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

Summary of 27th Meeting
May 17-18, 2012
Alexandria, VA

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) was convened for its 27th meeting at 8:30 a.m. on Thursday, May 17, 2012, at the Hilton Alexandria Old Town Hotel in Alexandria, VA. The meeting was adjourned at 2:52 p.m. on Friday, May 18, 2012. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments.

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Contents

I. Committee Business: May 17, 2012

A. Welcome, Roll Call, and Minutes

Joseph Bocchini, Jr., M.D.
Committee Chair
Professor and Chairman, Department of Pediatrics
Louisiana State University
Shreveport, Louisiana

Dr. Bocchini welcomed everyone and took roll call for the first day of the twenty-seventh meeting for the Secretary's Committee on Heritable Disorders in Newborns and Children (SACHDNC). The following voting members of the Committee were present: Dr. Don Bailey, Dr. Coleen Boyle, Dr. Sara Copeland, Dr. Denise Dougherty, Dr. Charles Homer, Dr. Kellie Kelm, Dr. Michael Lu, Dr. Stephen McDonough, Dr. Dietrich Matern, Dr. Melissa Parisi (alternate for Dr. Alan Guttmacher), Dr. Alexis Thompson, and Ms. Andrea Williams.

The following nonvoting, organizational liaison representatives to the Committee were also present:

- American Academy of Pediatrics (AAP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Mike Watson
- American College of Obstetricians and Gynecologists (ACOG): Dr. Nancy Rose
- Association of Public Health Laboratories (APHL): Dr. Jane Getchell
- Association of State and Territorial Officials (ASTHO): Dr. Christopher Kus
- Department of Defense (DoD): Dr. Mary Willis
- Genetic Alliance: Ms. Natasha Bonhomme (alternate for Ms. Sharon Terry)
- March of Dimes: Dr. Emile Wigode (alternate for Dr. Joe Leigh Simpson)
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

Committee members had no comments or corrections to the minutes of the SACHDNC's 26th meeting, held on January 26-27, 2012. Dr. Bocchini requested and received a voice to approve the minutes.

- *MOTION #1: To approve the minutes of the 26th meeting of the SACHDNC held on January 26-27, 2012. Motion approved by voice vote.*

B. Annual Report, Reauthorization, Nominations, and Procedures

Sara Copeland, M.D.
Designated Federal Official, SACHDNC
Chief, Genetic Services Branch
Maternal and Child Health Bureau
Health Resources and Services Administration (HRSA)

Dr. Copeland, the SACHDNC's Designated Federal Official, provided updates on the SACHDNC's annual report, the reauthorization of the Newborn Screening Saves Lives Act, and the Committee's policies and procedures for organizational representatives to the Committee.

Annual Report. The 2012 annual report of the SACHDNC, covering Committee activities during 2011, has been sent onto Health and Human Services (HHS).

Reauthorization. The Newborn Screening Saves Lives Act is up for reauthorization in 2013, but no action has been taken by Congress to date. The act does not "sunset." If Congress appropriates funds for programs authorized by the act, the programs can continue without reauthorization.

Nominations of Organizational Representatives. Dr. Copeland noted that HRSA appoints organizational representatives, terms are limited to allow more people to serve as representatives, and that an announcement for nominations of new organizational representatives will come out in several weeks. Currently, one at-large organizational liaison position is vacant, and the other at-large position will become open in January 2013. The term for the representative from the Association of Public Health Laboratories (APHL) will be ending in January 2013 as well. Dr. Copeland explained that written requests for nominations may be sent to her, the SACHDNC's Designated Federal Official. Dr. Copeland and Dr. Bocchini will initially review the nominations, then they are submitted to the full Committee for a vote. Information on how to submit nominations will be posted to the SACHDNC website.

Procedure Revisions: Requests for SACHDNC Support/Requests for Condition Review. Dr. Copeland presented a new procedure, for use by the three subcommittees, when requesting product or report (i.e., evidence) review: (a) support, (b) affirmation of value, or (c) acknowledgment of a report or project by the full Committee. This procedure also included a "voting slide" template for use when requesting full Committee support of a report or project.

Dr. Copeland also presented a revised Condition Nomination Form for nominating conditions to go forward to Condition Review. This revised form will include:

- a prospective population-based pilot,
- validation of the laboratory test, and
- widely available confirmatory testing, with a sensitive and specific diagnosis.

It is hoped that adding these requirements will assist nominators in knowing what is important in their nomination packages. At the suggestion of Dr. Bailey, there is also going to be an effort to explain the form and the requested information in everyday language.

II. Subcommittee Draft Priorities and Projects

During the Committee's previous meeting on January 26-27, 2012, it was agreed that the three subcommittees would prioritize their work with input from the full Committee. During this session, Dr. Bocchini asked representatives of each subcommittee to outline their draft priorities and projects, with the understanding that each subcommittee will work on refining these drafts, late on the first day, in order to provide updated priorities and projects, for full Committee review on the second day.

A. Education and Training Subcommittee

Don Bailey, Ph.D., M.Ed.
Education and Training Subcommittee Chair

Dr. Bailey presented the Education and Training Subcommittee's draft list of priorities and projects:

Draft Priority #1: Track, provide input on, and facilitate integration of national initiatives and committee-initiated activities.

- Major professional organizations (e.g., AAP, ACOG, AAFP).
- Major education and awareness activities (e.g., Genetics in Primary Care Initiative, Newborn Screening Clearinghouse).

- Research and policy developments (e.g., dried blood spot retention and use).

Draft Priority #2: Promote newborn screening awareness among the public and professionals.

- Support and provide input to the 2013 Newborn Screening Awareness Campaign, with help from HRSA.
- Develop recommendations for the SACHDNC in promoting ongoing awareness and support for newborn screening beyond the 2013 campaign.

Draft Priority #3: Provide better guidance for advocacy groups and others regarding the nomination and review process.

- Collaborative effort, with two goals, between the Education and Training Subcommittee and the Condition Review Workgroup:
  - Increase transparency of nomination and review process.
  - Provide guidance for "getting your condition ready for nomination and review."

Comments

- Committee members suggested that it may be a good idea for the Education and Training Subcommittee to broaden their focus of beyond newborn screening (NBS), to consider care for individuals with genetic conditions that are not detected via NBS.
- Committee members also suggested that the subcommittee may consider developing briefing books for the National Conference of State Legislatures (NCSL). Dr. Bocchini concurred.

B. Laboratory Standards and Procedures Subcommittee

Sara Copeland, M.D.
Designated Federal Official, SACHDNC
Chief, Genetic Services Branch
Maternal and Child Health Bureau
Health Resources and Services Administration

Dr. Copeland, in the absence of subcommittee chair Dr. Lorey, presented the Laboratory Standards and Procedures Subcommittee's draft list of priorities and projects for the upcoming year:

Draft Priority #1: Review new enabling/disruptive technologies.

Draft Priority #2: Provide guidance for states making decisions about implementation of new screening tests.

- Comparative performance metrics
- Overview of technologies

Draft Priority #3: Undertake discussion of point of origin vs. traditional newborn screening labs.

Draft Priority #4: Establish a process for regular review and revision of the standard (i.e., primary, core) Recommended Uniform Screening Panel (RUSP).

- Remove disorders
- Alter status from secondary disorder to primary core condition

Draft Priority #5: Recommend specific changes to technology when indicated.

- Tyrosinemia 1
- Succinylacetone

Draft Priority #6: Continue activity of the Health Information Technology Workgroup.

Draft Priority #7: Monitor new technologies.

Comments

- A Committee member recommended that the Laboratory Standards and Procedures Subcommittee engage with the National Institutes of Health (NIH) Genetic Testing Registry (GTR) on such issues as biochemical tests, which do not fit into the GTR. In addition, it is important to consider how new technologies (e.g., genome sequencing) affect NBS. Dr. Bocchini said that bringing in leaders from various areas to inform the Committee's work would be an excellent idea.
- Committee members discussed the merits of supporting states in making decisions about which conditions to add to their respective screening panels. Support in this area from the Laboratory Standards and Procedures Subcommittee would also assist endeavors by the Education and Training subcommittee.

C. Follow Up and Treatment Subcommittee

Coleen A. Boyle, Ph.D., M.S.
Follow Up and Treatment Subcommittee Chair (outgoing)

Dr. Boyle, in her final presentation as the chair of the Follow-Up and Treatment Subcommittee, acknowledged her fellow subcommittee members and Ms. Jill Shuger from HRSA as well as experts who have advised the subcommittee. In addition, Dr. Boyle provided the following draft list of priorities and projects for the Education and Training Subcommittee:

Draft Priority #1: Facilitating screening program implementation and follow-up.

- Ongoing evaluation of critical congenital heart disease (CCHD) implementation
- Hearing screening follow-up
- Connecting point-of-care testing with dried blood spot (DBS) screening

Draft Priority #2: Closing gaps in access to care and services.

- Roles and responsibilities in short-term and long-term follow-up
- Challenges and opportunities in the changing health care environment

Draft Priority #3: Improving clinical outcomes in children beyond clinical identification.

- Challenges of evolving technology and the health care system
- Sickle cell, as a condition, could serve as a test case:
    - Gaps between technology and disease management practices ("outstanding interventions but a very frustrated system of long-term care")
    - Variability in sickle cell trait notification and follow-up systems
- Consider options for overarching approaches and/or other case studies or comparisons

Comments

- Dr. Bocchini asked Dr. Boyle if the Follow Up and Treatment Subcommittee had considered the applicability of rare diseases to the model used by childhood oncology centers, who collaborate in aggregating and analyzing data on follow up. Representatives from NIH commented that the Newborn Screening Translational Research Network (NBSTRN) is currently working with 21 institutions in 13–15 states to aggregate data and develop the evidence base that may inform the Committee on decisions regarding the addition of a

condition to the RUSP. The NBSTRN is also working on developing tools in a systematic manner to not only facilitate long-term follow up, but also coordinate with electronic medical records.

- Dr. Copeland noted that the Follow up and Treatment Subcommittee could leverage the knowledge furnished in documents by the Clinical and Laboratory Standards Institute (CLSI), thereby avoiding potential replication of work. In addition, any work with sickle cell must be performed in collaboration with the HHS Secretary through the Sickle Cell Initiative.
- Dr. Boyle commented that reporting the findings of NBS tests to families would be an issue for the Follow Up and Treatment Subcommittee to consider, and asked if pediatricians report normal results to families. A Committee member replied that, currently, informing the family of normal screening results is not a standard of care, but that the Bronx Ongoing Pediatric Screening Program is developing a process where screening results get in the medical chart and results are discussed with the family. Another Committee member responded that the AAP's Quality Improvement Network demonstrated a successful intervention to get primary care doctors to discuss normal results with families. Such efforts could help increase public awareness of NBS.
- A professional in the audience commented that the Follow Up and Treatment Subcommittee may want to examine treatments involving hematopoietic stem cell transplantation (HSCT) or organ transplantation as a subgroup of disorders to track separately in follow up, citing severe combined immunodeficiency (SCID) as one example.
- A Committee member suggested that the Follow Up and Treatment Subcommittee could work on the use of electronic health information (e.g., link data from NBS). Dr. Copeland replied that the Laboratory Standards and Procedures Subcommittee is working closely with the National Library of Medicine (NLM) at NIH on terminology for electronic medical records. A consultant for NLM mentioned that developing electronic formats for documenting care plans between specialists, primary care, and families may be a topic for the Follow Up and Treatment Subcommittee.
- Dr. Bocchini, in response to a Committee member's comment, urged the subcommittee chairs to coordinate on overarching topics that are not the responsibility of any single subcommittee, such as health information technology or ethics.
- A Committee member expressed concern that children in some states may not have insurance coverage for conditions identified through NBS, and urged the Follow Up and Treatment Subcommittee and SACHDNC to work to ensure that all children living with heritable conditions have insurance coverage as well as access to care.

III. Surveillance Case Definitions for Disorders Detected by DBS Newborn Screening

Cynthia F. Hinton, Ph.D., M.S., M.P.H.
National Center on Birth Defects and Developmental Disabilities

Centers for Disease Control and Prevention (CDC)

Dr. Hinton presented about the ongoing work of a trans-agency collaborative group to develop surveillance case definitions for disorders detected by dried blood spot (DBS) NBS. She explained that there has been an exponential increase in genetic testing and newborn screening as well as movement towards uniformity in NBS panels and performance metrics; however diagnoses are often not comparable from practice to practice or between NBS programs. Public health systems and

clinical researchers need standard surveillance case definitions for harmonization across data systems, screening programs, and patients for conditions detected by NBS.

Surveillance case definitions are intended to establish uniform criteria for disease reporting—*not* as sole criteria for establishing clinical diagnoses, determining standard of care, setting guidelines for quality assurance, providing standards from reimbursement, or initiating public health actions. A physician may use clinical, epidemiological, and lab data to diagnose a disease even when disease symptoms do not agree with a surveillance case definition.

The Newborn Screening Saves Lives Act of 2008 required the SACHDNC to enhance the coordination of surveillance activities. Therefore, a collaborative group convened to discuss potential models for categorizing the diagnoses of specific conditions identified through NBS as well as identifying the strengths, weaknesses, and gaps of different diagnoses:

- Quantitative model: assigning a number to each of several diagnostic categories (> 10, definite diagnosis; 7 to 10, probable diagnosis; 5 to 7, possible diagnosis; < 5 unlikely to be diagnosis).
- Tier model: assigning a clear cut case of disease as first tier, then employing an algorithm to determine more ambiguous cases in subsequent tiers.
- Diagnostic model: assigning very basic diagnostic categories (definite, probable/possible, not a case).

This collaborative group, consisting of subject matter experts in cystic fibrosis, immunology, hemoglobinopathies, and metabolics, met in June 2011 and developed draft models for various conditions that have been sent to the Regional Genetics and Newborn Screening Service Collaboratives for feedback from their clinicians. This feedback from the Regional Collaboratives is due on May 31, 2012. Once feedback is received, the Association of Public Health Laboratories (APHL) will facilitate a one-year pilot test of surveillance case definitions by state NBS programs. After the pilot test, case definitions will be presented to the SACHDNC for approval and, if approved, case definitions will be submitted to HHS for approval. If HHS approves of the case definitions, they will be used nationally in the surveillance of NBS disorders. In addition, case definitions may also be shared internationally, as the countries of New Zealand and Australia. The International Society of Neonatal Screening have shown interest as well.

Comments

- Dr. Hinton stated that National Newborn Screening and Genetics Resources Center (NNSGRC) and the National Newborn Screening Information System (NNSIS) may use these surveillance case definitions, once developed.
- Dr. Copeland mentioned, in response to a Committee member's question, that a report on case definitions may be completed by early 2013.
- Dr. Hinton noted that surveillance data can be two to three years behind the actual cases. September is Newborn Screening Surveillance Month. States could file their report on data for 2011, and this would provide an opportunity. A Committee member added that if this were done, it would be important to include a disclaimer to ensure people understand that there is variability. A representative suggested that a major educational effort is needed to ensure that public health entities, providers, and insurers know that a child not meeting a surveillance case definition *still* has a heritable condition that requires treatment.

IV. Public Comments

Diane Kane, President, Run for ALD, Inc. Ms. Kane expressed the support of Run ALD, Inc. and other ALD advocacy organizations for the addition of Pompe disease and MPS I to the RUSP. Run ALD is an organization started by Ms. Kane's late husband Jack after he was diagnosed with adrenoleukodystrophy (ALD) ten years ago. Ms. Kane stated that ALD advocates would submit a nomination for including ALD on the RUSP at the September 2012 meeting of the Committee. She noted that early intervention dramatically alters the outcome of ALD and saves lives. The Mayo Clinic is reportedly testing a new method that combines screening for lysosomal disorders, including Pompe and MPS I, with screening for peroxisomal disorders such as ALD. Therefore, it might be possible to screen newborns for all three disorders with the same infrastructure.

Baby's First Test Consumer Task Force. Mr. William Morris offered a statement on behalf of ten individuals serving the Consumer Task Force: Amanda Beard (Nebraska); Ruth Caruthers (West Virginia); Kee Chan, Ph.D., (Massachusetts); Willa Doswell (Pennsylvania); Stacy Hines-Dowell (Tennessee); Mark Engman (District of Columbia); Julie Miller (Ohio); William C. Morris (Texas); Chantel H. Murray (Delaware); and Kristi Wees (Texas). Mr. Morris noted that the statement does not reflect the official position of the Genetic Alliance. The Consumer Task Force members commended the SACHDNC for the huge strides that have been made in adding conditions to the RUSP and establishing uniformity. The task force is concerned about closing the following gaps:

1. What screenings are available and recommended by the SACHDNC versus what screenings are actually conducted by the states.
2. Awareness at both the primary care and pediatric level, so that warning symptoms may be detected, preliminary testing can begin, and referrals can be given as early as possible.
3. Communication with and education of providers and public about NBS and about treatment protocol and options.
4. Informing parents as to what the treatment protocols, options, and testing should occur if their child has a positive newborn screen.
5. Standards of care and best practices that render a NBS system practical and effective for those with heritable disorders.

Steve Holland, President of the National MPS Society. Mr. Holland, a parent of three children with MPS I, appeared with his wife Amy and daughters Madison, age 20, and Laynie, age 18, to present a family's perspective on NBS for MPS I. His son Spencer passed away four years ago at the age of 19. He said it often takes months or years to get a diagnosis and treatment for MPS I, creating irreparable harm. With newborn screening for MPS I, all of a parent's regret, guilt, and conflict with the medical community over a delayed diagnosis is eliminated. Treatment by stem cell transplant, ERT, or whatever new treatments become available can start immediately. The evidence shows that the long-term clinical effects of MPS I can virtually be eliminated by early treatment. Another benefit from newborn screening for MPS and related diseases is the ability to provide genetic counseling to affected families.

Sean Clark, Genetic and Metabolic Disease Committee, Illinois Department of Public Health. Mr. Clark, a parent of a child with Pompe Disease, appeared with his wife Mary and their seven-year-old son Ryan to offer a family's perspective on the importance of NBS for Pompe disease. Ryan was diagnosed with Pompe disease in October 2004, at the age of nine months. Though Ryan began ERT about a year later, Mr. Clark and his wife believe that Ryan would be much healthier today if he had been diagnosed and began Myozyme infusions earlier. Given the great potential benefit and the ability to change young lives that NBS offers, Mr. Clark and his family strongly urged the Committee to move Pompe disease forward for a condition review and to add Pompe to the RUSP.

Krystal Hayes, R.N. As a parent of a child with Pompe Disease, Ms. Hayes appeared with her husband David and their six-year-old daughter Haley to offer a family's perspective on the importance of NBS for Pompe disease. When Haley was six months old, she was admitted to hospital for failure to thrive. Within the first week, she and her husband were told that Haley's heart was severely enlarged, barely functioning, and in congestive heart failure. It took several weeks to receive the diagnosis that Haley had Pompe disease. Though Ms. Hayes was a nurse, she had never heard of Pompe disease before. Soon after the diagnosis, Haley was started on ERT with infusions of Myozyme. By age three, her heart was basically normal. Haley now attends kindergarten and continues to get ERT infusions weekly. She remains very weak. If Haley had been started on ERT earlier in life, her physical disabilities would not be as severe as they are now. A friend of Haley's received treatment within two weeks of birth, and one would not know that this friend has Pompe disease. Ms. Hayes urged the Committee to add Pompe disease to the RUSP to prevent children from suffering severe physical disabilities due to late diagnosis.

Marsha Zimmerman, Acid Maltase Association (AMDA). As a patient advocate, Ms. Zimmerman urged the Committee to place Pompe disease on the RUSP. She emphasized that NBS for Pompe disease would make it possible to provide treatment to late-onset Pompe disease patients, such as Tiffany House, before irreversible muscle damage. Ms. House, who is AMDA's president, was diagnosed with late-onset Pompe disease in 1995 after about 12–13 years of searching for answers. She started on Myozyme infusions four years later, but because treatment was delayed, she suffered irreversible muscle damage, requiring total care from a caregiver.

Priya S. Kishnani, M.D., Duke University Medical Center. Dr. Kishnani, a clinical and biochemical geneticist involved in the care and management of children with Pompe disease for 21 years, nominated Pompe disease as a condition to be added to the RUSP in 2006. In 2008, the SACHDNC decided that Pompe disease was not ready for addition to the RUSP. Dr. Kishnani noted that considerable progress has been made since 2006, and recommended that the Committee add Pompe disease to the RUSP at this time. One question during the previous Pompe disease nomination was the lack of data evidence of from a NBS program. Now, six years of data exist from Taiwan's Pompe NBS program, showing that the false positive rate is very acceptable and that infants are detected through NBS have far better clinical outcomes than those detected clinically. Another previous question concerned cross-reactive immunologic material (CRIM) negative babies with Pompe disease, who showed a limited response to ERT and died. It is now possible to abrogate the immune response in such infants with simple immunomodulation. Children in the oldest cohort are now over age five, and doing well. As a treating clinician, Dr. Kishnani stressed that identifying individuals with late-onset Pompe disease is as important as identifying individuals with infantile-onset Pompe. Though individuals with the late-onset do not die within the first year of life, they experience significant mortality and morbidity. Taiwan's experience indicates that earlier treatment for those individuals has been helpful in preventing a diagnostic odyssey of 10+ years. Early intervention, made possible by NBS, has the potential to not only save the lives those affected with the infantile form of Pompe disease but to also greatly improve the quality of life to those children and to adults diagnosed with Pompe disease.

Hillary Gibson, Pompe Patient Advocate, Portland, Oregon. Ms. Gibson submitted a letter to the Committee on May 13, 2012, expressing support for the inclusion of Pompe disease to the RUSP. Ms. Gibson was diagnosed with late-onset Pompe in 2002 at age 24 after experiencing symptoms for six years. She stated that the patient community feels very strongly about the importance of identifying both infantile and late-onset Pompe disease through NBS.

V. MPS I

A. Nomination and Prioritization Report

Nancy Green, M.D.
Associate Dean for Clinical Research Operations
Associate Professor of Pediatric Hematology
Columbia University

Dr. Green presented a report and recommendation on MPS I from the Committee's Nomination Review and Prioritization Workgroup, recommending that the full Committee move MPS I forward to condition (i.e., evidence) review, with areas of specific inquiry.

- **Nominated condition is medically serious.** The infantile form is fatal within first decade of life. Individuals with later-onset forms of MPS generally present symptoms at a slower progression (e.g., age 5, less or no involvement of the central nervous system, some enzyme activity).
- **Case definition and disease spectrum**. There is a case definition for MPS I, and the spectrum of MPS I is well described. There are some uncertain genotype-phenotype correlates, and some variants have an unclear impact on enzyme function and the disease. There exists a pseudo-deficiency variant that, though rare, would have to be discerned.
- **Algorithm exists for NBS and diagnosis**. Screening for MPS I involves searching for low/absent levels of the enzyme α-L-iduronidase via tandem mass spectrometry (MS/MS), and MPS I screening can be multiplexed with other lysosomal disorders. Because of uncertainty regarding genotype/phenotype correlation, sequencing of the gene in family members (e.g., for novel mutations) may be something that the Condition Review Workgroup needs to consider. Another consideration is that gene sequencing could pose technical problems for some state NBS programs.
- **Screening test has analytic validity**. Screening test(s) characteristics are reasonable, i.e., a low rate of false negatives.
    - Washington State performed screening of 75,000 anonymized blood spots in a study using a tandem mass spectrometry (MS/MS) triplex assay for three lysosomal enzymes (α-L-iduronidase for MPS I, α-glucosidase for Pompe disease, and α-galactosidase A for Fabry disease). Results revealed that one screening was an early diagnosis, one had a later-onset form, one was a heterozygote, and two had no identifiable mutation. The false positive rate was approximated at 1:14,000.
    - In Missouri, assay development is underway. Several states (e.g., New Jersey, California) are deliberating about their screening approach for MPS I.
- **Screening test has clinical utility**. Screening newborns for MPS I has clinical utility in preventing or ameliorating adverse health outcomes (e.g., mortality, morbidity, or disability) through effective treatments.
- **Effective treatment is available**. Defined treatment protocols and FDA-approved drugs are all available. Available therapies for MPS I are hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT), to replace the deficiency of the lysosomal enzyme iduronidase.
    - HSCT, the standard of care for severe MPS I, arrests the impact of MIS I on the central nervous system and should be initiated early in the disease course, preferably before age 2. HSCT extends the lifespan in severe MPS I (15.6 years for transplanted vs. 7.9 years for not transplanted). There is a 10 percent mortality rate associated with the HSCT and a 10–15 percent incidence of chronic graft-versus-host disease (GVHD).

- ERT, approved as treatment for milder forms of MPS I, does not cross the blood-brain barrier to improve the central nervous system. Therefore, it does work for those who have the more severe form of MPS I.

The Nomination Review and Prioritization Workgroup provided the following recommendation to the full Committee with respect to MPS I:

- *Move MPS I forward to condition review, with areas of specific inquiry.*
  - Uncertain: Identifying various forms of MPS, though each type is serious and treatable: Phenotypic spectrum and genotypic mutations
  - Uncertain: Impact of treatment with HSCT and ERT, especially for variants (50 percent of those identified)
  - Uncertain: Acceptability to parents (e.g., Krabbe experience, other nononcologic disorders)
  - Uncertain: State NBS laboratory and program challenges
  - Uncertain: Public health challenges

B. Committee Discussion and Vote

After hearing the Nomination Review and Prioritization Workgroup's report and recommendation for MPS I, Dr. Bocchini opened the floor for comments before requesting a vote from the full Committee.

- A Committee member noted that it is important to obtain clinical input for a diagnosis of MPS I, because one infant can have two severe mutations and not be affected yet another infant can have zero mutations and be affected. Clear clinical diagnostic criteria exists for MPS I in the neonatal period, so a clinician can generally distinguish between a severe form or less severe form of MPS I, although some individuals will be in a middle, grey zone. Individuals with the later-onset form of MPS I may never get diagnosed at all, though they could benefit from treatment to avoid future risk of with heart failure and arthritis.
- Dr. Greene explained that, while clinicians can clearly determine diagnoses during examination, they cannot clearly determine the most effective treatment for infants with MPS I who present systemic problems but no central nervous system issues. Should these infants be treated with ERT rather than HSCT? There is a window of time to watch. DNA results, physical examination, biochemical testing, urine MPS screen, and X rays all play a role in determining treatment. Still, there will be a grey zone in the clinical diagnosis of MPS I.
- A Committee member commented that, if the MPS I nomination goes forward, the Condition Review Workgroup should contact Washington State about cases of MPS I with no identified mutations, communicate with centers administering HSCT and ERT treatments, and determine the number of patients who were clinically diagnosed but have enzyme deficiency, not mutations. In addition, are specific mutations associated with pseudo-deficiency, and are second-tier molecular tests conducted? Dr. Bocchini indicated that this was a good point, noting that the focus on the examination of infants who screen positive during NBS for MPS I will be during the neonatal period, rather than one or more months later.
- Dr. Green commented that New York State has developed an algorithm for the periodic clinical evaluation of children who screen positive for Krabbe disease. She noted that the

Condition Review Workgroup could incorporate structured clinical follow-up as part of an algorithm to clinically determine what type of MPS I a child will have.

- A Committee member added that there is a lot of published literature on treatment and follow-up for MPS I; his recollection is that there have been more than 100 HSCTs and lots of ERT therapy. Moreover, there is a registry with excellent data on the effectiveness of stem cell transplants for MPS I.
- An audience member offered his perspective as the parent of a child with early-onset MPS I, diagnosed at six months of age. His son first received ERT, then a HSCT. Although his son passed away due to complications from the stem cell transplant, the ERT did help. He suggested the possibility of first doing ERT while either (a) waiting for a HSCT, or (b) deciding whether an infant requires a HSCT, because ERT is beneficial and does help the child.

The following motion, made by Dr. McDonough and seconded by Dr. Homer, was approved (11 votes for, none against, and Dr. Matern abstaining):

- *MOTION #2 (APPROVED): To accept the recommendation of the Nomination Review and Prioritization Workgroup that MPS I receive a formal evidence review by the Condition Review Workgroup.*

VI. Pompe

A. Nomination and Prioritization Report

Nancy Green, M.D.
Associate Dean for Clinical Research Operations
Associate Professor of Pediatric Hematology
Columbia University

Dr. Green presented a report and recommendation on Pompe disease from the Committee's Nomination Review and Prioritization Workgroup. Because Pompe disease had been previously nominated back in 2006[*] and reviewed by the Committee in 2008, the workgroup focused primarily on specific areas that were previously deficient but improved since that time. The Nomination Review and Prioritization Workgroup recommended that the full Committee move Pompe disease forward to condition (i.e., evidence) review, and Dr. Green provided the following summary.

- **Nominated condition is medically serious**. About one-third of diagnosed cases have the infantile form, presenting aggressive symptoms as well as cardiac involvement at an average of two months of age. However, there are considerable and variable delays in diagnoses.
- **Case definition and disease spectrum**. Pompe disease manifests as a clinical spectrum from early-onset (infantile) to later onset. Later-onset Pompe disease is more variable in the age of onset as well as how it impacts health and treatment. Distinguishing infantile from later-onset Pompe disease can be challenging. There is also a pseudo-deficiency i.e., low-efficiency enzyme) prevalent among Asian populations that must be discerned by gene sequencing.
- **Algorithm exists for NBS and diagnosis**. First-tier screening for Pompe involves screening for low/absent levels of the enzyme GAA in blood-based assays by fluorometry or tandem mass spectrometry. Second-tier testing for Pompe disease involves (a) looking at leukocyte

[*] Priya S. Kishnani, M.D. of Duke University nominated Pompe disease in 2006.

GAA activity, not DBS assay; and (b) DNA sequencing of the GAA gene. A Western blot test, due to prognostic significance, is used to determine whether infants are CRIM-negative or CRIM-positive.

- **Screening test has analytic validity**. Screening test(s) are reasonable, i.e., a low rate of false negatives. Screening DBS for GAA enzyme activity appear comparable among different methods.
  - Washington State performed screening of 75,000 anonymized blood spots in a study using a tandem mass spectrometry (MS/MS) triplex assay for three lysosomal enzymes (α-L-iduronidase for MPS I, α-glucosidase for Pompe disease, and α-galactosidase A for Fabry disease). Results revealed a false positive of 0.01 percent rate for Pompe disease.
  - Illinois conducted a recent pilot screening among 8,002 infants. Results revealed two positive screens for Pompe disease, which subsequently proved to be false positives during follow-up testing.
  - Taiwan has a screening program for infants, with almost 130,000 screened and four infants diagnosed. Repeat blood testing rate is 0.082 percent; clinical recall rate is 0.091 percent.
  - Austria has screened about 35,000 babies, with a false positive rate of only .006 percent.
- **Screening test has clinical validity**. Screening newborns for Pompe disease has clinical utility in preventing or ameliorate adverse health outcomes (e.g., mortality, morbidity, or disability) through effective treatments.
  - Taiwan's screening program of 130,000 infants resulted in four diagnoses through NBS and three clinical diagnoses at three to six months.
  - The impact of diagnosis on therapy depends upon the form of Pompe disease. For instance, the clinical utility of NBS is not clear for children who present a later-onset form of the disease.
- **Effective treatment is available**. Defined treatment protocols and FDA-approved drugs are all available for Pompe disease.
  - ERT, with recombinant human GAA (rhGAA) (Myozyme), has FDA approval for patients. Early diagnosis and treatment has been shown to improve clinical outcomes, and a 2011 European consensus document supports this conclusion.
  - Open treatment issues: Approximately 20-30 percent of infants with the infantile form are CRIM negative, and have a poorer prognosis with ERT treatment due to developing, or at risk of developing, antibodies to ERT (African Americans are particularly susceptible). As noted, the clinical utility of NBS is not clear for the later-onset form that is expected to comprise about two-thirds of all detected cases. In addition, challenges in sequencing the genes of family members may impact some state newborn screening laboratories in understanding the effect of particular variants on enzyme function.

The Nomination Review and Prioritization Workgroup provided the following recommendation to the full Committee with respect to Pompe disease:

- *Move Pompe disease forward to condition review.*

B. Committee Discussion and Vote

After hearing the Nomination Review and Prioritization Workgroup's report and recommendation for Pompe disease, Dr. Bocchini opened the floor for comments before requesting a vote from the full Committee.

- Dr. Greene noted that clinical criteria do exist to determine when an individual should be treated for Pompe disease. Physical examination, including echocardiogram, permits a clinician to determine whether and when to administer treatment without a clear answer in the DNA. Although CRIM-negative individuals get worse on ERT, new protocols preventing this are showing promise.
- A Committee member, referring to the Asian population's pseudo-deficiency in Washington state, asked Dr. Kishnani if a second-tier molecular test in NBS was necessary to distinguish between infantile, later-onset, or pseudo-deficiency forms of Pompe disease. Dr. Kishnani replied that it is very easy to distinguish infantile Pompe disease from a pseudo-deficiency through clinical examination with an EKG and echocardiogram. If there is no enzyme activity, the doctor can look for a pseudo-deficiency, as doctors are doing in Taiwan.

The following motion, made by made by Dr. Homer and seconded by Dr. McDonough, was approved (11 votes for, none against, and Dr. Matern abstaining):

- *MOTION #3 (APPROVED): To accept the recommendation of the Nomination Review and Prioritization Workgroup that Pompe disease receive a formal evidence review by the Condition Review Workgroup.*

Following the vote, Dr. Bocchini noted that the general consensus for the full Committee was that the Condition Review Workgroup would first review Pompe disease prior to beginning the review for MPS I. There was no objection by the Committee.

VII. Committee Business: May 18, 2012

A. Welcome and Roll Call

Joseph Bocchini, Jr., M.D.
Committee Chair
Professor and Chairman, Department of Pediatrics
Louisiana State University
Shreveport, Louisiana

Dr. Bocchini began by taking roll call for the second day of the twenty-seventh meeting for the Secretary's Committee on Heritable Disorders in Newborns and Children (SACHDNC). In addition to Dr. Bocchini, the following voting members of the Committee were present: Dr. Don Bailey, Dr. Coleen Boyle, Dr. Sara Copeland, Dr. Denise Dougherty, Dr. Charles Homer, Dr. Kellie Kelm, Dr. Michael Lu, Dr. Stephen McDonough, Dr. Dietrich Matern, Dr. Melissa Parisi (alternate for Dr. Alan Guttmacher), Dr. Alexis Thompson, and Ms. Andrea Williams.

The following nonvoting, organizational liaison representatives to the Committee were also present:

- American Academy of Family Physicians (AAFP): Dr. Frederick Chen (by phone)
- American Academy of Pediatrics (AAP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Mike Watson
- American College of Obstetricians and Gynecologists (ACOG): Dr. Nancy Rose
- Association of Public Health Laboratories (APHL): Dr. Jane Getchell
- Department of Defense (DoD): Dr. Mary Willis
- Genetic Alliance: Ms. Natasha Bonhomme (alternate for Ms. Sharon Terry)
- March of Dimes: Dr. Emile Wigode (alternate for Dr. Joe Leigh Simpson)

- Society for Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

VIII. Subcommittee Proposed Priorities and Projects

The full Committee heard reports from the subcommittees, consisting of each subcommittee's activities as well as three proposed priorities and related projects. At the conclusion of the May 17 full Committee session, each subcommittee convened separately to further refine their draft priorities into proposed priorities to present before the full Committee on May 18. Once each report was presented, the full Committee offered comments regarding proposed priorities and projects. No vote was taken because the Committee appeared to be in general agreement concerning each subcommittee's proposed priorities.

A. Education and Training Subcommittee

Don Bailey, Ph.D., M.Ed.
Education and Training Subcommittee Chair

Dr. Don Bailey acknowledged new members to the Education and Training Subcommittee: Dr. Emily Drake, professor in nursing, University of Virginia; Joan Scott, CEO of the National Coalition for Health Professional Education in Genetics; and Mr. Jeremy Penn, the parent of a child with SCID. A new representative, Dr. Nancy Rose has replaced Dr. Allen Hogge as ACOG's representative, and the subcommittee is pleased to have her .

Dr. Bailey also covered highlights of the subcommittee's May 17 meeting, including (a) activities related to the 2013 Newborn Screening Awareness Campaign and 50th anniversary of NBS; (b) potential collaboration, with SACHDNC's Condition Review Workgroup, to provide guidance on the nomination and review process, and (c) updates concerning Baby's First Test Consumer Task Force and the Genetic Alliance. In addition, the subcommittee heard a preliminary report on whether states collect NBS refusals, and brief reports on the Genetics and Primary Care Initiative to introduce genetic medicine into primary care training, ACOG recommendations for NBS information to parents, and the National Coalition for Health Professional Education in Genetics' family history project for prenatal providers.

Dr. Bailey then turned his attention to reporting on the following proposed priorities and projects of Education and Training Subcommittee.

Priority A. Enhance our ability to track, provide input on, and facilitate integration of national and community initiatives.

Project 1

- Work with professional organizations to identify specific priorities for NBS awareness efforts.

  Comments from Committee

  - Dr. Bocchini observed that strong interactions with professional organizations such as AAP, ACOG, and the AAFP had led to projects that have encouraged providers to modify their approaches to genetic diagnosis and neonatal screening. Dr. Bailey added that the subcommittee would like to obtain a member from a major nursing organization.

- A Committee member noted that it also important to obtain the involvement of parents of affected children, and another member suggested that the subcommittee could gain parental involvement by sending questionnaires to parents before Committee meetings. In addition, another member suggested leveraging existing studies and data related to parents into the subcommittee's work.

Project 2

- Conduct a scan to determine major educational and training needs that extend into areas other than NBS. Goal is to have identified at least one major education and training goal that addresses a need related to genetic and metabolic disorders outside of NBS (e.g., reduce the time from symptoms onset to genetic diagnosis).

Comments from Committee

- Dr. Bocchini said this appeared to be a very worthwhile project in moving the SACHDNC forward as a committee toward diagnosis outside the newborn period, adding that project 2 may be an easier project to begin with than project 1. Perhaps a first step would be to pick a prototype disorder, then look at reducing the time from onset of symptoms to diagnosis.

Priority B. Promote NBS awareness among public and professionals.

Project 1

- Continue to support and provide input on 2013 NBS Awareness Campaign plans and activities:
  - To what extent should the Education and Training Subcommittee and the Committee be involved with activities surrounding the 50th anniversary of NBS, planned by CDC and APHL.

  Comments from Committee

  - Dr. Bocchini that involvement with the 2013 campaign should not only be a top priority for the subcommittee and the SACHDNC, but also an opportunity to raise awareness about NBS. He added that advocacy groups would be welcome to undertake activities and events in conjunction with the campaign. A Committee member added the campaign was a good opportunity to use lay language to educate the public and primary care providers about NBS.
  - A Committee member suggested that the SACHDNC's fall 2013 meeting be held in conjunction with the 50th year celebrations, and that the leadership of government agencies such as HHS, NIH, CDC, and HRSA be invited.
  - Audience members from APHL and CDC provided notice on two upcoming events, an APHL NBS Symposium May 5–10, 2013 in Atlanta, GA and an event, tentatively scheduled for fall 2013, to bring NBS achievements to the awareness to lawmakers, advocacy groups, and parents regarding the need to reauthorize the NBS Saves Lives Act.

Project 2

- Develop an action plan with specific objectives regarding professional practices in NBS.
  - What change in professional practice would likely create increased public awareness about NBS, and how can we facilitate this change?

  Comments from Committee

- Dr. Bocchini recommended folding project 2 into project 1. Dr. Bailey added that there would be some integration of projects 2 and 1, but project 2 is really more about institutional changes after the celebration of the 50th anniversary of NBS.

Project 3

- Identify potential partner(s) to develop a plan that would inform state legislators about the SACHDNC and the condition review process (e.g., partner with the National Conference of State Legislatures).

  Comments from Committee

  - Dr. Bocchini that project 3 might be a longer term effort as opposed to an immediate priority.

Priority C. Provide better guidance for advocacy groups and others regarding the condition nomination and review process.

Project 1

- Collaborate with the Condition Review Workgroup to develop public-friendly summaries of previously conducted condition (i.e., evidence) reviews.

  Comments from Committee

  - Dr. Bocchini stated that developing public-friendly summaries was a good idea.

Project 2

- Create a subcommittee to recommend strategies for supporting nominators and advocacy groups (e.g., increase clarity of the process, guidance for preparing condition for nomination and review, feedback regarding next steps for conditions not ready or not approved to the RUSP).

  Comments from Committee

  - Dr. Bocchini commented that recommending strategies to support nominators and advocacy groups was a good idea, but that it was a secondary priority.

B. Laboratory Standards and Procedures Subcommittee

Dietrich Matern, M.D.
Member, Laboratory Standards and Procedures Subcommittee

Dr. Matern, substituting for Committee chair Dr. Lorey, noted that Dr. Kemper spoke during the subcommittee's May 17 meeting about proposed changes to the condition review process. Dr. Matern then proceeded to report on the following proposed priorities and projects of Laboratory Standards and Procedures Subcommittee.

Priority A. Review of new enabling/disrupting technologies.

Project 1

- Provide the pros/cons, including uncertainties, of the various platforms (old and new) of screening for the nominated and current conditions on the recommended uniform screening panel, to assist states in making informed decisions about platforms (e.g., succinylacetone as part of amino acid/acylcarnitine analysis).

  (For Project #1, the subcommittee requests guidance on which platforms to examine first.)

  Comments from Committee

- Dr. Bocchini commented that this is a primary project that would have good and immediate benefit, and suggested that a report and recommendation on current data in CDC's *Morbidity and Mortality Weekly Report*. An audience member from the CDC was responsive to this suggestion.
- Responding to the subcommittee's request for guidance, Dr. Bocchini suggested their example (i.e., succinylacetone as part of amino acid/acylcarnitine analysis).
- A Committee member noted that synergy existed between this project and the work of the Follow Up and Treatment Subcommittee, and perhaps the Education and Training Subcommittee as well. Dr. Bocchini stressed that, in such cases, it is paramount for the SACHDNC to ensure there is coordination between the different subcommittees.

Project 2

- Provide an implementation toolkit for new conditions on the recommended uniform newborn screening panel to help states in their implementation of screening for newly added conditions (e.g., SCID).
  - Standard operating procedures
  - "Slide sets" that can be used for the education of advisory boards, administrators, legislatures, etc.

Comments from Committee

- Dr. Bocchini remarked that an implementation toolkit worked very well for SCID, and that this could be done on a condition-by-condition basis since it is not required for every heritable condition. He also added that partnerships with the CDC and APHL would help.

Project 3

- Region 4 Tandem Mass Spectrometry (MS/MS) Data Project summary.
  - Review data collected and tools developed as part of the project.
  - Assess project impact on newborn screening programs using R4S (i.e., Laboratory Performance Database) data and tools.
  - Review training course offered by the project.

Comments from Committee

- Dr. Bocchini commented that project 1 was more important , even though it would be good to have awareness about the Region 4 Tandem Mass Spectrometry (MS/MS) Data Project.

Priority B. Provide guidance for state newborn screening programs in making decisions about implementation, integration, follow-up, and quality assurance.

Project 1

- Comparative performance metrics.
  - Review APHL Quality Indicators metrics.
  - Review newborn screening case definitions.

Comments from Committee

- A Committee member commented that project 1 was the project most needed under Priority B. Dr. Bocchini and other Committee members concurred that this was the best project to undertake immediately.

Project 2

- Point of care newborn screening
  - What is the landscape with respect to point-of-care newborn screening? Review and outline roles of public health programs in point-of-care newborn testing (i.e., who is responsible for administration/quality? Compare loss to follow-up for different models; using hearing loss screening as an example).
  - Is there a perfect model?

Comments from Committee

- Dr. Bocchini remarked that project 2 was more applicable to the full Committee (i.e., SACHDNC), and a Committee member concurred.

Project 3

- Develop a tool for delayed/missed diagnoses.

Comments from Committee

- Dr. Bocchini commented that project 3 would be difficult to accomplish without electronic health records, except in a large organization. He suggested that there may be a pilot project for this.

Priority C. Establish a process for regular review and revisions of the recommended uniform screening panel, and recommend specific changes to technology when indicated.

Project 1

- How to remove disorders from the recommended uniform newborn screening panel.

Project 2

- How to move a condition from being a secondary to a primary target on the recommended uniform screening panel.

  (Provide input to the Condition Review Workgroup on lab and technical aspects related to testing for conditions.)

Comments from Committee, Projects 1 and 2

- Dr. Copeland commented that the subcommittee could subcontract with an external entity, such as the Condition Review Workgroup, to work on these projects. Dr. Bocchini felt that establishing a process for the review and revision of the recommended uniform screening panel was a good idea.
- Dr. Matern noted that a 2006 ACMG report *Newborn Screening: Toward a Uniform Screening Panel and System* included a flowchart on how to do this.

C. Follow Up and Treatment Subcommittee

Carol Greene, M.D.
Follow Up and Treatment Subcommittee Chair (incoming)

Dr. Greene began by making a formal request to the SACHDNC that Dr. Christopher Kus be appointed as co-chair of the Follow Up and Treatment Subcommittee. Dr. Bocchini accepted this request, and appointed Dr. Kus as co-chair.

Dr. Greene also covered highlights of the subcommittee's May 17 meeting, including (a) manuscript updates on the medical home, from National Coordinating Center (NCC) for the Regional Genetics

and Newborn Screening Service Collaboratives, and Medical Foods, from Medical Foods Workgroup of the Follow-Up & Treatment Subcommittee; (b) presentations by Dr. Alexis Thompson and Ms. Andrea Williams regarding the use of sickle cell disease for long-term follow up (LTFU) plus the family perspective on LTFU; (c) formation of a Sickle Cell Workgroup within the subcommittee, to align with the HHS Sickle Cell Disease Initiative; (d) a presentation by Dr. Boyle on subcommittee work regarding NBS LTFU and treatment; and (e) a presentation by Dr. Kus on public health programs involved in the LTFU and treatment of individuals with conditions detected by NBS.

Dr. Greene added that the subcommittee decided not to expand its focus beyond NBS screening, though it will be possible to revisit this decision in the future. The subcommittee's present focus will remain on critical questions surrounding NBS.

Dr. Greene then turned her attention to reporting on the following proposed priorities and projects of Follow Up and Treatment Subcommittee. (*Note:* Since comments on these priorities focused on one or more projects concurrently, Committee comments are listed last beneath each priority.)

Priority A. Screening program implementation—possible case studies/projects

Short and long-term follow-up and treatment—what are/should be the metrics; what are the costs, what is the impact on families. Explore current and possible models (e.g., impact of false positives, specific metrics focused on process/outcomes, such as developmental outcomes in CCHD).

Project 1

- Ongoing evaluation of CCHD implementation.

Project 2

- Hearing screening follow-up.

Project 3

- Connecting point-of-care testing with DBS screening, perhaps using health information technology.

Comments from Committee

- Dr. Bocchini thought the first priority, with possible case studies on CCHD and hearing screening, was very important, adding that it focused on (a) the need to follow up after the Committee makes a recommendation; and (2) the importance of partnerships with NBS implementation and follow-up for conditions added to the RUSP, e.g., CCHD, SCID. Dr. Bocchini recommended that the subcommittee move ahead with project 2, then project 1, partnering with APHL and CDC to review NBS implementation for these conditions.
- Dr. Bocchini stated that project 3 should be deferred because health information technology is still in the early stages.

- Dr. Bocchini asked representatives of federal agencies if questions could be identified to drive research. A CDC representative replied that her agency could work on hearing screening and check with CDC regarding questions for CCHD and CID. A NIH representative noted that a LTFU tool is under development at the NBSTRN. A Committee member added that AHRQ has an Action II Network that functions as a rapid cycle evaluation network. Dr. Greene stated that ASTHO and the Association of Managers of Obstetrics and Gynecology (AMGO) would have some perspectives on questions. A parent member of the Baby's First Test Consumer Task Force commented that she had worked with the American Heart Association regarding NBS for heart defects, and that The March of Dimes is involved with similar efforts in other states.

Priority B. Closing gaps in systems of care: Possible Case Studies/Projects.

Project 1

- Roles and responsibilities in LTFU
  - As part of case studies, include focus on learning: current/variable roles and responsibilities in LTFU for children with hearing impairment and sickle cell (disease or carrier).
  - Consider a focused case study of NBS results in electronic medical records (EMRs) and the use of EMRs as a source of LTFU data.

Note to SACHDNC: Request a presenter once the U.S. Supreme Court issues a decision on the Affordable Care Act, to explain the impact of health care system changes on children with heritable disorders. Some subcommittee members have been told to expect profound cuts in safety net programs at the state level because all care will be provided within the community.

Comments from Committee

- Dr. Bocchini said that it would be important to get ideas from HRSA and other agencies pertaining to projects currently in place for sickle cell. Dr. Greene agreed, and suggested consulting other groups such as ASTHO, but also added that the subcommittee's goal is to understand what is happening and if there are gaps in systems of health care for hearing impairment and sickle cell disease.
- A Committee member commented that she viewed embedding metrics in the EMR as a way to effect *overall* change without resorting to change only one condition at a time. Dr. Greene responded by saying that this actually ties in with what the subcommittee had mentioned in the first priority. Dr. Bocchini said that this was a good point.

Priority C. Real World Impacts and Outcomes: Possible Case Studies/Projects

Project 1

- Explore the extent to which we can document improved clinical outcomes; whether we are realizing the potential of newborn screening.
  - Sickle cell as a "test case," studying gaps between technology and disease management, variability in sickle cell trait notification and follow up conditions.

Project 2

- Consider options for overarching approaches and/or other case studies or comparisons that might provide guidance for follow-up of conditions in the panel, or conditions that will be in the panel.

Comments from Committee

- Dr. Bocchini, noting the connections between the case studies in this priority and those in the previous priorities, suggested applying the same concepts to Priority C and the related projects.

IX. Medical Home Manuscript

A. Report

Alex Kemper, M.D., M.P. H., M.S.
Medical Home Workgroup
National Coordinating Center for the Regional Genetic Services Collaboratives
Associate Professor, Department of Pediatrics
Duke University

Dr. Kemper presented a report on *Family-Centered Coordinated Co-Management for Individuals with Heritable Conditions*, developed by the Medical Home Workgroup of the NCC for the Regional Genetic and Newborn Screening Service Collaboratives. As part of his presentation, Dr. Kemper requested a Motion for Committee Action for the Committee to review and acknowledge the report's (a) enhanced description of the medical home, and (b) strategies for improving linkage to the medical home for children with heritable disorders. This acknowledgement would be posted to the SACHDNC's website. As part of this motion, Dr. Kemper stated that no formal actions are requested of the Secretary or the Committee.

The NCC's report provides a foundation upon which specific structures and processes of health care can be developed and implemented in a variety of settings. Some of this work is already underway through projects in the HRSA-funded Regional Genetics and Newborn Screening Service Collaboratives as well as other nationally coordinated efforts related to specific conditions. The report offered the following recommendations:

1. Identify innovative programs, including care planning and coordination tools that address coordinated co-management.
2. Leverage existing system redesign efforts to incorporate care planning, coordinated co-management, and family access functions into electronic medical records and health information systems.
3. Collect survey data from specialists, primary care clinicians, and families regarding preferences, concerns, and needs related to the care of children with rare or complex conditions.
4. Promote outcomes-based clinical and health systems research to study the impact of coordinated co-management on patient health, patient and family functioning, patient and provider satisfaction, and costs of care.
5. Incorporate the Model of Coordinated Co-management, including the skills needed for leading and participating in team-based care, into the education and training of generalist and specialist physicians and other professionals involved in the care of children with rare and complex conditions.
6. Develop methods to incentivize coordination of care and to support necessary communication.

B. Committee Discussion and Vote

After hearing Dr. Kemper's report on *Family-Centered Coordinated Co-Management for Individuals with Heritable Conditions*, Dr. Bocchini opened the floor for comments before requesting a vote from the full Committee.

- A Committee member commented on two issues: (1) the importance of payment reform to support medical home models; and (2) the need for high-functioning, interprofessional teams in the provision of care. Dr. Kemper said he agreed with those comments.
- Another Committee member recommended changing the manuscript's title from "Individuals with Heritable Conditions" to "Children with Heritable Conditions" to clarify that the focus is on newborn screening.
- A Committee member observed that, after reviewing literature for years, most meta-analyses report that family-centered approaches get better outcomes, but the implementation of such approaches leaves much to be desired. He suggested that there are education and training issues as well as other barriers that go beyond funding. Dr. Kemper agreed, noting that the report does address some of these issues, and that Dr. Mann at HRSA's Maternal and Child Health Bureau is very interested in exploring ways to resolve these issues.
- Dr. Kemper said that Dr. Carl Cooley, chair of the NCC Medical Home Workgroup, views the medical home as a rethinking of what primary care ought to be. Different conditions over time may determine a different locus of control, but primary care physicians would still have an important role in providing care to individuals with heritable conditions. Formal communication is needed to understand who is doing what. A Committee member replied that he was not sure that the distinction between locus of management and the medical home was sufficiently clarified in the report, explaining that determining the locus of control is the job of the medical home. An excellent medical home is expected to develop a care plan that delineates health care for the patient, the specialist, and the primary care provider and where the locus of control will be (e.g., this doctor will do thyroid, this doctor will do immunizations, the patient or family will do this). Though determining the locus of control is the job of the medical home, the locus of control may be any number of places.
- An audience member commented that there has to be a communication between the medical home and insurers, because there have been incidences where a payer will not allow for a particular physician to order a particular test. Dr. Greene agreed, suggesting that the medical home develop a care plan with restrictions by insurers in mind.

The following motion, made by Dr. Bailey and seconded by Dr. Matern, was approved (12 votes for, none against):

- *MOTION #4 (APPROVED): To acknowledge the enhanced description of the medical home, and strategies for improving linkage to the medical home, for children with heritable disorders in the paper "Family Centered Coordinated Co-Management for Individuals with Heritable Conditions," by the NCC's Medical Home Workgroup.*

X. Medical Foods Manuscript

A. Report

Susan A. Berry, M.D.
Member. Follow Up and Treatment Subcommittee

Department of Pediatrics
University of Minnesota

Dr. Berry presented a report on *Insurance Coverage of Medical Foods for Treatment of Inherited Metabolic Disorders*, developed by the Follow-Up and Treatment Subcommittee's survey of parents about insurance coverage of medical foods and supplements as well as modified, low-protein foods for the treatment of children with inborn errors of metabolism (IEM). As part of her presentation, Dr. Berry requested a Motion for Committee Action for the Committee to review and acknowledge the report's significance in conveying the challenges parents face in paying for these treatments, due to lack of insurance coverage. Acknowledgement of this report would be posted to the SACHDNC's website. As part of this motion, Dr. Berry stated that no formal actions are requested of the Secretary or the Committee.

Nutritional treatments for individuals with IEM include:

- medical foods (specially compounded formulas supplying a substantial portion of nutrition for treatment of IEM);
- supplements (e.g., pharmacologic doses of cofactors or vitamins, amino acids, MCT oil, other vitamin-like drugs providing benefit); and
- specially manufactured, modified low-protein foods.

The survey and report stemmed from a Medical Foods Workgroup meeting of June 2008 as well as a medical foods survey by three of the HRSA-funded Regional Genetics and Newborn Screening Service Collaboratives (NY–mid Atlantic, Southeast, Great Lakes). During the June 2008 meeting, the workgroup heard from invited experts that each insurer has its own practices for the coverage of medical foods; and public practices vary from state to state. Furthermore, each state has different laws for the provision of medical foods. The survey, administered to 305 families anonymously, asked the parents of children from birth to age 18 about their (a) children's needs for metabolic foods and formulas, modifier low-protein foods, prescribed dietary supplements, medical feeding supplies and equipment; (b) out-of-pocket expense for medical food; and (c) the proportion or expenses for medical foods paid for by health insurance.

Survey results revealed that:

- Nearly all children had some degree of health care coverage, even if medical foods were not covered by the insurers.
- Most children needed more than one category of food/supplies. Though patterns of coverage varied from region to region, all regions observed significant challenges to families in paying for medical foods.
- Self-payment constituted a substantial portion of expenses for medical foods, a large portion for modified low-protein foods, and a portion of dietary supplements and feeding supplies. Coverage was variable. Families incurred at least some pocket expenses for about 20 percent of families using medical foods, about 30 percent of families using supplements, about 35 percent of families using feeding supplies, and about 60 percent of families using modified low-protein foods.
- Some families paid more than $500/month for modified low-protein foods, which are poorly supported by health insurers. Though coverage varies from region to region, all regions observed significant challenges for families that paid for these essential products. Need-based supports such as Medicaid and WIC are important sources of support. While some states that do pay for these products, those particular states were not involved in this survey.

Dr. Berry noted that the SACHDNC sent a letter to the Secretary in June 2010, addressing the insurance coverage of medical foods, foods modified to be low in protein, and pharmacological

doses of vitamins and amino acids. The Secretary said she could not adopt the recommendations until she had the results of a Department of Labor survey and recommendations from the Institute of Medicine (IOM).

Dr. Berry concluded her presentation by saying that insurance coverage for medical foods was not made part of essential health benefits in the Affordable Care Act. Therefore, efforts to ensure adequate coverage for medical foods may have to be determined on a state-by-state basis. Dr. Berry commented that working on a state-by-state basis to obtain coverage for medical foods will be extremely difficult.

B. Committee Discussion and Vote

After hearing Dr. Berry's presentation on *Insurance Coverage of Medical Foods for Treatment of Inherited Metabolic Disorders*, Dr. Bocchini opened the floor for comments before requesting a vote from the full Committee.

- An audience member from the IOM confirmed that the institute's 2011 draft report references medical foods as exempt from insurance coverage, and that the definition of an essential health benefits package under the Affordable Care Act (ACA) is now determined by the states.
- A Committee member noted that, in his state, all very young children get Medicaid and Women, Infants, and Children (WIC) coverage but, by age three, they are "on their own."
- An audience member who is a clinical dietician from Oregon stated that, according to the Council on Affordable Health Care, the cost of insuring for medical foods is estimated to be less than 1 percent of total health care dollars, adding that in Oregon only children up until five years of age are covered.
- An audience member and parent of a 13-year old son with PKU commented that coverage of medical foods is a big concern, noting that insurance coverage is not a huge cost to insurance companies. He encouraged the SACHDNC to continue monitoring this issue. Another audience member, having two children with metabolic conditions but one child who was denied coverage, added that the only way to ensure coverage is provided to resolve the issue at the federal level.
- Dr. Berry added her care coordinator spends about one-third of her time writing appeal letters to insurance companies, and that medical foods coverage could be resolved by a federal mandate, via legislative solution, or a uniform benefit package. However, since an essential health benefits package under the ACA is now determined by the states, insurance coverage will be chaotic.

The following motion, made by Dr. Bailey and seconded by Dr. Matern, was approved (12 votes for, none against):

- *MOTION #5 (APPROVED): To acknowledge the paper "Insurance Coverage of Medical Foods for Treatment of Inherited Metabolic Disorders" by the Follow-Up and Treatment Subcommittee of the SACHDNC.*

XI. Population-Based Carrier Screening Work Group: Update

Meredith Weaver, Ph.D., Sc.M., CGC
American College of Medical Genetics and Genomics
SACHDNC Carrier Screening Taskforce

Dr. Weaver provided an update on the Population-Based Carrier Screening Workgroup, charged by the SACHDNC to collect and document perspectives on public health, personal health, and the health care system readiness and needs for expanded population-based carrier screening for genetic conditions. To collect and document these perspectives, the workgroup engaged the NCC for the Regional Genetic and Newborn Screening Service Collaboratives to administer a modified policy Delphi survey. The survey, administered in April and May/June 2011, identified areas of consensus and lack of consensus.

Survey respondents indicated consensus for the following:

- Require informed consent.
- Consider burden to administer screening.
- Consider cost of follow-up/test procedures and actions.
- Shared decision making is desirable.
- Kits are desirable for screening.
- Comprehensive science and empirical evidence is feasible.

Respondent indicated lack of consensus about the following:

- Social issues (release, ownership, access, storage of test results)
- Psychological issues (implications and individual life experiences)
- Economic issues (cost-effectiveness, scope, purpose, desirability)
- Education and Communication issues (shared-decision making, providing comprehensive genetic counseling)
- Test issues (reporting secondary or evolving information, duty to inform/re-contact, potential/eventual use of whole genome sequencing for screening)

Report. A draft report is slated for submission to, and comments from, the SACHDNC in September 2012. Subsequently, the report will be distributed for public comments during October 2012, with a final presentation to the SACHDNC slated for January 2013.

XII. NBS Strategy Summit and 50th Anniversary NBS Campaign for 2013

Don Bailey, Ph.D., M.Ed.
Education and Training Subcommittee Chair

Dr. Bailey presented a report on the Newborn Screening Strategy Summit and the 50th Anniversary Newborn Screening Campaign for 2013.

NBS Strategy Summit. ACOG, AAP, IOM, APHL, CDC, and HRSA all recommend educating expectant parents about NBS; however, opinions vary widely as to how to best accomplish this task. Therefore, a planning group, in conjunction with HRSA and the communications firm Porter Novelli, convened a strategy summit on April 26–27, 2012 in Washington, D.C. to discuss strategies to inform and educate parents and the public about NBS.

At Porter Novelli's suggestion, summit participants defined the following audiences and "calls to action" for the campaign:

- Expectant parents: "Ask about newborn screening, and newborn screening results"
- Health care professionals: "Talk with patients, promote the benefits of newborn screening."
- Policymakers: "Support newborn screening in states."

- General public: "Support newborn screening."

Calls to action can serve as the basis for targeted messaging to specific audiences. The definitions of each audience will have to be refined to facilitate greater specificity of roles, messages, and outreach strategies to enable the development and testing of specific messages to target audiences through focus groups, interviews, or other qualitative research.

50th Anniversary NBS Campaign for 2013. The CDC and APHL are organizing the 50th Anniversary NBS Campaign for 2013, with coordination and collaboration with the SACHDNC and the Education and Training Subcommittee. Potential audiences are expectant parents and families, health care providers, policymakers, and state/national media, with final audience focus dependent on available funds. If funds are limited, the campaign will focus on reaching policymakers, state/national media, and health care providers. If funds are available, a variety of public service announcements may be targeted to the general public.

In addition, there are two planned activities for the campaign:

- Newborn Screening Symposium, May 5–10, 2013, Atlanta, Georgia. This symposium will feature: (a) site visits to the Georgia state public health lab and CDC's Newborn Screening and Molecular Biology Branch, (b) an exhibit of newborn screening artifacts and historical memorabilia, and (c) a celebration book with interactive media, presenting patient/parent perspectives for both the general public and legislative decision makers.
- National Newborn Screening Commemorative Event, Fall 2013, Washington, D.C. This event will focus on legislative decision makers. Scope and themes are under development at this time. Parent representatives to the Education and Training Subcommittee have indicated interest in inviting advocacy groups to bring affected children to visit their representatives in Congress. Another suggestion involved inviting high-profile speakers and the media to attend as well.

At present, CDC and APHL are exploring themes and messaging for the 50th Anniversary NBS Campaign. Dr. Bailey, chair of the Education and Training Subcommittee, will participate in monthly calls and discussions to talk both about these upcoming activities and provide input as needed.

Comments

- Dr. Bailey commented that planners of the NBS Awareness Campaign want to send the message that NBS is a great program that needs more support to ensure that newborns identified with a heritable condition receive needed care.
- An audience member from APHL noted that it will be a challenge to devise messages that work with the general public as well as scientists at the CDC. Another audience member, a patient advocate, added that the biggest impetus for spreading awareness are affected family members like her.
- A Committee member from the CDC spoke with a colleague about the possibility of including a special supplement on NBS in the *Morbidity and Mortality Weekly Report*, and perhaps one long-range plan could involve securing private donors. Dr. Bailey said both of ideas were exciting. Another Committee member said that professional organizations such as the Society for Inherited Metabolic Disorders (SIMD) would be willing to help with the NBS Campaign for 2013.
- Dr. Bocchini observed that there were many good ideas for the NBS Awareness Campaign, and that interactions with other organizations such as the CDC, APHL, and Genetic Alliance

will be helpful. Dr. Bailey added that agreeing on, and continuity with, core messages to targeted audiences would be great.

XIII. Condition Review Process Report: Update

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

Dr. Kemper presented a report on Condition Review Workgroup's evidence review summit, held April 24–25, 2012 in Washington, D.C. The summit provided an opportunity to improve the review process and examine issues surrounding public health evaluation.

First, Dr. Kemper conveyed:

- Recommendations are evidence-based.
- Outcomes that matter most are health benefits to the screened individual.
- Recommendations must account for the readiness and feasibility of screening within state public health systems.
- Recommendations are not modified to accommodate concerns about insurance coverage, medico-legal liability, or legislation.

Three Separate Report Components. Future reports by the Condition Review Workgroup will include three separate components:

1. **Systematic evidence review**, which involves (a) examining the body, and coherence of, evidence according the criteria specified in eight key questions; and (b) ranking the evidence as convincing, adequate, or inadequate.

2. **Estimation of bounds of benefit and harm** (i.e. effect on public health), using decision-analytic modeling similar to the methodology employed during the evidence review for hyperbilirubinemia. Key inputs will be prevalence, test accuracy, treatment effectiveness, and estimation of harm, resulting in a matrix of *net benefit assessment*.

3. **Assessment of readiness and feasibility of implementing comprehensive NBS from the state public health department perspective** (i.e., effect on health system at large) which entails (a) classifying readiness of the evidence as ready, developmental, or unprepared; and (b) assessing feasibility as high, moderate, or low. This results in a matrix of *readiness and feasibility*.

Dr. Kemper then displayed a combined matrix of net benefit assessment with readiness and feasibility to illustrate a revised review process that incorporates a public health evaluation. This combined matrix will be circulated for comment and feedback. Dr. Kemper stated that he will ask the Committee to approve and review a final revised decision making process at the next Committee meeting.

Comments

- Dr. Kemper said that these proposed revisions will allow the Condition Review Workgroup to include the family perspective more than ever (e.g., benefits from screening). He also mentioned that the Condition Review Workgroup will answer key questions and provide verbiage about the strength of the evidence at each step, but will not assign a grade (i.e.,

matrix 1 is an "A"). Instead, the objective is just to ensure that there is a common approach that can be used consistently in grading by the SACHDNC.

- Dr. Bocchini noted that adding feasibility and readiness in the proposed revisions incorporate review of the public health impact and provide transparency and attunement to the evidence. It will be the collective wisdom of the full Committee to make the final decision. Since two members of the full Committee will be part of the Condition Review Working Group, the full Committee will be informed of any issues (e.g., data) that may missing or incomplete.
- A Committee member asked about the role of the SACHDNC in the process of pilot studies, and suggested inviting an expert to address the Committee about the pilot study process at a future meeting. Dr. Bocchini agreed that this could be a topic to address at a subsequent Committee meeting.
- Dr. Kemper commented that full Committee will have to define distinctions (i.e., how great the net benefit must be before determining if it is "significant"). For instance, if a condition has a very, very low prevalence, even with a good test, one may likely end up with a lot more false positives than true positives. Determining exactly the right threshold is challenging. If one can prevent a horrible outcome in a tiny number of children, yet a huge number of children must be screened in order to locate this tiny number, how do you weigh and compare this against any potential harm?

XIV. Nutrition/Dietary Supplement Interventions for Inborn Errors of Metabolism: Update

Kathryn Camp, M.S., R.D., CSP
Office of Dietary Supplements
National Institutes of Health

Ms. Camp informed the Committee about the NIH initiative for Nutrition and Dietary Supplements Interventions for Inborn Errors of Metabolism (NDSI-IEM). Though early intervention and treatment saves lives and prevents morbidity/mortality in individuals with IEM, robust data are lacking regarding many treatments because of the small size of IEM-affected populations. The initiative's mission is to (a) identify knowledge gaps regarding safety/effectiveness of nutrition/dietary supplement interventions, and (b) collaborate/partner with a wide range of stakeholders in developing/implementing a framework for conducting evidence-based research.

In December 2011, the Office of Dietary Supplements collaborated with advocacy organizations, clinical researchers, academics, Regional Genetic and Newborn Screening Service Collaboratives, industry representatives, and federal partners in developing the NDSI-IEM initiative. The initiative will strive to use small pilot data or phase two studies, not phase three trials, for the data gathering of IEM interventions. The NIH Office of Rare Diseases will coordinate with the FDA to obtain approval of the proposed study designs and assessments prior to project implementation, and the National Center for Advancing Translational Sciences (NCATS) as well as other NIH translational research programs exist as resources for bridging the gap between scientific discovery and clinical application.

Among other activities, a core planning group is developing a list of all screened IEM conditions and their treatments, to survey metabolic specialists and determine which metabolic conditions require the most immediate need for research infrastructure. A web portal is also in development, to provide available information and resources to researchers/clinicians as well as patients/families concerning nutrition/dietary supplements for IEM conditions.

Future activities include the following:

- Build a framework for any disease and treatment.
- Foster cooperation and facilitate successful grant applications through collaboration among clinical/research teams in NIH and FDA.
- Use of existing mechanisms, i.e., the ISSIEM and IRDRC, to foster international collaboration.
- Conduct natural history studies.
- Develop an education/mentoring plan, especially for new researchers.
- Standardize database information and language.
- Build or utilize registries.

Comments

- Ms. Camp commented that there is currently no specific NIH funding for this initiative; however, she hopes that the development of requests for proposals with institute partners, or funders from each of the major NIH institutes, could address this issue.
- Ms. Camp noted that another hope for the initiative is to build a multicenter research infrastructure. Since it won't be possible to do randomized trials for all IEM conditions, efforts will also entail determining alternative ways of conducting research.

XV. NIH PKU: Update

Melissa A. Parisi, M.D., Ph.D.
The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
National Institutes of Health

Dr. Parisi reported on an NIH Phenylketonuria (PKU) Scientific Review Conference, held during February 2012 and sponsored by the Office of Rare Diseases Research, the Office of Dietary Supplements, and NICHD. NIH recognized that PKU screening/management guidelines required update, since the previous version was established in 2000. For example, the FDA approved Kuvan® for treatment in December 2007, but not all individuals affected by PKU respond to Kuvan. In addition, though PKU was one of the first conditions subject to NBS, many questions still remain unanswered.

The purpose of the conference was to review the state-of-science regarding PKU as well as required future research. Highlights of the conference consist of the following:

- **An AHRQ comparative effectiveness review on adjuvant treatments**. This review found (a) strong support and evidence for necessary, life-long treatment of PKU; (b) an absence of long-term data to determine patient issues with cognition and quality of life; and (c) the need for large, rigorous, randomized clinical trials—or at least carefully designed studies—to obtain adequate evidence to support conclusions reached regarding management/care of patients with PKU.
- **Significant points to inform revised guideline development for PKU study, treatment, and care**. Five working groups from NIH convened at least eight times over a one-year period to compile significant points and inform the development of updated guidelines for PKU. These points are that: (a) lifelong treatment is essential, (b) critical elements were identified for the medical, nutritional, cognitive, emotional, behavioral, and social management of PKU throughout the lifespan, including pregnancy; (c) optimal management

is essential to prevent maternal PKU syndrome; (d) double-blind, placebo controlled studies have the greatest rigor for determining responsiveness to sapropterin; (e) genotyping is valuable to categorize PKU severity of PKU and responsiveness to sapropterin; (f) insurance coverage and psychosocial factors influence access to/compliance with nutritional/other therapies; (g) a critical need exists for further treatment options for individuals with no/minimal PAH enzyme activity; and (h) revised practice guidelines are necessary.

Dr. Parisi presented grids, developed by one of the five NIH working groups, to screen/measure treatment across an individual's life span—medical, nutritional, metabolic, neurological, cognitive, and behavioral/emotional/social outcomes. Such grids could possibly be used for populations affected by conditions other than PKU.

New treatments discussed were (a) gene therapy, and (b) PEG-PAL (PEGylated phenylalanine ammonia lyase), an enzyme that does not require a co-factor. PEG-PAL is in phase two trials and appears to be a promising therapy.

Future research needs encompassed the following areas:

- Outcomes/measures
- Basic science/neurological effects
- Access/social supports
- Clinical trial design
- Genotyping
- Resources/technology

Dr. Parisi concluded by noting that a white paper on the conference is in development, and that a conference webcast is available on the NIH video cast site.

Comments

- Dr. Bocchini observed that the presentation on PKU by Dr. Parisi was an appropriate conclusion to the SACHDNC's meeting. PKU was first condition subjected to NBS, and the conference indicates just how much work remains to be done as well as how new technologies and treatments change what can be done for individuals affected with a heritable condition.
- A Committee member who had attended the NIH conference mentioned that unanswered questions about PKU should not mean that new treatments should not be seriously considered—one must weigh the potential benefits of treatment versus the harm created by not administering the new treatment. She also added that a crosscutting workgroup at the conference worked on developing some workable PKU definitions (e.g., classic, severe).

XVI. Adjournment

Dr. Bocchini thanked Committee and audience members for their contributions, and adjourned the meeting at 2:52 p.m. on May 18, 2012.