that the screening test for Krabbe disease has a false positive rate of < 0.02%, which is quite good. Dr. Rinaldo similarly estimated that the positive predictive value of the screening test (with a possible range of 2% and 40%) is between 5% and 15%. He believes that the existing estimate of the incidence of EIKD of 1 per 100,000 births is probably fairly accurate.
- **Key Question #5:** What is the *clinical utility of the screening test* or screening algorithm?
    - **5a. What are the *benefits associated with the use of the screening test*? Answer: Dr. Rinaldo said potential benefits of screening for EIKD include the time-limited option of getting treated for the condition by HSCT, improved survival, improved neurological status, and slower progression of disease. He thinks it is likely that transplantation in asymptomatic patients will do better than symptomatic patients, but more data are needed. HSCT appears to attenuate Krabbe disease, but over time most children who have received treatment have developed slowly progressing spasticity, leading to eventual inability to walk without assistive devices, somatic growth failure, expressive language deficits, and poor brain growth. It is unclear whether HSCT significantly lengthens survival.**
    - **5b. What are the *harms associated with screening, diagnosis, and treatment?* Answer. Dr. Rinaldo said there are clearly recognizable harms. The possibility of false positive results from the Krabbe screening test is low, but the impact of false positives on individual families could be quite substantial. Detection of carriers is another harm cited in the evidence review. Uncertainty of clinical outcome in case with moderate and low risk infants is a huge issue. The evidence review reported "family stress and even hostility" in the case of such infants. Given the aggressive follow-up of such infants,**

definitions of clinical endpoints are needed. Finally, there is a real risk of mortality among infants who receive transplants for EIKD. The public perception of controversy among care specialists could also be detrimental.

- **Key Question #6:** How *cost-effective is the screening, diagnosis, and treatment* for this disorder compared to usual clinical case detection and treatment? Answer: Dr. Rinaldo said the evidence review indicated there is not sufficient information to evaluate this.

Turning to critical gaps in the evidence needed for the Committee to recommend adding Krabbe disease to the uniform newborn screening panel, Dr. Rinaldo cited the following. First, the testing algorithm for Krabbe may need to be revised. Second, the case definition of the condition is unresolved. Third, the benefits of treatment of affected infants with HSCT are uncertain at this time. Fourth, substantial harm from screening, diagnosis, and treatment is possible. Fifth, the cost-effectiveness of screening is undetermined.

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

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

Dr. Rinaldo said he believes that if the Committee decided that it did not have enough information to recommend adding Pompe or SCID to the uniform panel, then it did not have enough information to recommend adding Krabbe disease either. For that reason, Dr. Rinaldo believes that the Committee's recommendation for Krabbe disease should be #2: *Recommend not adding the condition to the core panel now and recommend additional studies.*

Questions & Comments

Dr. Howell thanked Dr. Kemper for his presentation and asked for Committee members' comments. Dr. Calonge agreed with Dr. Rinaldo's conclusion that the recommendation #2 was probably the one the Committee should adopt for Krabbe disease.

Requests for Additional Information or Clarification. Numerous Committee members asked for more information or clarification about the information in the Evidence Review Workgroup's report. Dr. Kemper promised to revisit these questions and get as much information as possible prior to the Committee's meeting in September 2009:

- Dr. Boyle asked about the case definition of EIKD in the Escolar case series (2005). Page 19 of the evidence review says the Escolar study did not provide the case definition used to diagnose Krabbe disease. In comparing data from the Escolar study on newborns with EIKD and data from the New York pilot screening program where the case definition is based on a combination of laboratory and clinical findings and requires frequent follow-up examination and testing over 2 years, it is important that the Committee not be comparing apples to oranges. Dr. Howell suggested that it would be very informative to submit dried blood spots used in the Escolar study to the New York screening program for comparisons, and Dr. Boyle agreed.
- Dr. Rinaldo requested more information from the New York pilot Krabbe disease newborn screening program, including specific numbers, about how New York defined low, moderate, and high risk infants. Dr. Kemper said he thought it was a consensus decision. Committee members urged him to get the data from New York. Dr. Vockley said without numbers in each box in the diagram showing the algorithm used for screening for Krabbe disease in New York (which were not in the program's publication), he does not think the Committee has sufficient information to act on the Krabbe disease nomination. It is impossible to tell from New York data how many babies had screens exceeding 0% of the daily mean activity, 8% to 10% of the daily mean, or less than or equal to 8% of the daily mean activity. Other Committee members agreed that this information was crucial.
- Dr. Calonge asked at what age a child would no longer be considered to have EIKD. He also asked how asymptomatic babies with EIKD were detected in the Escolar study. Were they infants who would be picked up by screening? And why weren't the symptomatic infants picked up?
- Dr. Buckley asked why five of the seven newborns classified as high risk for EIKD in New York were not referred for HSCT, given the advantages of early treatment. Dr. Boyle asked which of the two children referred for HSCT in New York died. Dr. Kemper said the infant who was homozygous for the 30-kb deletion died.
- Dr. Vockley drew Committee members' attention to the discussion of the outcomes of treatment for presymptomatic infants transplanted for EIKD on page 22 of the draft evidence review, noting that there seems to be a discrepancy in the findings of Dr. Duffner and Dr. Escolar. The paragraph beginning "Dr. Duffner reported from a workshop/meeting that was held in July 2008" suggests that the outcomes of presymptomatic infants treated with HSCT for EIKD are much worse than the outcomes for such infants found in the 2005 study by Dr. Escolar, which is cited in the subsequent paragraph. Dr. Vockley asked the Evidence Review Workgroup to verify the accuracy of the information from Dr. Duffner and to get the data behind the summary comments to enable the Committee to evaluate the outcomes of treatment more fully before making a recommendation on screening for Krabbe disease.
- Dr. Vockley asked for more data from the New York pilot program about how soon cord blood transplants of infants with EIKD has to be done. Dr. Kemper said that the Evidence

Review Workgroup had been interviewing Dr. Barbara Burton about her patients and that one infant was transplanted at a month of age and still developed symptoms. There is even discussion of delivering babies early to intervene. Dr. Burton suggested that it would be helpful to see if there is guidance in the literature on the variability of symptoms of patients in EIKD and to understand what fraction of patients would not benefit from a transplant because it would not be feasible to get them a transplant in time. She also said it would be helpful for the Committee to have detail from New York about what the average age of infants at the time of their assignment to the highest risk group is. Dr. Kus said it would be helpful to get data on timelines for doing a transplant once the decision to do a transplant has been made.

- Ms. Monaco, referring to Key Question #5 on the clinical utility of the screening algorithm, asked: Why is detecting a Krabbe disease carrier by screening considered a harm? Dr. Rinaldo said he was quoting from the nomination form in citing that as a harm. He said he did not know how substantial harm could occur if something was found biochemically that could not be confirmed at the molecular level, causing uncertainty. Dr. Vockley said you might make a mistake in finding a carrier, or you could go the other way in transplanting a patient who did not need it. The issue seems to be the ongoing concern about the psychological aspects of being screened positive and then the uncertainty at the end of it, the clinical relevance of being a carrier.
- Dr. Skeels asked whether New York had estimated the cost per true positive found.
- Dr. Ohene-Frempong said the preliminary evidence review made it sound as though every child with EIKD would be able to get a donor. Although cord blood can come from unrelated donors, not any cord blood can be transplanted without some matching.

Process Suggestions. There were a few suggestions for improving the process for the Committee's consideration of conditions nominated for inclusion on the uniform panel:

- Dr. Calonge requested that HRSA distribute copies of any key article (or two or three articles) in the External Evidence Workgroup's evidence review to Committee members in the future prior to the Committee's deliberations. Dr. Lloyd-Puryear said that was a good idea and indicated that HRSA could do that.
- Dr. Vockley asked whether the Committee might be interested in having one or more experts in to give direct testimony to the Committee rather than relying solely on the Evidence Review Workgroup's report on a nominated condition. Dr. Lloyd-Puryear said that doing this would certainly be possible—in fact, this had been done in the case of SCID; but the Committee should figure out which experts it wanted to invite. Dr. Howell agreed. Dr. Howell noted that the Committee was relying heavily on expert opinions and stated that he would like the Evidence Review Group to define how it defines and chooses experts.

VI. PUBLIC COMMENTS

1. Jacque Waggoner
Hunter's Hope Foundation

Ms. Waggoner said that although she had planned to provide written comments, she had decided not to because of the long list of comments in favor of adding Krabbe to the uniform newborn

screening panel. She expressed her appreciation for the hard work of the Committee and the Evidence Review Workgroup on Krabbe disease and said she will continue to hope and pray for the day when we can identify and treat every child with Krabbe disease at birth.

VII. COMMITTEE BUSINESS

R. 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 noted that the next meeting of the Committee would be a face-to-face meeting on September 24-25, 2009. Committee members were asked to get their calendars in to Dr. Lloyd-Puryear by the end of May. Finally, with no other business at hand, Dr. Howell adjourned the meeting at 4:40 p.m.

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

/s/ _____

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

/s/_____

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

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