Advisory Committee on Heritable Disorders in Newborns and Children

Summary of Second Meeting
August 27-28, 2015

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) convened for its second meeting at 8:30 a.m. EDT on Thursday, August 27, 2015. The meeting was adjourned at 12:30 p.m. EDT on Friday, August 28, 2015. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

COMMITTEE MEMBERS

Don Bailey, Ph.D., M.Ed.
Distinguished Fellow
Early Childhood Development
RTI International

Joseph A. Bocchini, Jr., M.D.
(Committee Chairperson)
Professor and Chairman
Department of Pediatrics
Louisiana State University
Health Sciences Center in Shreveport

Jeffrey Botkin, M.D., M.P.H.
Professor of Pediatrics and Medical Ethics
Associate Vice President for Research
University of Utah

Fred Lorey, Ph.D.
The International Society for Neonatal Screening
North American Council Representative

Dietrich Matern, M.D., Ph.D.
Professor of Laboratory Medicine
Medical Genetics and Pediatrics
Mayo Clinic

Stephen McDonough, M.D.
Sanford Health Bismarck
Bismarck, ND 58502-5505

Alexis Thompson, M.D.
Division of Hematology/Oncology
Children's Memorial Hospital

Catherine A. L. Wicklund, M.S., C.G.C.
Feinberg School of Medicine
Center for Genetic Medicine
Northwestern University

Andrea M. Williams, B.A.
Executive Director
The Children’s Sickle Cell Foundation, Inc.

EX-OFFICIO MEMBERS

Agency for Healthcare Research and Quality
Kamila Mistry, Ph.D., M.P.H.
Staff Service Fellow
Office of Extramural Research, Education and Priority Populations

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

Food and Drug Administration
Kellie B. Kelm, Ph.D.
Chief, Cardio-Renal Diagnostic Devices Branch
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostic Devices Evaluation and Safety

Health Resources and Services Administration
Michael Lu, M.D., M.P.H.
Associate Administrator
Maternal and Child Health Bureau

National Institutes of Health
Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development

DESIGNATED FEDERAL OFFICIAL
Debi Sarkar. M.P.H.
Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau

ORGANIZATIONAL REPRESENTATIVES

American Academy of Family Physicians
Frederick M. Chen, M.D., M.P.H., F.A.A.F.P.
Family Practitioner
Department of Family Medicine
University of Washington

American Academy of Pediatrics
Beth Tarini, M.D., M.S., F.A.A.P.
University of Michigan Health System

American College of Medical Genetics and Genomics
Michael S. Watson, Ph.D., F.A.C.M.G.
Executive Director

American College of Obstetricians and Gynecologists
Joseph R. Biggio, Jr., M.D.
Director and Professor,
Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology

Association of Maternal and Child Health Programs
Debbie Badawi, M.D.
Medical Director
Office for Genetics and People with Special Health Care Needs
Prevention and Health Promotion Administration
Maryland Department of Health and Mental Hygiene

Association of Public Health Laboratories
Susan M. Tanksley, Ph.D.
Manager, Laboratory Operations Unit
Texas Department of State Health Services

Association of State and Territorial Health Officials
Christopher Kus, M.D., M.P.H.
Associate Medical Director
Division of Family Health
New York State Department of Health

Department of Defense
LTC Adam B. Kanis
Tripler Army Medical Center

Genetic Alliance
Natasha F. Bonhomme
Vice President of Strategic Development
Genetic Alliance

March of Dimes
Siobhan Dolan, M.D., M.P.H.
Medical Advisor
March of Dimes

National Society of Genetic Counselors
Cate Walsh Vockley, M.S., C.G.C.
Senior Genetic Counselor
Division of Medical Genetics
Children's Hospital of Pittsburgh

Society for Inherited Metabolic Disorders
Carol Greene, M.D.
University of Maryland Medical System
Pediatric Genetics

Table of Contents

I. Administrative Business: August 27, 2015

A. Welcome and Roll Call

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

Debi Sarkar, M.P.H.
Designated Federal Official
Health Resources and Services Administration

Dr. Joseph Bocchini welcomed the Committee members and other participants to the second meeting of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC). Prior to taking roll, he announced that Dr. Kamila Mistry was the new ex-officio member representing the Agency for Healthcare Research and Quality (AHRQ) and that Dr. Joseph Biggio was the new organizational representative for the American College of Obstetricians and Gynecologists (ACOG).

Voting members present were:

- Dr. Don Bailey
- Dr. Bocchini
- Dr. Jeffrey Botkin
- Dr. Fred Lorey
- Dr. Dietrich Matern
- Dr. Stephen McDonough
- Dr. Alexis Thompson
- Ms. Catherine Wicklund
- Ms. Andrea Williams

Ex Officio members present were:

- Agency for Healthcare Research and Quality: Dr. Kamila Mistry
- Centers for Disease Control and Prevention: Dr. Colleen Boyle
- Food and Drug Administration: Dr. Kellie Kelm
- Health Resources and Services Administration (HRSA): Ms. Joan Scott (for Dr. Michael Lu)
- National Institutes of Health: Dr. Tina Irv and Dr. Melissa Parisi (for Dr. Alan Guttmacher)

Nonvoting Organizational representatives present were:

- American Academy of Pediatrics (AAFP): Dr. Robert Ostrander
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- Association of Maternal and Child Health: Dr. Debbie Badawi
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Association of State and Territorial Health Officials: Dr. Christopher Kus
- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes: Dr. Edward McCabe
- National Society of Genetic Counselors: Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders: Dr. Carole Greene

Dr. Bocchini reminded the participants that during its previous meeting the Committee decided to prioritize work in response to its reauthorization by forming three workgroups, the Pilot Study Workgroup, the Cost Analysis Workgroup, and the Timeliness Workgroup. The Committee is also working to identify the essential elements needed for the nomination of a condition in order to be able to meet the nine-month deadline for making recommendations concerning a nominated condition. The existing subcommittees are on hold until the Committee addresses these issues. Dr. Bocchini anticipated that the subcommittees would identify potential projects for evaluation by the full Committee during the February 2016 meeting.

The next Committee meeting will be a webinar on November 2-3. The four 2016 meetings will take place on February 11-12, May 9-10, July 25-26, and November 3-4.

Ms. Debi Sarkar, the Health Resources and Services Administration's (HRSA) Designated Federal Official (DFO), also greeted the participants. She announced that there are three openings for membership that are coming open for next year. HRSA released a solicitation asking for nominations to fill the openings and received multiple nominations. The clearance process is underway and will take approximately one year to complete. She anticipated that the terms for the new voting members would begin in July 2016.

Concerning the organizational representatives, Ms. Sarkar indicated that consideration is being given to expanding the number of organizations represented. Such a move would require changes to the Committee's bylaws. She anticipated that more information concerning this issue would be shared during the November webinar.

Ms. Sarkar reviewed the conflict of interest recusal requirements for voting members and outlined that process for participating in the webcast for the public.

B. **Committee Correspondence**

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

Dr. Bocchini reported that the ACHDNC sent correspondence to the Secretary of the U.S. Department of Health and Human Services (HHS), Dr. Sylvia Mathews Burwell that included a recommendation to include mucopolysaccharidosis 1 (MPS1) on the Recommended Uniform Screening Panel (RUSP) and recommendations concerning the timeliness of the newborn screening (NBS) process. The Secretary acknowledged receipt of the timeliness recommendations. The MPS1 recommendation is currently under review at HHS.

The Committee also sent a letter to the Secretary expressing support for the recommendations for NBS informed consent. The Secretary had not yet responded to this letter.

C. **Approval of May 2015 Meeting Minutes**

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

Dr. Bocchini indicated that minutes for the May 2015 ACHDNC meeting were included in the briefing book. There were no recommendations for substantive changes to the minutes, but a few members and representatives identified minor typographical corrections. The Committee approved the minutes unanimously.

II. Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) Presentation

Marci Sontag, Ph. D.
Associate Director, NewSTEPs
Assistant Professor of Epidemiology
Colorado School of Public Health
Aurora, CO

Dr. Marci Sontag presented a summary of the state of NBS in the United States and of the Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) program. She began by describing the funding and administrative structure of NewSTEPs, which provides a technical assistance and resource center and data repository in support of the NBS system throughout the United States. Her remarks focused on the data available to NBS programs as they work to improve their systems.

The NewSTEPs data repository was designed to provide tools to NBS systems to help them evaluate, analyze, and benchmark their programs. It has three main components: state profiles (including demographics and information about state policies), case definitions, and quality indicators. It took several years to build the data repository, and it was built in partnership with many NBS community members. Dr. Sontag acknowledged that difficulties involved in obtaining data, specifically the time it takes to enter data. NewSTEPs found that interviewing program personnel was helpful as it enabled it to both collect data and educate NBS program staff about the resource. Data collection is an iterative process based on a continuous process of data entry, correction, and curation designed to ensure that the repository contents correctly represent the state NBS programs.

Dr. Sontag shared a map of the NBS process that begins with the pre-analytic stage and goes through several stages before ending at the post-analytic stage. She emphasized that different states have different needs based on their size (50 percent of states have between 29,000 and 87,000 births per year). Birth rates vary between states with the highest birthrates in Utah, Texas, and Alaska and the lowest rates in New England, Oregon, and Florida. Including Puerto Rico, there are 52 NBS programs in the United States that use 36 laboratories. There are multiple factors (including birth rate and geographic size) that affect timeliness and access to care. NewSTEPs is working with states to identify their needs based on their various geographic and birthrate characteristics.

Dried Blood Spot Collection
The Heartland Regional Collaborative did a survey of all 50 states and the District of Columbia concerning the mechanisms through which they allow refusals of NBS. Consent is implied in most states, but most states allow parents to opt out of NBS for religious or other reasons. Three states have no conditions for refusals.

States store dried blood spots (DBS) for a wide range of time periods (from one month to indefinite periods). On the short end, tests are saved just long enough to confirm abnormal tests. States also vary in their data storage polices. Some states do not have data retention policies. Storage periods range from less than two years to more than 20 years. There are many issues connected to data storage, including who can request data.

Informed Consent for Research and Storage of DBS

The Newborn Screening Saves Lives Act emphasized the idea of the need to provide consent for research use of DBS. Research on DBS is considered human subject research and requires consent. States vary on their policies concerning research on DBS, but all are concerned about the implications for use of DBS. Dr. Sontag indicated that some state policies on the use of residual DBS for research would change as a result of the Newborn Screening Saves Lives Act Reauthorization (NBSSLRA), specifically that consent will be required in the future. NewSTEPs has not collected data on whether the residual DBS used for research are used for surveillance or research external to state and/or laboratory needs; the program is working to determine how to ask questions concerning how laboratories define research, including use for quality assurance (QA)/quality control (QC). Dr. Sontag noted that there is a grey area between research and QA/QC that is currently in the process of being defined.

NBS Timeliness

NewSTEPs has been looking into timeliness of NBS from the state perspective. Within the data repository, NewSTEPs has information on approximately 900 reported cases with a disorder diagnosed by NBS from states with signed memoranda of understanding (MOUs) (this data includes a limited number of disorders). The program is collecting specific types of information in a pilot format to support the refinement of the case definitions.

Dr. Sontag reported that the median time of sample collection for the 900 cases was slightly less than 40 hours of life; most samples were collected within 48 hours. There was a small number that were collected much too late; these cases help NewSTEPs identify states that might need help with regard to collection time. She stressed the importance of looking at the range of collection times in individual states, not just their median collection time.

NewSTEPS also looked at shipment, arrival at the laboratories, and laboratory hours of operation. Some states provide a courier service for DBS samples; in others, the birthing centers provide the courier services, and some states are in the process of implementing a service. Courier services include both private services that pick up on a schedule set by the NBS program and public carriers such as FedEx that pick up on predetermined schedules. In the past five years, the number of states using couriers has increased significantly. Tennessee recently implemented a courier system that gets samples from all over the state to the laboratory in a much timelier manner.

Laboratories must be open in order to test samples. NewSTEPS looked at laboratory weekend hours and follow-up weekend hours. Only a limited number of states have laboratories with Saturday and Sunday hours; a majority of state laboratories have Saturday only hours. A similar pattern holds for to follow-up services, although many states without set weekend hours for follow-up keep staff on call for this purpose. Colorado is one of the states that has recently expanded its NBS screening program to weekends and implemented courier services six days a week, including Sunday, which allows samples to be in the laboratory on Monday morning. The state also collaborated with the Colorado Hospital Association to improve timeliness of specimen collection and shipment.

Data Entry and Confirmation

Data entry and confirmation is a challenge for state NBS programs. States use laboratory information management systems (LIMS) to track the entry of samples into their programs, their progress through the system, and the data that is sent out to clinicians. More information on the LIMS in use in each state can be found on NewSTEPs' website.

States face many challenges in entering the DBS card information (e.g., cards may be illegible or missing information), which can delay screening and follow-up. Work on improving this process is ongoing.

NBS Processes

States fall into two categories based on the number of screens that they run. There is some overlap between the one-screen states and the two-screen states because some states have one mandatory screen with a highly recommended second screen (e.g., Washington and Wyoming). It is not clear whether there is a greater benefit to doing one screen or two screens, in part because the cut-offs are different. The states that conduct two screens identify a lot of children with congenital hypothyroidism (CH) on the second screen;

however, there is some question about whether these children would have been identified on the first screen if the cut-offs were different. A recent study concluded that two-screen states might be able to convert to a single screen for CH without loss of performance (it did not address other conditions for which these states use the second screening).

Fees charged for NBS vary greatly among the states. Some states are completely dependent on fees, while others use general funds and other billing mechanisms. Activities covered by NBS screening fees include program staff, courier services, running the laboratory tests, and follow-up services.

There are currently 32 disorders on the RUSP. To assess states based on the conditions for which they screen, NewSTEPs organized the screens into a core panel (the 32 conditions on the RUSP), a recommended panel (conditions that can be detected in the differential diagnosis of a core disorder), and all other screens. Currently, only Illinois and New York are screening for all 32 core conditions, but many other states are very close to doing so. Information on the conditions screened and being considered for screening in each state can be found in the screened conditions reports on the NewSTEPs website.

Decision Making and Policies
States rely on input from sources such as advisory committees, boards of health, and health commissioners to inform decisions concerning NBS. Legislatures often are responsible for decision making. The process can be murky and require many iterations.

Eleven states have advisory committees that are mandated by statute or law. A majority of states have voluntary advisory committees. Two states do not have any type of advisory committees. Advisory committees generally include consumers, laboratory representatives (pathology and chemistry), public health laboratory representatives, clinicians, hospital association representatives, March of Dimes representatives, medical ethicists, and NBS program representatives. NewSTEPs collects, but does not verify, information on the frequency with which state advisory committees meet; the website includes links to minutes of some of the advisory committee minutes. NewSTEPs does not distinguish between internal and external advisory boards.

Analytic to Post-Analytic Processes
Dr. Sontag presented a snapshot of the types of data that NewSTEPs anticipates being able to present as its data repository grows by discussing timeliness of diagnosis. The median time from birth to receipt by the laboratory is four days of life, from time to release of out-of-range results is seven days (critical and non-critical combined), and from intervention and diagnosis is wide ranging. NewSTEPs can break out the data on timeliness by condition. States are aware of the need for timely reporting of results, but there is still room to improve. With regard to time to intervention, NewSTEPs relies on its clinician partners to help it interpret the data and identify aspects of the process that could be improved. The data also show a wide range in times to diagnosis.

Using data from five states for cystic fibrosis (CF) based on a single screen; Dr. Sontag showed how timeliness varies for receipt by laboratory, receipt of results, intervention, and diagnosis. In many cases, children are receiving intervention even though they do not have a confirmed diagnosis. Similar data is available for other conditions.

Quality Indicators
Dr. Sontag stressed the value of taking the data from individual cases and applying the information to the quality indicators. A set of eight quality indicators spans the course of NBS. Each state has its own process for collecting the quality indicators, which means that data collected from different states might not be comparable. One way to improve the comparability of the data is to collaborate with the LIMS vendors. Currently, NewSTEPs is collaborating with the two largest LIMS vendors, PerkinElmer and Natus that provide access to data from more than half of the states. NewSTEPs plans to expand its partnerships to other vendors and states with locally developed systems.

NewSTEPs identified some challenges in data collection. Dr. Sontag highlighted the difficulties in determining the percent of invalid DBS specimens due to improper collection. On the surface, this should

not be a difficult question to answer; however, some states can have subfields addressing specific reasons for specimens not being valid while other states might take different approaches to reporting on invalid DBS samples. NewSTEPS will continue to work with the LIMS vendors on the data collection effort, specifically to ensure that data is extracted as soon as it is available within the system. Outreach to other vendors and states will continue.

The final step in the process is evaluating the newborn and ensuring that the diagnosis is confirmed. Case definitions become very important in this phase. The data repository helps support the development of the accurate characterization of the frequency of specific newborn disorders at both the local and national level. Ensuring consistency of how disorders are counted across physicians and hospitals is essential. Case definitions allow cases to be more consistently categorized.

Challenges associated with the case definitions include the need to change the culture and the time involved. Many states are incorporating information on diagnostic information into their NBS data systems, laboratory systems, and follow-up systems, but many are not. NewSTEPs has a Condition Definition Implementation Workgroup that is helping it work through issues related to marketing and implementation of case definitions.

Timeliness Projects
NewSTEPs has been participating in the Collaborative Improvement and Innovation Network (CoIIN) to support the improvement of timeliness in NBS. Eight states are voluntarily participating in CoIIN's continuous quality improvement activities that address challenges in NBS timeliness. Each state appointed a five-member team consisting of representatives from laboratories, follow-up programs, and hospitals to work on the 15-month project. The teams are working together to share ideas and identify solutions.

Building on the work of CoIIN, NewSTEPs will offer a new funding opportunity, NewSTEPs 360. This program, which begins on September 1, will provide funding to 20 states to improve NBS timeliness over the course of three years. Awards will be made on a competitive basis.

NewSTEPs is also using its Project Instant Gratification (PIGs) to give something back to the states in return for their entering data into the data repository. PIGs provides "Did You Know?" emails, personalized quality indicator reports that show how each state compares with the other states, and run charts. The emails are distributed by the NewSTEPs list serve and include information gained with the data in the data repository, fun facts, and features about activities in the various states. Run charts help states see how the changes that they are implementing are affecting their timeliness month to month. Run charts will be built into the NewSTEPs 360 website, which will make them more widely available.

Next Steps
Dr. Sontag concluded her remarks by thanking all of the groups that contributed to the work she described during her presentation, including the NewSTEPS Steering Committee, workgroups, NBS programs, regional collaboratives, federal and private partners, and vendors.

Moving forward, NewSTEPS is partnering with NBS programs to develop solutions that strengthen the system by focusing on quality data, technical assistance, and bringing people together to share ideas and experiences.

Committee Discussion:

- An organizational representative affirmed that QA/QC activities are not considered research as they are required by the Clinical Laboratory Improvement Amendments (CLIA) for laboratories to continue operations.
- In response to a question about delays in laboratory processing and follow-up due to missing information, Dr. Sontag indicated that the missing information varies from state to state because of the individual states' processes.
- An organizational representative pointed out that states that rely solely on fees to pay for NBS have a potentially limited well from which they can draw. Fees are often paid by the hospitals, which limits the potential growth in the fees.

- An organizational representative inquired whether case definitions should be developed for candidate disorders, which would prevent the need to define them after the fact as NewSTEPs is currently doing. Dr. Sontag replied affirmatively given that it has taken much effort to develop case definitions for conditions on the RUSP. It would be very helpful to know how the diagnosis of a condition is confirmed.
- Concerning implied consent, a Committee member noted that most parents know little about NBS and the associated processes. Implied consent is not the best way to characterize the way in which NBS programs are organized. Dr. Sontag agreed to work on altering the wording.
- With regard to the data comparing states to each other, an organizational representative asked whether the state-specific data is available to groups other than the state, specifically to groups that might be involved in advocating for NBS and are looking for ways to bolster NBS programs. Dr. Sontag indicated that NewSTEPs is just beginning to develop these policies. Requests for data will have to go through a data review group made up of members with experience in the areas of institutional review boards and advocacy as well as parents and state and local NBS program representatives. NewSTEPs is working on developing the policies that will be used by the group to provide access to the data in a way that is sensitive to the states and ensures that it is used appropriately.
- An organizational representative noted that much more information concerning diagnosis and intervention would be needed before conclusions could be drawn about the outliers. In some conditions, interventions might not be needed by all patients.
- Concerning the retention of data, an organizational representative noted that CLIA requires the retention of test results for at least two years after reporting. Dr. Sontag clarified that the shortest retention time for reports in the data presented was two years (sample retention might be shorter).
- A Committee member suggested being more specific in future references to data as it would help people who are not as well versed in NBS better understand the breadth of the information collected by NewSTEPs.
- Committee members inquired whether California, which has a 12-hour collection time, was included in the slide showing the ranges of specimen collection times. Dr. Sontag indicated that it was not and stressed that the information she presented was a snapshot that illustrated the information that NewSTEPs would be able to provide on a larger scale.
- An organization representative highlighted the difference between clinical case definition and surveillance case definition. The needs for both types of case definitions are different and they do not necessarily have consequences for the other. These differences should be kept in mind when considering case definitions and their implications for condition nomination.
- An audience member from an NBS program echoed the comment about implied consent and emphasized the importance of understanding what is happening at a regional level, not just the local level. In some cases, regional organizations might handle activities that are not supported by a state (e.g., around-the-clock reporting). NewSTEPs should account for these arrangements. Dr. Sontag indicated that NewSTEPs had considered the idea of reaching out to regional laboratories and collaboratives but relied on state reporting; the program will look into broadening the reporting sources.

III. Public Comments

Ms. Elisa Seeger, President, Aidan Jack Seeger Foundation: Ms. Seeger, who lost her seven-year-old son due to a late diagnosis of adrenoleukodystrophy (ALD), expressed her hope that the Committee's review of the evidence shows why ALD NBS is so important. The test is accurate, there is a viable treatment method, and early diagnosis saves lives and prevents an early death for thousands of boys. She strongly encouraged the Committee to recommend the addition of ALD to the RUSP to give affected children a chance for a normal life.

Mr. Spencer Barsh, Stop ALD Foundation: Mr. Barsh, who is 15 years old, was born with ALD and diagnosed when he was 1 year old; following which he received a stem cell transplant. He described his

athletic, academic, and volunteer activities, all of which would not be possible without early diagnosis and treatment. His cousin was less fortunate and died at age 12, a few years after being diagnosed.

Dr. Amber Salzman, Fight ALD: Fighting Illness through Education and Stop ALD Foundation: Dr. Salzman, Mr. Barsh's mother, related how her nephew's late ALD diagnosis alerted the family to the need to screen for the condition and take the necessary measures to ensure the birth of healthy children. There is an effective ALD screen, an infrastructure to support diagnosed families, and available treatments. Currently, only one state, New York, screens for ALD; newborns and their older siblings in the state are receiving screenings in time for interventions. Additionally, adults with a milder form of the disease are also obtaining diagnoses. Early diagnosis reduces costs to the health care system and saves lives. She strongly advocated for the nationwide implementation of ALD screening.

Ms. Janice Sherwood, Fight ALD: Ms. Sherwood recounted how she lost her son to ALD at age 8, six months after his diagnosis. Working with several other organizations, Fight ALD worked to get legislative approval of ALD NBS in California. Although the governor signed the bill almost a year ago, screening has not been implemented because of a requirement in the legislation that requires the condition be on the RUSP before screening begins. In the interim, boys are dying unnecessarily due to lack of screening. She asked the Committee to recommend the addition of ALD to the RUSP so that states that are waiting for its addition can begin screening.

Mr. James Wuzak: Mr. Wuzak has adult onset ALD; he began showing symptoms around age 25. Over the past 20 years he has been on a diagnostic odyssey, which included a $100,000 back surgery, multiple treatments and numerous visits to specialists, all of which only treated symptoms without finding a root cause. He estimated that this odyssey cost more than $500,000, most of which was paid by taxpayers. He was only diagnosed in June at age 44 because his niece gave birth to a girl in New York who screened positive for ALD. Comparing the symptoms, he began to suspect that it was the cause of his problems. He stressed that knowledge is the best ammunition in the fight against ALD.

Ms. Kathleen Kelley, Brian's Hope Foundation: Ms. Kelley's brother received his ALD diagnosis at age six following a CT scan that was done because of a sledding accident and a subsequent MRI. Now at age 27, he is a 20-year bone marrow transplant survivor. Because of her brother's diagnosis, she learned that she is an ALD carrier and can benefit from genetic counseling and good medical care and has the hope of having healthy children. The girls born and screened in New York will have similar opportunities and the hope of avoiding the heartache that comes with a later diagnosis of ALD. She strongly advocated for the Committee to take action and recommend the addition of ALD to the RUSP so that newborns can receive the lifesaving screening and early intervention.

IV. ALD Final Evidence Review Report

Alex Kemper, M.D., M.P.H., M.S.
Condition Review Workgroup
Duke Clinical Research Institute
Department of Pediatrics
Duke University
Durham, NC

Dr. Alex Kemper expressed his appreciation for the comments from the public as they put much of his presentation into perspective. ALD is a complex condition with a broad phenotype. The Condition Review Workgroup (CRW) conceptualized and thought about the condition with the goal of understanding what NBS for ALD would mean, particularly the benefits of pre-symptomatic screening and the potential harms of NBS. For this ALD evidence review, the CRW had to obtain primary data to fill in gaps in the evidence. He concluded his introductory remarks by recognizing the members of the CRW and thanking them for their contributions to the effort.

Condition Characteristics, Treatment, and Key Evidence Review Findings
Dr. Kemper briefly reviewed the natural history of ALD, which is a peroxisomal disorder that affects the adrenal cortex and the central nervous system through cerebral demyelination and spinal cord/peripheral neuropathy. The condition has a broad phenotype with symptom presentation occurring in infancy through adulthood. About 90 percent of males (hemizygotes) are affected and have multi-system problems with onset ranging from early childhood through adulthood. Female heterozygotes develop symptoms (including myelopathy, peripheral neuropathy, and fecal incontinence) mostly in adulthood. Although there is a lack of data on their disease course, one small study found that almost one-fifth had symptoms before age 40 and 88 percent had symptoms by age 60.

The overall disease prevalence of X-linked ALD (X-ALD) is one in 16,900. In males, the prevalence is one in 42,000; in females, it is estimated at one in 28,000. Dr. Kemper cautioned that these frequency rates were based on findings from two U.S.-based referral centers and extended family testing from these centers, not population-level epidemiology. One study conducted in the late 1990s estimated that the prevalence of X-ALD in males is 2.3 per 100,000.

Dr. Kemper described the clinical spectrum of ALD. The large majority of males (90+ percent) will develop adrenal insufficiency symptoms during childhood. Between 31 and 35 percent of males will develop the most severe form of the condition, the childhood cerebral form (CCALD). Affected males can develop the cerebral form in adulthood, although it is less common. The adrenomyeloneuropathy (ANM) form is more common in adults. Women who are heterozygous for ALD have a slower, more variable progression in adulthood.

ALD is caused by mutations of the ABCD1 gene. The gene encodes adrenoleukodystrophy protein (ALDP), which facilitates transport of very long-chain fatty acids (VLCFA) into peroxisomes. ALPD deficiency results in elevated levels of VLCFAs, which is the basis for detection. There are more than 600 mutations, most of which are unique. There is no genotype - phenotype correlation, even within families. As a result, multiple family members with the same mutation may not have the same onset or severity of the disease.

NBS for ALD is based on the measurement of C26:0 lysophosphatidylcholine (26:0-lyso-PC) as a marker for VLCFA in dried-blood spots (DBS) through tandem mass spectrometry (MS/MS). Newborn screening for X-ALD in New York State is multiplexed with Krabbe disease and Pompe disease. Centers for Disease Control and Prevention (CDC) proficiency test (quality assurance) is expected to be available in the very near future. One small prospective pilot study from Maryland (n=5,000 newborns screened) have found no (zero) newborns with X-ALD. NY State NBS, currently the only state screening for X-ALD since December 2013, has found a low number of overall positives for X-ALD, and has identified some babies with secondary targets of other peroxisomal disorders (these are not the primary target and there are no known interventions for them) and an infant with a disorder not targeted for screening. Screening will pick up approximately 80 to 90 percent of all heterozygote females because some do not appear to have elevated VLCFA levels in dried blood spots or plasma.

The most important test in confirming an ALD diagnosis in males is the verification of the elevation of VLCFA in plasma. The New York NBS program includes an assessment for mutations of the ABCD1 gene, primarily for the benefit of the referral centers, not for diagnosis. Neuroimaging using MRI is the mainstay for the clinical diagnosis and treatment of CCALD. Dr. Kemper described the Loes severity scale for demyelination patterns shown by MRI that correlates with other measures of neurological function, and is found to predict treatment outcomes. It is difficult to base a diagnosis on clinical symptoms only. Symptoms could include signs of inattention and hyperactivity; signs of dementia; difficulty understanding spoken language; progressive disturbances in behavior, coordination, handwriting, and vision; and neurological disturbances. Adrenocortical insufficiency co-occurs in approximately 90 percent of boys with CCALD. Newborns identified with X-ALD at birth (ABCD1 mutation and elevated VLCFAs) will be asymptomatic and require follow-up and monitoring of adrenal function and neurologic involvement (i.e., MRI).

Before discussing treatment approaches, Dr. Kemper explained that the CRW focused on X-ALD forms with childhood onset – adrenal insufficiency and CCALD, especially CCALD because it is the most devastating form of the disease. Dr. Kemper stressed that the focus on this form was not meant to diminish in any way the effect of ANM on older individuals; it simply reflected the Committee's charge to assess the benefit of NBS to affected individuals during childhood.

The main treatment for the childhood cerebral form of X-ALD is stem cell transplantation using a matched, related donor or closely-matched cord blood (this does not have to be as closely matched as donor-related transplants). Stem cell transplantation can reduce the risk of progression of neurologic symptoms if the condition is detected early enough. Risks associated with transplantation include graft-versus-host disease (acute and chronic), mortality from non-cancerous conditions (approximately 5 percent in the first couple of years), and failure to engraft. Transplantation does not affect the adrenal problems associated with the condition. Individuals with adrenal insufficiency will need adrenal cortisol replacement. Other non-standard care treatments, such as gene therapy and Lorenzo's oil, were not factored into the CRW's analysis of the benefits of therapy because they are experimental (gene therapy) or have not demonstrated any benefits in clinical trials (Lorenzo's oil). Dr. Kemper indicated that transplantation and adrenal cortisol replacement are independent but related treatments (one does not eliminate the need for the other). Adrenal cortisol deficiency complicates transplantation, and clinicians need to be careful in these situations; however the adrenal cortisol replacement does not alter the outcomes for the transplant itself.

Clinical guidelines use Loes scores (MRI/neurological status) to monitor disease progression and to determine when to initiate treatment. In response to a question concerning the correlation between the Loes score and functional status, Dr. Kemper indicated that some studies found a linear association between the Loes score and several measures of neurological function and development, though these studies have small sample sizes. He did not have specific clinical interpretations for Loes scores to characterize functioning for each Loes score, but he indicated that someone with a score above 9 or 10 would have advanced neurological progression, and likely serious developmental problems.

Dr. Kemper presented an algorithm for managing pre-symptomatic ALD. In this algorithm, MRI is a reliable and sensitive marker for disease progression. Patients with a Loes score greater than 1 or 2, but less than 9 are recommended for transplantation. Under the algorithm, once a diagnosis of X-ALD is made, the individual should have an MRI and be referred to an endocrinologist for monitoring of adrenal function. An abnormal MRI with early stage progression would likely result in a recommendation for transplant. Patients with normal MRIs will be monitored regularly for signs of neurological disease progression – usually every six months for those between 3 and 12 years of age, but specific follow up plans may vary for each individual. Specialty treatment centers will manage follow up and monitoring guidelines.

Dr. Kemper briefly reviewed the process used by the CRW to conduct the literature review before moving on to a discussion of the New York NBS short-term follow-up algorithm. The process begins with an MS/MS screen (flow injection) of a DBS. If the first screen is abnormal, the test is repeated on the same DBS. If the repeat screen is positive, a second specimen is requested and tested for a second-tier screen with MS/MS (liquid chromatography). Newborns with a positive second-tier screen are referred for confirmatory/follow-up testing. As of the end of July 2015, approximately 1.8 percent of the 360,000 newborns screened had an abnormal first tier screen and returned for an independent specimen; 33 had a positive second-tier screen and were referred for follow up. In addition, the NY NBS program conducts (in-house) mutation analysis of referred newborns. As a result of this screening and mutation analysis, 13 boys were identified with an ABCD1 mutation. Of these 13, as of the end of July 2015, seven were confirmed to have X-ALD based on laboratory measurements of VLCFAs (all 13 may be confirmed, but all of the reports are not yet available). Additionally, the testing identified 14 female heterozygotes and five individuals with disorders that are secondary targets or other conditions.

Dr. Kemper pointed out that the Committee will need to determine the screening target (i.e., only newborn males with X-ALD, or male and [heterozygote] females with X-ALD).

Committee Discussion:

- A Committee member asked whether New York detected more cases than expected based on the previous estimated prevalence. Dr. Kemper indicated that the results were generally within the expected range of X-ALD. Since the cases were detected so recently, it is difficult to determine how many individuals will develop CCALD or other forms/symptoms of X-ALD, or when onset may occur. Screening could pick up milder cases that might not have come to clinical attention in the same way.
- In response to a request for more information about the boys in New York with the ABCD1 mutation, Dr. Kemper explained that once the children are identified they are referred to and followed by the treatment centers. The NBS program does not have much control over the information about these individuals that it receives back from the treatment center. Dr. Michele Caggana, an expert in ALD screening, added that the New York NBS program closes a screening case with a diagnosis when it receives a results back from the referral center or from a provider that the child has been seen and has elevated VLCFAs. There can be a lag in getting information back from providers; sometimes the program has to follow up with providers. She also added that the positive screen results have been reported back in two group clusters/batches and did not occur at a steady rate over time.
- An organizational representative pointed out that about 30 percent of boys identified by NBS would be likely to have the cerebral form, not the majority. Dr. Kemper acknowledges that the 30 percent figure was the correct estimate for the U.S. currently available.
- Dr. Caggana explained that Tier 1 and Tier 2 screening tests are done in the laboratory using the same dried blood spot sample. Tier 1 testing (MS/MS with Krabbe and Pompe tests) are run first. If the sample screens positive, the laboratory takes another punch from the same card for the Tier 2 testing. The rate of in-laboratory retesting is 1.84 percent and does not represent testing of a second specimen.
- A Committee member asked whether there is a higher rate of the cerebral form of the condition within families that have at least one child affected by ALD. Dr. Kemper replied that he did not have the necessary data to answer the question but stressed that there is no evidence for genotype - phenotype correlation.
- Concerning the way that New York handles female heterozygotes, Dr. Kemper indicated that they are referred to the treatment centers, which handle any subsequent management, including counseling and family testing. Dr. Caggana indicated that all females are referred to treatment centers and receive genetic counseling and undergo a full family history. This procedure also helps identify males who could be potentially affected.
- Dr. Caggana responded to an organizational representative's inquiry about the ALD follow-up system in New York by explaining that the NBS program worked with the nine metabolic centers in the state to develop protocols for minimum sets of testing for newborns that screen positive.
- A Committee member asked whether there has been any discussion of reclassifying the terminology regarding ALD given the fairly high percentage of female ('carriers') with X-ALD who experience symptoms. Dr. Kemper responded that this issue was outside of the scope of the review. He believed that there was some simplification of the terminology that was taking place.

Benefits and Harms Associated with Pre-Symptomatic Versus Clinical Detection
The CRW was charged with determining the benefits and harms associated with identifying a newborn with ALD.

Untreated adrenal insufficiency can lead to death, but there is no study that compares treatment outcomes based on the timing of diagnosis. One study published in 2011 considered whether there were missed opportunities for diagnosis of ALD among those who were treated for adrenal insufficiency at treatment centers; it did not compare outcomes for early versus late diagnosis of ALD. No other studies were identified that reported on treatment outcomes of adrenal insufficiency among X-ALD patients. Dr. Kemper indicated that adrenal insufficiency was therefore not a focus in the review of treatment outcomes.

Dr. Kemper addressed using the Loes score as both an outcome and a predictor of childhood cerebral X-ALD. Historically, there is a 66 percent survival after symptom development without treatment with transplant. At 10 years, the survival rate is 43 percent. This information is difficult for the CRW to interpret

because the time is not measured from birth but from the development of disease symptoms, which varies by child; this helps describe the rise in mortality after the appearance of disease symptoms, but it does not shed light on the age of the child.

The five-year survival probability after first abnormal MRI for individuals with Loes scores less than 9 and neurological function scores less than or equal to zero is 95 percent for individuals who received transplants and 54 percent for those who did not. Another study compared the outcomes of transplanted individuals based on their Loes score. The group with Loes scores less than 9 and no other gross neurocognitive deficits had better outcomes at five years after transplant than those with Loes scores greater than or equal to 9 and more neurocognitive deficits. Dr. Kemper indicated that this pattern has been shown in multiple small-cohort (case series) studies. Transplantation arrests cerebral involvement (Loes scores plateau). Transplantation is most effective when Loes scores are low; most treatment centers will not transplant patients after a certain amount of involvement.

In response to a question about the effects of the degree of pre-transplant neurological damage on mortality rates versus whether neurological damage continues after transplant and has an effect on mortality, Dr. Kemper noted that interpretation of the studies is difficult because the Loes score, which changes over time, is both a predictor and an outcome. Analysis is further confounded by the age at which a patient comes to attention and factors that are not reported (e.g., age at transplant, type of transplant, final cause of death). The goal of the evidence review was to determine whether identifying affected children earlier would make a difference.

Dr. Kemper shared the results of a small study that looked at cognitive and gross motor development outcomes following transplant. Individuals with lower Loes scores did better than those with higher scores.

In general, Dr. Kemper indicated that the published studies seemed to indicate that outcomes after transplantation are better if the procedure is done when the Loes score is lower. Secondly, transplantation does not lead to restoration of significant brain involvement.
Following the lunch break, Dr. Kemper addressed two questions that were asked during the break. One question related to the reason why there is so much variation within the phenotype when this is a single gene disorder. He stated that this is an active area of investigation. There are likely promoter genes and environmental and epigenetic factors involved. The second question concerned the availability of transplantation. Accessibility of centers that are able to do stem cell transplantation is the key factor; moving forward, partnerships need to be developed that facilitate transplants. The more significant question is how many people will find a match. With siblings, there is a one in eight chance for a good match; however, heterozygotes would not be a good match. Race and ethnicity also play a factor (only 15 percent of African Americans can find a good match). Umbilical cord transplantation allows for a lesser match.

Dr. Kemper returned to the question of whether pre-symptomatic identification leads to better outcomes. Studies have shown that transplantation when Loes scores are below a certain threshold results in better outcomes. Given the lack of direct evidence about population-based screening outcomes, the CRW was interested in comparing outcomes for people who were detected clinically based on symptoms with cases identified through family testing.

One of the questions asked by the CRW was whether those identified by family testing receive transplants at an earlier age and at a lower Loes score. No published studies were identified that examine this, so unpublished data analysis were requested from researchers for this review. The CRW obtained data from a single-center medical institution, provided by Dr. Florian Eichler, on 30 people with ALD, 17 of whom were identified through family testing and 13 of whom were identified based on symptoms. Outcome data was available for 19 subjects (the rest were enrolled in clinical treatment studies and excluded from further analysis). Of the seven identified by family testing, three received transplants, one was undergoing evaluation, and three had arrested cases of the disease. Of the 12 identified by symptoms, seven received transplants, four had advanced symptoms, and one had arrested disease and has been undergoing monitoring. A second data set was obtained with 59 subjects from multiple treatment centers that did not overlap with the subjects in the first set. Twenty-five boys were identified through family testing, and the rest (n=34) were identified through symptoms; all 59 received transplants.

For both groups, the CRW asked for the first available Loes score. For the single-center group, the median first Loes score for individuals detected through extended family testing was zero and median scores for the symptomatic group (median age of 7) was 12. The most recent Loes scores were 3 in the family testing group (median age 10) and 12 in the symptoms group (median age 11). In the multi-center group, the first Loes score for the family testing group was 4 versus 7.5 for the symptomatic group. The most recent Loes scores were 5.75 for the family testing group and 13 for the symptoms group. There was little information for these groups about how they came into care.

Outcome data (survival, communicative, and ambulatory) for the single-center group indicated that 7 of 7 patients in the family testing group were alive, and ambulatory and communicative. In the symptomatic group, 2 of 12 had died, 7 were non-ambulatory and non-communicative, and 3 were alive and ambulatory and communicative. Similar outcome patterns were observed for those who were treated with HSCT. Outcomes (survival) for the multi-center group, all of whom underwent HSCT, showed a similar pattern with those identified by family testing having no disease progression and those with symptoms experiencing a decline over time. Dr. Kemper stressed that these data were supportive of positive benefits of newborn screening for X-ALD, but were limited by the small groups of boys with CCALD, variable follow-up, and limited information about the patients. It would be helpful to have more information on their treatment, follow-up, and disease status. This data might not reflect the full spectrum of cases that would be detected through NBS.

Dr. Kemper summarized the CRW's findings by saying that there is no direct evidence concerning the benefit of pre-symptomatic identification of adrenal insufficiency, that stem cell transplantation improves outcomes, and that treatment at a lower Loes score improves outcomes (it is not apparent that there is a specific Loes score at which treatment is optimal). Unpublished data suggests that identification through family testing leads to improved survival in late childhood (up to age 15) as compared to detection after the development of symptoms.

Committee Discussion:

- Dr. Kemper responded to a question about the Loes scale by stating that it goes up to 34.
- An organizational member expressed concern about the phrase "no direct evidence about the benefit of pre-symptomatic identification of adrenal insufficiency." There is much clinical evidence that those with adrenal insufficiency do not die of causes such as ear infections. Dr. Kemper clarified that there is no high-quality, comparative evidence of children who are identified with ALD pre-symptomatically versus when they develop symptoms in terms of the outcomes for adrenal insufficiency. The CRW specifically looked for unpublished data on this topic. Gaps in evidence do not indicate that something does or does not work, it simply means that the evidence does not exist. The organizational representative strongly recommended reworking the summary slide to provide more context for the statement.
- Another organizational representative noted that even though the populations in question during evidence reviews are small, their limited size does not excuse the Committee from obtaining more data. Additionally, lack of evidence does not mean that there is no evidence or evidence of benefit. Dr. Kemper stressed the importance of researchers and clinicians being careful about how they measure things.
- Ascertainment bias in the symptomatic and family-detected groups was a concern of one of the Committee members, even though he believed that the differences were great enough that they could not be explained by ascertainment bias. Dr. Kemper agreed that it is important to compare like things. The data in the two unpublished data sets is consistent and fits together. It is not possible to resolve confounding factors given the currently available evidence.
- An organizational representative pointed out that there might be a presumption being made that children identified through NBS and monitored are transplanted at the earliest possible point in time, which does not take into account the potential loss to follow-up if a parent elects to not do another sedated MRI because of previous normal results. There is an assumption that the system retains identified children. Dr. Kemper indicated that this issue would be addressed during the discussion of implementation issues.

Lisa Prosser, Ph.D.
Associate Professor
Child Health Evaluation and Research
Division of General Pediatrics
University of Michigan Medical School
Ann Arbor, MI

Decision Modeling
Dr. Lisa Prosser explained that the CRW used decision analysis as a validated approach to evidence synthesis. It allowed the group to use small sample sizes in areas for which there is no direct evidence by including assumptions in the model for these areas. Assumptions can be made based on expert input and what is believed to be true. The model can be used to estimate population health benefits. Creating the decision model requires that all assumptions be identified and that key areas of uncertainty be highlighted.

A computer simulation model was used to simulate outcomes for a hypothetical U.S. cohort of four million babies that undergoes universal NBS for X-ALD compared with clinical identification. An expert panel met three times to work on the model and identified the key endpoints (i.e., the number of cases identified and the number of deaths averted by 15 years of age). Dr. Prosser noted that there were multiple outcomes that were considered for modeling, but there was not enough evidence to model many of them, including several of the neurocognitive outcomes.

Dr. Prosser shared a schematic diagram of the decision model. The model begins with two cohorts of four million newborns each, one of which goes through NBS and one of which goes through clinical identification. In the NBS arm, the process includes the screening process and outcomes, abnormal screening results, and confirmatory testing. The model groups newborns identified with the ABCD1 mutation at screening, into three categories: CCALD (with and without adrenal insufficiency), adrenal insufficiency (alone), and asymptomatic. Earlier iterations of the model attempted to tease out the children with both CCALD and adrenal insufficiency, but there was not enough data to do so. Children in the first category, CCALD, were the only group for which long-term outcomes were modeled. The long-term outcomes (15 years) were whether or not the children died. There is some uncertainty with regard to the asymptomatic group because some will have adult-onset ALD and others will remain symptom free.

In the clinical identification arm, the three initial groups are males with X-ALD, female heterozygotes, and children not affected by X-ALD. The X-ALD group is further subdivided in to those with CCALD, adrenal insufficiency only, and adult onset. Modeling for 15-year outcomes was done for the first two groups. The model did not address the possible number of children with adrenal insufficiency that might die prior to having their condition detected due to lack of data.

The model only considers the individual cases, not the potential impacts for others identified through family testing. The cohort consists of babies that are not at high risk for X-ALD; therefore it excludes family members of identified cases.

All of the data going into the model were based on the categories of evidence identified during the evidence review. The screening projections were based on the New York data. Other model components were derived from the evidence review and supplemented by the expert panel's assumptions. One of the assumptions was that the potential benefits of earlier treatment are uncertain but could include improved survival and potentially improved cognitive outcomes. The group was not able to model cognitive outcomes, except for the very severe non-ambulatory, non-communicative state.

The model projects that for a healthy annual newborn cohort of four million babies, 143 newborns with be identified (range 64 to 211) by NBS as compared to 92 (range 64 to 132) identified by clinical evaluation. The ranges do not represent confidence intervals; instead they reflect the minimum and maximum ranges. The model projects that under both newborn screening and clinical detection, 46 cases of CCALD (with and without adrenal insufficiency) and 12 cases of adrenal insufficiency would be detected. The model predicts 85 cases of potential adult onset ALD (these could include asymptomatic cases), 154 females with

X-ALD, and 66 peroxisomal and other disorders identified by newborn screening, versus 34 adult-onset cases, 143 females with X-ALD, and 0 other disorders identified by clinical detection. A long-term outcome is projected only for the childhood onset cases (CCALD and adrenal insufficiency only). With regard to the range of cases identified by NBS, Dr. Prosser noted that point estimates and ranges generally are higher than for clinical identification because under the clinical detection, cases may otherwise be missed, succumb to the condition before diagnosis, be identified until later in life, or never receive a diagnosis. Additionally, the higher upper end for the adult onset ALD identified by NBS reflects the range of possible outcomes by extrapolating the New York data.

In response to a question concerning whether the clinical identification group included cases diagnosed as something else or, for the adrenal insufficiency group, diagnosed postmortem, Dr. Prosser indicated that the group tried to use data for the model that closely matched cases that would have been diagnosed before death.

Dr. Prosser reported the modeling results for long-term health outcomes (alive, ambulatory, and communicative, or death or non-ambulatory and non-communicative). The projected 15-year survival outcomes for CCALD when detected by newborn screening were 46 patients who would be alive, ambulatory, and communicative, and no patients (0) who would die or become non-ambulatory or non-communicative [NANC]. Projected 15-year outcomes for CCALD under clinical identification were nine patients who would be alive, ambulatory, communicative, and 37 cases with NANC status. Projected overall survival outcomes at 15 years of age, accounting for HSCT treatment (based on the unpublished, multi-center data) were 46 survivors under newborn screening, compared with 28 survivors under clinical identification.

In summary, Dr. Prosser stated that newborn screening for X-ALD would likely result in 18 averted deaths (range between 7 and 44) and 37 cases of death or NANC (range between 17 and 64). The baseline assumptions were conservative and assumed that the same number of cases of CCALD would be identified by newborn screening and by clinical identification. However, the number of cases could be higher due to cases that could have potentially been missed without newborn screening. Additionally, under certain scenarios, the number of adult cases could be as high as 76 cases per year.

Jelili Ojodu, M.P.H.
Director
Newborn Screening and Genetics
Association of Public Health Laboratories
Silver Spring, MD

Public Health Impact
Mr. Jelili Ojodu focused on the public health impact of X-ALD, including APHL's role, the methods used to collect information from state NBS systems, and the information collected concerning X-ALD. Recommendations for adding conditions to the RUSP are based on two broad considerations: certainty of net benefit, which was presented by Drs. Kemper and Prosser, and the feasibility of and readiness to implement a comprehensive screening program.

For the purpose of the discussion, Mr. Ojodu defined readiness as consisting of three levels:

- ***Ready***: A NBS program would be able to bring a new condition onto its core panel of disorders and implement screening within one year once the authority to screen is in place.
- **Developmental Readiness**: An NBS program with the authority to screen would be ready to implement screening for a condition within one to three years.
- **Unprepared**: A state would not be ready to implement a screen within three years of having the authority to screen.

Mr. Ojodu identified four components of NBS feasibility:

- There is an established and available screening test.
- There is a clear approach to diagnostic confirmation.
- There is an acceptable treatment plan.
- There is an established approach to long-term follow-up (LTFU) plans.

The purpose of the public health impact assessment is to understand the real-world barriers to implementation, factors that facilitate implementation, and the opportunity costs of implementation. Information was gathered through key informant interviews and surveys. APHL asked states to provide information on conditions for which they are not currently screening.

APHL developed a fact sheet concerning X-ALD screening and distributed it to state NBS programs. The fact sheet described the screening process (screening methodologies, resources, capacities, personnel, and quality control), the incidence X-ALD, treatment, and follow-up. APHL also hosted a webinar for state NBS programs to help them understand how to respond to the survey. The survey was sent to NBS programs in 53 states and territories. APHL also conducted four in-depth, telephone interviews with NBS program representatives from California, Connecticut, New Jersey, and New York, states that have legislative ALD screening authority and are either screening for or planning to screen for X-ALD.

The New York interview provided much useful information on the challenges associated with implementing ALD screening, including validating the assay, multiplexing the assay with assays for other lysosomal storage disorders (LSDs) in a way that produces consistent results, adjusting the screening cut-off to capture as many cases as possible, and resolving follow-up issues associated with identifying asymptomatic males and secondary targets. There were several factors that aided implementation of the screen in the state, including having consistent communication and good relationships with specialty centers, health care providers, and diagnostic centers. Other factors supporting implementation were the ability to multiplex the test withthose for Krabbe disease and Pompe disease (no new equipment was required) and having the authority and resources to screen.

The interviews with the other three states provided additional information on challenges and supporting factors. California has a mandate to screen once a condition is added to the RUSP. There is no specified timeline for implementation of X-ALD screening. In Connecticut, there is no requirement to begin screening once a condition is added to the RUSP, but the state mandated X-ALD screening in 2013. The state program needs to develop and validate an assay or elect to use a Food and Drug Administration (FDA) kit as well as to stock the required reagents for testing. There is no specific timeframe for implementation. New Jersey also mandated testing for ALD in 2013. The state must meet several milestones, including development of a test, availability of quality assurance materials, and procurement of equipment. Mr. Ojodu anticipated that the state could begin screening within six months once the condition is added to the RUSP.

Challenges faced by states that are not screening but have a mandate to screen include having a realistic timeframe for bringing a new condition onboard the state's screening panel, ensuring that the program has sufficient time to work with neurologists to put in place referral processes, determining the duration of tracking of patients, resolving follow-up issues, ensuring availability of specimens for validation, and ensuring proper staffing. Factors cited during the interviews as being helpful in these states' efforts to implement screening included sharing information with other NBS programs, participating in training opportunities, having access to adequate clinical and follow-up data, having the condition on the RUSP, applying insights gained from other programs, and having adequate time to implement screening.

Mr. Ojodu reported that APHL had a 70 percent response rate (37 responses) to the electronic survey sent to the 53 state and territorial NBS programs. Programs were asked to share the survey with all parts of their NBS system (e.g., laboratory, follow-up, commissions, etc.). APHL received responses from 27 state NBS programs and six responses from regional programs or programs that contract out NBS work (the four programs that participated in the interviews were excluded from this analysis).

When asked about how long it would take to implement ALD screening after ALD was added to the RUSP, the majority of programs (61 percent) indicated that it would take between one and three years. Almost one-quarter (24 percent) indicated that it would take more than three years to implement.

The top three challenges identified by respondents were providing the screening test (61 percent), conducting short-term follow-up of abnormal results (61 percent) and increasing the NBS screening fee (49 percent). APHL also asked respondents to indicate their programs' readiness to implement ALD screening in 12 areas. Responses varied widely. Access to diagnostic services, treatment centers with adequate capacity to handle the anticipated case load, a sufficient number of specialists and personnel to provide treatment and follow-up and track cases, appropriate technical expertise, and a LIMS system that can incorporate the new test were among the mechanisms that states indicated that they already had in place. States were also asked about the extent to which factors such as the cost of the specimen, ongoing activities, the addition of other conditions, the cost of treatment, the cost-benefit of conducting screening, and the ability to multiplex with other conditions impede or facilitate the adoption of ALD into NBS programs.

15 programs cited funding as the primary barrier to implementing new NBS screens. Other barriers cited include staffing issues, the assay itself, and the legislative approval to bring the condition onto the state panel. Facilitating factors included the potential for multiplexing new screens with other tests, advocacy activities, and benefits of early detection.

APHL asked respondents to estimate how long it would take to add ALD to their panels, specifically as it related to nine types of activities. None of the programs is ready to begin screening immediately. Mr. Ojodu indicated that it would take most programs one to three years to hire the necessary staff, pilot test and validate the test, and report out the full implementation of ALD screening.

Mr. Ojodu identified several strengths of the survey, including the high response rate, the opportunities for NBS programs to learn more about ALD screening through the webinar and the fact sheet, and the ability of programs to extrapolate from their experiences implementing other screening programs. Being able to conduct an in-depth interview with the one program that is currently screening was extremely helpful. Limiting factors associated with the survey were the fact that the questions were hypothetical (states are not currently screening for ALD) and limited data concerning newborn X-ALD screening.

In conclusion, Mr. Ojodu stated that 61 percent of responding states, including two-thirds of the states with a mandate, indicated that it would take between one and three years to implement an X-ALD screening program once the program is approved and funds are allocated. Most programs are at the developmental stage of readiness. Concerning the feasibility of implementing X-ALD screening programs, plans for LTFU remain an issue. Factors contributing to this situation are the uncertainty concerning the age of onset, the length of time patients will need to be tracked, uncertainty over the development of ALD or adrenal insufficiency, the timing of the onset of the condition, and the referral process. Funding is an ongoing issue, both with regard to implementation and to sustained screening.

Committee Discussion:

- A Committee member inquired about the impact of implementing screening for Pompe disease on the implementation of ALD screening, especially on the need for staff and equipment, and about the possibility of speeding up implementation timeframes by making federal funding available. Mr. Ojodu indicated that funding opportunities of any sort are helpful to states as they add conditions. Dr. Kemper indicated that adding ALD when multiplexing would represent an incremental addition rather than a more significant one requiring new equipment for programs that are already using MS/MS to screen for Pompe.

Overall Summary

Dr. Kemper briefly summarized all three presentations that made up the ALD evidence review report:

- X-ALD is associated with significantly higher morbidity and mortality in affected males.
- Stem cell transplantation can be an effective therapy for the cerebral form.

    - Published studies indicated improvement in outcomes when there is less cerebral involvement.
    - Unpublished data suggests decreased morbidity and mortality in late childhood among those diagnosed through family testing as compared to those who are clinically identified.
- Adrenal insufficiency is common and can be treated with replacement therapy.
    - There is a gap in the evidence concerning the risk reduction related to morbidity and mortality related to pre-symptomatic identification.
- Harms need to balance against the benefits.
    - Screening picks up other conditions that are not targets, including heterozygote females and other peroxisomal disorders.
    - Individuals identified through screening may require many years of follow-up due to the uncertain course of the disease.
    - Transplantation is associated with a risk of mortality (5 to 8 percent). Shifting transplantation to earlier in the lifecycle shifts the risks of transplantation to an earlier stage in life.
- Most states will need between one and three years to implement screening after funding becomes available.

Committee Discussion:

- Cord blood transplants were the subject of a question from a Committee member. Dr. Kemper indicated that he specifically looked into this issue. Based on data from a single treatment center for non-cancerous related transplantation, he estimated that the risk is in the same range. The Committee member indicated that cord blood transplantation might not be an option for some affected individuals because of disparities in availability of matched donors. Furthermore, individual units of cord blood can have varying numbers of stem cells.
- An organizational representative asked whether the information in Mr. Ojodu's slide concerning implementation resources could be formatted to represent the percentage of babies born, not the number of states. Mr. Ojodu indicated that APHL did not calculate the results based on number of babies born but hoped to do so in the future. He anticipated that much of the public health information impact data would be used to supplement the findings from the data repository once states start loading information into it.
- An organizational representative asked whether the authority to screen was solely a legislative issue. Mr. Ojodu indicated that it would vary by state depending on where it gets its authority to screen. Most states use a legislative mandate because adding a screen is often accompanied by a fee increase.
- Mr. Ojodu said that different conditions require different activities to bring them onto screening panels. It is difficult to estimate where states would be in one to three years as the process for implementing each condition is very dynamic. Other conditions can serve as guidelines for what might happen.
- The lack of evidence for a benefit beyond survival was a concern for a Committee member, especially over the next three years. She asked whether there is any information that might become available during that time that would increase the confidence in the existence of a benefit to children who are diagnosed as newborns. Dr. Kemper anticipated that it would take at least three years for the current cohort to age enough to produce the needed data. Meanwhile, new cases are coming into the system. The new funding mechanisms designed to help states implement screening should help states get over operational barriers to screening and to develop data registries that can be used to understand whether their approaches make a difference. He generally agreed that one to three years might be sufficient to accrue enough cases to conduct the analysis.
- Concerning the unpublished data presented by Dr. Kemper, a Committee member asked if he had any insight into why only half of the cases at the single center were transplanted and all of the cases from the multi-site set received transplants. Dr. Kemper indicated that the latter set only included transplanted cases because that was what was requested. Neither the single center study nor the multi-center study was set up to answer the questions posed by the CRW.
- The Committee member followed up with a question concerning how decisions concerning follow-up are made for the children identified through the New York NBS program. Dr. Jennifer Kwon indicated that the treatment centers have not yet set up a joint clinical outcomes registry to study how patients are followed. There have been some proposals and some effort to collect short-term follow-

up data. Currently, individuals who are diagnosed as a result of family history are identified pre-symptomatically and are followed using a defined strategy that is guided by experts. The follow-up includes looking for true disease progression. It is important that people who do not need transplants do not receive them.

- With regard to the evidence for benefit, an organizational representative noted that the CRW did not consider the benefits to the 10 percent of identified children with adrenal insufficiency and asked whether there were any studies on acute events related to the condition. Dr. Kemper indicated that children with adrenal insufficiency cannot be compared to those with some sort of adrenal injury because they come to attention differently, which makes it easy to underestimate or overestimate the risks. The CRW attempted to identify what it does not know concerning adrenal insufficiency and describe the magnitude of the problem. There is some anecdotal evidence in this area, but no population level data. The general approach would be to monitor children until they need replacement therapy and then treat them. There is a possibility that some children who might not need treatment receive it.
- An organizational representative reminded the group that screening for ALD could affect many more people than just those with ALD.
- Concerning the one-to-three year implementation timeline, an organizational representative noted that the requirement for having both authority to screen and funding would explain why many states would provide the same answer in a two or three years. Texas statute requires the NBS program to screen for conditions on the RUSP as funding allows; thus the state has the authority immediately but must secure the funding to implement and sustain the screening. This could explain why there has been little movement with regard to implementation. The authority and funding caveats allows states to focus on other issues that would need to be resolved to implement screening. Different states have different processes for providing authority to screen.
- In response to a question concerning the Loes scores in the various groups in the unpublished data, Dr. Kemper indicated that the first Loes score in the family identification group was zero versus 12 in the symptom group in the single center group. In the multi-center group the family identification group was 4 compared to 7.5 in the symptom group. The CRW did not have scores for the point of transplant.
- An organizational representative asked whether any of the babies screened in New York had begun exhibiting symptoms. Dr. Caggana stated that one child had findings on its MRI and received a transplant at 10 months of age, and one child has been on adrenal replacement therapy since six months of age; the rest are asymptomatic.
- A Committee member asked whether it would be possible to model the results of screening, should the Committee recommend the additional of ALD to the RUSP, in such a way as to determine that the decision was a good one (i.e., how much data would need to be collected from screening, given the historic controls, to determine the success of the program). Dr. Kemper indicated that all NBS programs would not begin screening for ALD at the same time, which would enable comparisons and help in the evaluation of success. Dr. Prosser confirmed that the difference in implementation of screening would enable the modeling, particularly if data could be collected from states that have not yet implemented screening.
- The Committee member clarified his question and asked about the number of children who would need to be identified to demonstrate that the anticipated benefit has been achieved if there is an assumed level of benefit for transplants for a certain subset of children with X-ALD, Dr. Prosser indicated that it would be difficult to estimate the required sample size given the data currently available.
- Concerning a question about the tracking of Loes scores over time and the intervention of transplants, Dr. Kemper indicated that such data was not available.

V. Committee Report: ALD and the Committee's Decision Matrix

Fred Lorey, Ph.D.
Genetic Disease Screening Program
California Department of Public Health

Richmond, CA

Dr. Bailey and Dr. Lorey serve as liaisons from the Committee to the CRW and have participated in the group's work on ALD. Dr. Lorey presented their initial recommendation to the Committee based on this participation in the review.

Net Benefit
The AC Representatives believe that the data demonstrate a reduction in mortality based on early intervention resulting from early family testing as compared to treatment following clinical detection. Based on the unpublished studies presented by Dr. Kemper, the projected benefits at 15 years show that the number of averted deaths/survival would range from 17 to 64 and the number of averted deaths would range from seven to 44 for treated patients. Although there is no published data that would confirm or disprove a net benefit for early detection of adrenal insufficiency, the X-ALD Technical Expert Panel members informing the CRW believe that there is a benefit.

ALD screening will pick up other conditions, some of which can be treated.

The New York state screening data includes zero reports of false positives from one-and one-half years of screening (based on the second screen). The referral rate, which is the percentage of screened infants referred for diagnostic workup, is 0.009 percent. There is a risk of morbidity and mortality related to stem cell transplant; however, the risk is the same as that for children identified clinically.

The AC Representatives concluded that the net benefit of early detection through family testing or NBS for children with cerebral X-ALD are fairly definitive based on the findings of two outcome studies and unpublished data. NBS will pick up children with additional disorders who might benefit from early detection. Female carriers will also benefit from early detection if they are or become symptomatic. A certain number of female carriers will be missed and it is unknown whether these individuals are likely to become symptomatic. The AC Representatives determined that there is a high certainty of net benefit.

Feasibility
The AC Representatives believe that the available test platform and an appropriate screening protocol (New York) has been established. There are additional testing protocols that may also work well. Most screening programs are familiar with the technology because they are already using MS/MS. Dedicated instruments may or may not be required. X-ALD screening can be combined with screenings for other Lysosomal Storage Disorders (LSDs) and other diseases using multi-platform methodologies. The New York screening experience has produced no significant issues in the year and a half that it has been in operation; the Mayo Biochemical Laboratory has had a similar experience. Because of this, the AC Representatives assigned a rating of high feasibility for X-ALD screening. Dr. Lorey indicated that this is likely the strongest factor in their assessment.

Readiness
Dr. Lorey pointed out that the APHL public health impact survey indicated that most states have a one-to-three year window for implementing X-ALD screening once they have the authority to screen and the funding to do so. California is one of three states that have a mandate with a contingency that screening can only begin after the condition is approved for the RUSP. This is an advantage because, in California, the legislation must be in place before fees can be raised to fund the test. Several states have mandates, and most are working on test development. Overall, the feedback from the APHL survey on readiness is mixed.

The AC Representatives determined that readiness falls into the A-2 (developmental) category for readiness, although it initially considered the A-3 (unprepared) category. Given that one program is already screening for X-ALD and a few others have begun working on screening, the developmental category is the more accurate one.

Recommendations
The AC Representatives recommended that NBS for X-ALD be approved under the matrix category A-2. It acknowledged that substantial work will be required in most states to fund, develop, and implement

screening for the condition. States should be encouraged to implement X-ALD screening within one to three years of the addition of the condition to the RUSP. Based on the experience with other conditions, new programs might require as many as five years to implement the screening.

The AC Representatives also recommended that early adopters, such as New York, be encouraged to rigorously collect data to promote the continuous improvement of the evidence base regarding the risks and benefits of screening. Specifically, this means tracking screened babies through monitoring until they experience symptom onset, which could occur as early as the first one or two years of age.

VI. Committee Discussion on ALD and Vote

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

Dr. Bocchini opened the meeting up for discussion of the Committee's position on the nomination of ALD for inclusion on the RUSP.

Dr. McDonough expressed his support of the AC Representative's recommendation that X-ALD be added to the RUSP. As a practicing physician, he indicated that he would like to know that one of his patients had a condition such as X-ALD or adrenal insufficiency as soon as possible. Based on the New York experience, the testing is feasible and off to a good start. There is substantial information concerning screening's impact on mortality and he anticipated a tremendous impact on morbidity, particularly with regard to reducing disability. The Committee should also indicate in its recommendation to the Secretary that funding be provided to implement the screening.

Dr. McDonough made a motion that the Committee support the recommendation for the A-2 designation for ALD and recommend that the Secretary develop a comprehensive program to assist states, especially those with limited budgets, in their efforts to meet the recommendation. Dr. Lorey seconded the motion.

Dr. Botkin supported the analysis. His main concern related to the collection of data, specifically how to ensure the collection of better data. Data needs to be collected at the gross level to determine whether screening is working. Data should also be collected concerning barriers and problems to ensure that programs are serving their populations at an optimal level. He suggested that the Committee's recommendation include a specific request for HHS resources to support better data collection so that better comparisons will be able to be made once data from the screening programs are available. Dr. Bocchini stated that the Committee could include a request that data from early adopting states be utilized to help inform later adopting states about issues such as test development. Dr. Lorey noted that there is already an ALD entry on the R4S data collection system.

Dr. Parisi pointed out that there is a precedent for the Newborn Screening Translational Research Network (NBSTRN) to compile data from early adopting states for conditions that have added to the RUSP over the past several years. Dr. Bocchini indicated that this could be included in the recommendations.

Dr. Kelm indicated that although the AC Representatives recommended an A-2 rating for readiness, she did not see the situation with ALD as being much different from that of MPS 1, which was an A-3, when it was discussed by the Committee. For the sake of consistency, the Committee should consider rating ALD as having an A-3 level of readiness. Dr. Lorey indicated that the AC Representatives originally ranked it as A-3 but changed the rating because the A-3 description indicates that states are not ready. Since New York is already screening and California, Connecticut, and New Jersey are working on screening, the CRW moved it up to A-2. Additionally, the strength of the test supported the higher ranking.

Dr. Kelm asked whether there had been push back against any previous recommendations concerning funding and questioned whether the Committee should make such a request if previous attempts were unsuccessful. Dr. Bocchini indicated that the way in which the request is worded is important. The recommendation concerning Pompe disease included a recommendation that pilot studies be conducted. The feedback on the recommendation indicated that the National Institutes of Health (NIH) were involved in funding states for pilot studies.

Ms. Williams recommended that the request for funding simply request it for states as opposed to states with limited funding.

Dr. Bailey thanked all of those who worked on the condition review. He indicated that the Committee should identify the lessons learned through this experience and determine how those lessons might affect expectations concerning future nominations. ALD has been studied for years, and treatments have been available for years. He believed that someone should have been collecting and analyzing data much earlier, which would have made the CRW's job easier. In the future, having additional data not readily available will be important to the Committee.

Ms. Scott distinguished between A-level and B-level data on the matrix. New A-level data is data that would not change the conclusions; new B-level data, which could depend on small numbers or unpublished data, could have the potential to change the conclusions. The data presented during the meeting should be considered B-level data because of the quality and quantity.

Ms. Williams echoed Ms. Scott's point of view. The Committee spent much time developing the matrix in order to provide guidance to community organizations, disease-specific organizations, and to the Committee itself. She did not believe that the data presented was as high a quality as it has been marked; it is B-level data at best. She was supportive of the effort, but feared that this sets the bar remarkably high on very little data.

With regard to states' readiness to screen, Dr. Tanksley commented that two states already had some degree of screening for MSP 1 when the Committee made its recommendation.

Dr. Tarini concurred with the statements about the importance of data. Data, even incomplete data, must meet the level that the Committee sees fit to implement mandatory screening. Thus it seems that if approved, the data that exists is enough upon which to base a mandatory public NBS program. If the request for additional data is simply to fill the uncertainties, the current data may be a point estimate that has some movement to it. Currently, there is no mechanism to review additional data that might be collected. She did not believe that the Committee could, in good conscious, conduct the evidence review on the front end, collect data on the back end, and not have a system for reviewing it by the same rigorous standards.

Dr. McCabe pointed out that the investigators were the ones holding back the data, not the families. If the Committee states that adequate data is required to bring a condition up for nomination, it puts the onus on the advocates. He believed that the responsibility should be placed on the investigators. Ms. Wicklund agreed with Dr. McCabe. One of the lessons learned is that data exists, but it has not been published. Thought should be given to alternative ways to disseminate the data through channels other than peer-reviewed journals.

An audience member reported that one of the mandates of the ALD Connect organization is to collect data on ALD. She anticipated that moving forward, family organizations would make obtaining the necessary data concerning the efficacy of newborn screening for ALD a priority. She also reported that she developed a two-minute assay that can be done on an AB SCIEX 3200 using CDC standards at very low cost. She planned to publish the methods so that states could use it to establish a stand-alone test for ALD.

Dr. Greene asked whether ALD should be held to a different standard than previous conditions because a data system is not in place. She hoped that the discussion of the data system could be separate from the

discussion of ALD. She suggested that even though the data for ALD is quite thin, it all seems to be going in the same direction, and none of it overlaps zero. Using the matrix language, there is a high certainty of significant benefit, although how much benefit is not clear. A 'B' rating would indicate that the Committee is not certain that screening is a good idea. There is a significant difference between the lives saved and the lives saved walking and talking. She believed that the 'A' ranking was appropriate.

Committee Vote
Dr. Bocchini stated that there was a motion before the Committee to recommend the inclusion of ALD on the RUSP with an A-2 rating coupled with a request that the Secretary provide additional support for implementation. The recommendation would also include a request to use data from early adopting states to provide additional information concerning the finding on ALD. Ms. Scott added that the data should include everyone who is identified by NBS, including infant girls and mothers who are heterozygotes.

VOTE: Dr. Bocchini called for a vote on the recommendation of ALD for inclusion on the RUSP with the additional requests concerning funding and data collection. Dr. Matern recused himself from voting due to a potential conflict of interest. Dr. Thompson was the only member to vote against the motion; all of the other Committee members voted to recommend the inclusion of ALD on the RUSP.

Dr. Bocchini indicated that a letter recommending the inclusion of ALD on the RUSP would be sent to the Secretary as soon as possible.

Dr. Bocchini thanked the members of the CRW for their work, specifically the effort to identify the unpublished data, and the APHL team for its contributions to the evidence review. He also recognized the parents, families, and individuals affected by ALD who helped the Committee understand the impact of the condition on families.

Dr. Bocchini adjourned the meeting for the day.

VII. Committee Business: August 28, 2015

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

Dr. Bocchini welcomed the Committee members, organizational representatives, and other participants to the second day of the meeting and took the roll.

Voting members present were:

- Dr. Don Bailey
- Dr. Bocchini
- Dr. Jeffrey Botkin
- Dr. Fred Lorey
- Dr. Dietrich Matern
- Dr. Stephen McDonough
- Dr. Alexis Thompson
- Ms. Catherine Wicklund
- Ms. Andrea Williams

Ex Officio members present were:

- Agency for Healthcare Research and Quality: Dr. Kamila Mistry

- Centers for Disease Control and Prevention: Dr. Colleen Boyle
- Food and Drug Administration: Dr. Kellie Kelm
- Health Resources and Services Administration (HRSA): Ms. Joan Scott (for Dr. Michael Lu)
- National Institutes of Health: Dr. Melissa Parisi (for Dr. Alan Guttmacher)

Nonvoting organizational representatives participating in the meeting were:

- AAFP: Dr. Chen
- AAP: Dr. Beth Tarini
- ACMG: Dr. Watson
- ACOG: Dr. Biggio
- AMCHP: Dr. Badawi
- APHL: Dr. Tanksley
- ASTHO: Dr. Kus
- DoD: Dr. Kanis
- Genetic Alliance: Ms. Bonhomme
- March of Dimes: Dr. McCabe
- NSGC: Ms. Vockley
- SIMD: Dr. Greene

VIII. National Implementation of Screening for Severe Combined Immunodeficiency, Critical Congenital Heart Disease, and Pompe Disease

Jelili Ojodu, M.P.H.
Director
Newborn Screening and Genetics
Association of Public Health Laboratories

Marci Sontag, Ph.D.
Associate Director, NewSTEPs
Assistant Professor of Epidemiology
Colorado School of Public Health
Aurora, CO

Mr. Ojodu and Dr. Sontag reported on the implementation of the last three conditions added to the RUSP: severe combined immunodeficiency (SCID), critical congenital heart disease (CCHD), and Pompe disease. This project was conducted under a cooperative agreement with HRSA.

SCID

In 2010, SCID was the first condition added to the RUSP since 29 conditions were listed in 2005. The addition of SCID served as a model for NBS programs and showed that state public health programs can bring molecular testing to NBS programs. Wisconsin, with help from the Jeffery Modell Foundation and the Medical School of Wisconsin, led the way on SCID screening. CDC funded the first SCID NBS program in 2008.

SCID was the first condition for which the Committee developed the evidence base and the criteria by which new conditions are added to the RUSP. When it was presented to the Committee in 2008, there was data from only one state (70,000 babies screened in 2008), the Committee indicated that there was not enough data to support addition of the condition. It recommended that more population-based pilot studies should be conducted for new conditions and that funding be made available for these studies. About one-and-one-half years later, the condition was brought back to the Committee for consideration. At that time, additional states were bringing SCID onto their panels. Funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and NIH helped California and New York add the condition. Having the additional data from these two states ultimately led to the addition of SCID to the RUSP in 2010.

There was an unprecedented level of support and funding for SCID implementation from private organizations, institutions, and advocacy groups as well as federal entities. However, there are still challenges regarding SCID screening. The authority to screen is still a major issue, as is funding. In the laboratory setting, having the appropriate equipment and related training continues to be a challenge. The CDC has provided much training on molecular screening to help states address these challenges. In the follow-up phase, work on developing clinical networks and ensuring the availability of immunologists is still ongoing. Education is still a challenge, especially in states that are not screening for SCID.

Currently, 33 states (representing 71 percent of the number of babies born in the United States annually) have universal screening for SCID. Wisconsin was the only state screening in 2008, followed closely by Massachusetts. NICHD within the NIH funding helped bring on the two largest states, California and New York in 2010. Also in 2010, SCID implementation pilot studies was conducted with the Navajo Nation. Michigan came onboard in 2011. Florida collaborated with a private entity to implement screening in 2012. By 2014, about half of the states were testing for the condition. APHL is using HRSA funding to help 10 states implement SCID screening, help one state to bring on the molecular capabilities for SCID, and one entity to assist states with their implementation strategies. By the end of 2016, Mr. Ojodu anticipated that only seven states would not have SCID screening programs.

Vermont, which contracts out its screening to Massachusetts, does not have a universal screening program. Dr. Anne Comeau with the Massachusetts NBS program indicated that the state offers SCID screening to all of its clients in the New England region. She anticipated that Vermont would bring on SCID in 2016. A representative from the Western States Genetic Services Collaborative reported that Alaska should begin screening in January 2016 and that Idaho will begin screening this October. Dr. Mei Baker from the Wisconsin NBS program reported that the state began running the SCID screen for Montana in July. Dr. Comeau added that immunologists tended to be the group with the greatest hesitation to begin screening. She stressed the need for more education about SCID screening.

Mr. Ojodu indicated that there has been much support from a wide range of sources to ensure nationwide screening for SCID. CDC has provided funding for about 20 percent of the states to implement the screen. NIH funding helped the large states begin their programs. CDC also provided technical assistance and trainings to states interested in implementing programs. NBSTRN/NewSTEPs have held monthly technical assistance conference calls to assist states develop implementation strategies. APHL used HRSA funding to host an in-person meeting in July for the 12 grantee states funded through the cooperative agreement; this funding provided states with $150,000 per year for two years to support implementation activities. Activities focus on understanding issues related to legislation; logistics, implementation, and development of follow-up strategies and clinical networks; education; and full implementation. Additionally, multiple websites provide information on SCID and SCID screening.

Mr. Ojodu reported that FDA approved an assay for SCID that is now being implemented by multiple states in their screening programs.

The APHL includes several NewSTEPs resources on its website. States that have instituted MOUs with APHL to collect data are adding their data to the NewSTEPs data repository. This allows APHL to count the different classifications of SCID and other T-cell lymphopenias.

In conclusion, Mr. Ojodu indicated that approximately 72 percent of babies in the United States are born in states with universal screening for SCID. This figure should increase to 86 percent by the end of 2016 (five years after the Secretarial recommendation to add SCID to the RUSP.

Committee Discussion:

- In response to a question concerning the number of babies identified with SCID as a result of NBS, Mr. Ojodu indicated that APHL tried to collect information on the detection of SCID, but did not have time to do so prior to the meeting. He anticipated being about to report on it at future Committee meetings. The Committee member recommended that this type of information be included in an annual “state of the state” report on NBS similar to the Morbidity and Mortality

Weekly Report (MMWR), which she volunteered to help develop. Dr. Sontag indicated that NewSTEPs would be willing to partner with the Committee on such a report.

CCHD

Dr. Sontag noted that the foundation for CCHD screening was laid in Sweden, where the technique for population-based screening was developed. Dr. Kemper took a lead role in developing the algorithm that is used in the United States; this algorithm has been modified multiple times to improve its performance. A paper comparing the performance of the various versions of the algorithm should be coming out soon.

CCHD was added to the RUSP in September 2011 with several caveats. The Secretary's approval included requirements for studying the screening at altitude and developing surveillance systems. CCHD was the first condition on the RUSP that had a point-of-care test; however, the test came with its own unique challenges.

With regard to challenges related to CCHD implementation, having the authority to screen presented unique challenges. Many states have the authority to screen using DBS tests but states had to go through the legislative process to obtain authority to screen for CCHD. A variety of professional and advocacy groups supported the implementation of CCHD and pushed for its adoption. Since CCHID is a point-of-care test, responsibility for having the appropriate equipment and testing procedures fell to the hospitals instead of the NBS laboratories. This required additional training. Additionally, there was much discussion over how to appropriately test special populations, such as infants in the neonatal intensive care unit (NICU), children born at home, children born at high altitudes, and those in rural areas that lack cardiology support. Data collection represented another challenge. Data needed to be collected not just for newborns identified with CCHD but also for all babies (to ensure that they were screened and to define the spectrum of screenings). Typically, data is generated by the NBS program and pushed back to the hospitals; for CCHD the data must be collected from hospitals and sent to the NBS program. Some states incorporated this authority into their legislation, and others did not. As a result, some public health departments are not allowed to collect this data from hospitals. Additionally, states had to develop mechanisms to collect this data; hospitals must be willing to participate in any systems developed for data collection. Funding for surveillance and implementation of QA/QC systems were also challenges identified by Dr. Sontag.

CCHD screening represented an opportunity to partner with the birth defects registries. The registries are already collecting this information, especially as the screening programs are identifying false negatives.

Education is a common challenge for all of the conditions. Because CCHD was a new type of screen, the issue was how to share information about CCHD with state leadership, clinicians (specialists and primary care providers), and the community and advocacy groups.

A large majority of the states are currently screening for CCHD. When screening began in 2012, only about a half dozen states were screening. HRSA funded implementation activities in six states in this time period, and in 2013 almost half of the states were screening. By the end of 2016, all but four of the states should be screening for CCHD. Dr. Sontag pointed out that CCHD screening expanded more rapidly than SCID screening, in part because of the wide variety of public health involvement. Some states have complete data collection on every newborn with CCHD, including test values, monitoring data, etc. Many of the states have a public health mandate. In these states, every baby is screened, but no data is collected. As a result, there is no data or infrastructure available to determine what is actually going on and whether babies are being screened appropriately.

Dr. Sontag highlighted an MMWR article that summarized the CCHD implementation experience across the United States. It looked at the ways in which states added the condition to their panels and how they implemented screening as well as the information collected on the babies that were being screened. With regard to data collection, 24 of the states that had implemented or were in the process of implementing CCHD screening had current data collection programs, 14 were planning to collect data, and 13 had no plans for collection. Many of the states elected to collect aggregated data only, many are collecting pass/fail data, and some have oxygen saturation levels for all newborns. Mechanisms for collecting data

include electronic birth certificates, birth defect registries, hospital electronic medical records, DBS cards, paper forms, and Health Level-7 messaging and automatic file transfer. More focus needs to be put on data collection for CCHD.

NewSTEPs maintains a HRSA-funded repository to collect data on the number of children identified with CCHD. The repository also collects information such as time of birth, time of collection, and time of screening.

The NYMAC Regional Genetics Collaborative initiated a series of technical assistance webinars that were subsequently transferred to NewSTEPs in 2013. Recordings and transcripts of these webinars are available on the NewSTEPs website. Webinars continue on a bi-monthly basis.

Committee Discussion:

- In response to a question from a Committee member, Dr. Sontag indicated that the testing for CCHD is unique to the condition, but the follow-up is not. Because the NBS program does not hand identified infants off to a provider, the programs do not know what happens to them because they are not involved. Dr. McDonough pointed out that after North Dakota passed a CCHD screening law, the health department sent a letter to hospitals indicating that they could screen children for CCHD. The state has no way to know how extensively hospitals are screening. Dr. Sontag indicated that this highlights the situation where there is something in place that implements screening, but there is no real understanding of what is actually happening.
- A Committee member believed that CCHD screening presents a unique opportunity because every state has birth defects surveillance programs. These programs could be used to obtain a better sense of what is going on.
- An organizational representative noted that that the point-of-care screenings have not been incorporated into the public health NBS system for reasons related to quality and follow-up.
- An organizational representative questioned whether CCHD should be better incorporated into NBS programs or whether a coming together of the birth defects registry, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), AAP, and clinical guidelines would be the more appropriate approach.
- A Committee member commented that he did not believe that hospital-based tests belonged with the public health NBS programs, which run blood tests and genetic tests and take pride in quality control. It is not appropriate for data to be accumulated by someone else and sent to the NBS programs. In California, CCHD was moved under the same umbrella as newborn hearing screening, which is separate from the NBS program.
- Concerning the relatively speedy implementation of CCHD screening, Dr. Baker noted that Wisconsin used its HRSA grant to conduct a survey that found that 65 percent of hospitals were already doing CCHD screening. Wisconsin uses the NBS cards to obtain CCHD screening data. Dr. Comeau added that prior to implementation, many hospitals were screening for CCHD in their NICUs. Implementation was, in many cases, simply an expansion of the screening to all babies.
- Dr. Comeau noted that all of the obstetric/prenatal screening data, which helps identify babies at risk who might also be found by NBS, has been left out of the equation. Looking at the overlaps between these types of data could help public health programs identify barriers and determine who needs the most help. She did not know how this data could be collected. Dr. Sontag noted that in large urban areas many of the babies with CCHD are being identified prenatally, which results in low yields for screening in large obstetrical centers. The greatest benefit for CCHD may be in rural areas.
- An organizational representative inquired whether the maps for CCHD and SCID implementation have been overlaid in an effort to understand the differences between early adopting states and late adopting states, specifically with regard to barriers to adoption. Metabolic and biochemical disorders seem to be a bigger hurdle.
- Unbundling the NBS tests, along with preventive services, in the hospital billing codes was one way to monitor CCHD screening suggested by a Committee member. Codes for the individual services exist. An organizational representative stressed that unbundling the birth code is highly

unlikely. It might be easier to look for individual line items. Also, it would be very difficult to increase the billing for normal newborns (NICU patients can have itemized bills).

- An organizational representative stressed the need for updated outcomes data. There are process measures (implementation), but little information on how well programs are performing. The implementation stories are very similar across conditions. Implementation should not be the only reason a condition does not move forward; as a result, a better and more critical analysis of the data should be conducted. The Committee has struggled with a lack of good outcomes data when it considers conditions.

Pompe Disease

Mr. Ojodu reminded the Committee that Pompe disease was first brought to the group for consideration in 2013. The Committee recommended it for addition to the RUSP based on data from a single NBS screening program in Missouri in June 2013. The Secretary accepted the recommendation in March 2015, making it the first LSD on the RUSP.

New York began universal population screening for Pompe in October 2014; this coincided with NIH funding for pilot testing of population screening for Pompe (two other states also received funding. Illinois began screening for the condition earlier in the summer. Since New York began screening, it has referred 33 cases for additional follow-up out of approximately 210,000 births. Missouri has referred 107 cases for additional follow-up out of approximately the same number of births. New York uses an MS/MS methodology and molecular testing (Dr. Caggana indicated that the state uses the molecular test and babies with only pseudodeficiency are not referred). Illinois also uses a liquid chromatography MS/MS. The different testing approaches could account for the difference in results in the two states. States need dedicated mass spectrometers for the LSDs. Missouri uses a digital microfluidics methodology. Digital microfluidics is not a testing methods that has been used previously by states.

Currently, only three states are universally screening for Pompe. Several states are considering adding Pompe to their uniform screening panels. Missouri's pilot study contributed to the evidence base reviewed by the Committee prior to its recommendation of the condition. The state currently screens for Pompe and three additional LSDs using digital microfluidics. It uses a stand-alone fluorometry for Krabbe and, in the near future, Niemann Pick A/B. Wisconsin used NICHD funds to pilot test Pompe screening. A bill has been introduced in the legislature to provide authority to screen for Krabbe, Fabry, Pompe, Niemann Pick, Gaucher, and MPS 1. Mr. Ojodu anticipated that the state would begin screening for Pompe in the near future. New York is using NIH funds to pilot test screening for Pompe. It is also pilot testing Fabry Gaucher, Niemann Pick A/B, and MPS 1 in four hospitals in New York City. The state is screening for Krabbe and Pompe by multiplexing these conditions with ALD. Washington has conducted a pilot test using de-identified DBS to test for Pompe, Fabry, and Gaucher using MS/MS and molecular analysis. There are plans to expand the pilot into three additional LSDs. The state does not have a mandate to screen for LSDs. Kentucky, Michigan, New Jersey, and Texas have testing mandates for Pompe but have not fully implemented it. Colorado and Ohio are considering adding Pompe to their panels.

Challenges related to the implementation of Pompe screening include the late onset of the condition and its effect on LTFU, the cost of treatment ($300,000 based on weight of infant with incremental increases over the lifespan), the incremental increase in the number of conditions on the RUSP, the need for dedicated equipment and LIMS software, and the need for appropriate staffing.

Mr. Ojodu indicated that, in the past, there was a lack of limited assessment of the public health impact for conditions added to the RUSP (e.g., CCHD, SCID, and Pompe). The Committee began to consider the impact with the Pompe nomination. Currently, the impact assessments for MPS 1 and X-ALD have been completed. These assessments provide information on implementation strategies and outcome measures before conditions are added to the RUSP. He stressed that there will always be challenges within individual states that prevent conditions from being added to the screening panel within three years of addition to the RUSP even though evidence is available to support such action.

Committee Discussion:

- An organizational representative observed that having a couple of states up and running, which results in data that could be used in the evaluation of the feasibility of implementation, does not necessarily predict the feasibility of implementation within a three-year period. Dr. Sontag indicated that the main issues with regard to timeliness of implementation are securing approval to screen and to fund screening; setting up the actual processes is often relatively quick in comparison. There is no data on how long the approval and funding takes in comparison to implementation.
- A Committee member pointed out that because of the rate at which the Committee has been approving conditions, they are essentially in competition with each other for implementation. It may take longer to add a particular condition to a state's panel because it is still working on implementing another condition. A NewSTEPs representative added that it is impossible for programs to keep up with the pace at which conditions are being added. In general it takes one to three years to obtain approval and funding for screening, and implementation takes another one to three years.
- A representative from the Iowa State Hygienic Laboratory recommended that the public health impact assessment should also consider whether it is appropriate for states to impact a population by mandate for a condition that may have enough uncertainty around it that is would be more appropriately classified as research rather than as a mandate through which the state exerts its authority to screen.
- In response to a question concerning the requirement for FDA approval of a kit prior to states being able to implement a screening, Mr. Ojodu indicated that an FDA-approved kit enhances implementation, but is not required. He was unaware of any states that have statutory language requiring the use of an FDA-approved kit.
- An organizational representative suggested that it might be the responsibility of the Committee to determine whether states are ready to begin implementation, rather than putting the burden on the states to decide whether they are ready for population screening or research.
- A Committee member asked whether there is a mechanism that would enable the group to have additional discussions about how to collect data and determine whether its recommendations are improving health outcomes and about how conditions could be taken off the RUSP. She anticipated that the Committee would be considering more rare disorders with less evidence. Dr. Bocchini indicated that one of the goals of the workgroups is to reframe the information needed before a condition goes through the nomination process. The Committee could begin considering outcome data and ways to obtain the data that it needs to consider a condition.
- The difference between the decision matrix, which is a tool to help evaluate the quantity and quality of data, and the ability to collect long-term outcome data were identified by a Committee member as two separate outcomes. The inability to collect outcome data should not, necessarily, serve as a basis for changing a decision.
- A Committee member indicated that future discussion topics for the Committee could include the effectiveness of the decision matrix, how well implementation is occurring at a more refined level than gross states data, and how to better understand the impact of screening programs and whether they are delivering the anticipated health benefit. Another member added that the paper developed by the LTFU Subcommittee outlines a framework of data required to determine whether babies are benefiting from screening has been submitted for publication.
- Dr. Comeau asserted that NBS is conducted under state authority, which takes away parents' rights. Screening should not be mandated in order to collect data to determine whether a condition should be screened, which is essentially research. States that are screening for LSDs are doing so by legislative mandate. If screening is a really good thing, states will do it before a condition is added to the RUSP. People will be more willing to have their children screened if the NBS community is honest with them and acknowledges that it is not certain that screening will result in a good outcome. People need to understand that some of this activity is really a study and could be helpful in the future. If any of the screening programs go badly, it would put the rest of the program in question.
- Dr. Caggana pointed out that in addition to bringing on new conditions and adding molecular components, NBS programs have been working on and made great progress with regard to timeliness. Data collection is a problem because there are already so many different registries and

data reporting systems, many of which are duplicative. Responsibility for data reporting needs to be part of the daily management process.

- A participant from NIH stated that researchers can apply for NIH grants to follow children identified by NBS. Family groups that are advocating the addition of a condition should work with their research communities to encourage them to continue to follow identified children.
- A Committee member stressed the importance of being able to show the need for federal funding for the development of follow-up systems and to show how such funding would improve the quality of services.
- The lack of information concerning the number of children being identified was identified as a concern by a Committee member. There is a lack of staff dedicated to the management of data. States could be systematically underestimating the kit fees increases associated with new modalities; a few extra dollars per fee could pay for data managers and education coordinators that would improve the system overall. The Committee should address the staffing issue.
- A Committee member noted that if California used the federally-funded R4S system, it would reduce its false positive rate for certain tests by 90 percent. This would result in significant savings with regard to follow-up.

IX. Public Comments

Mr. William Morris: Mr. Morris related how one of his four sons has PKU and was saved by the NBS program in Texas. Another one of his sons died just short of his first birthday from Krabbe disease because he was not identified through NBS. He stressed the need for NBS education for health care professionals and parents concerning the process and intent of NBS. The problems related to lack of education are compounded as new conditions are added to the RUSP. There is an urgent need for a uniform set of educational guidelines for providers during their training and for parents during the prenatal period. He advocated for the Committee to recommend establishment of such guidelines to the HHS Secretary.

Mr. Dean Suhr, MLD Foundation: Mr. Suhr reported on a RUSP roundtable meeting organized by the MLD Foundation and attended by public health, laboratory, clinical, pharmaceutical, genetic sequencing, and advocacy representatives. The participants discussed topics including quality of life as a metric; the impact of NBS on families, carriers, caregivers, and society as extended beneficiaries; the role of research in NBS as a public health initiative; viable therapies; funding; and emerging therapies in the private sector and the public health system. A summary of the meeting will be posted at www.newbornscreening.us. A similar meeting will be scheduled to coincide with the February ACHDNC meeting.

X. Workgroup Updates: Cost Analysis Workgroup

Lisa Prosser, Ph.D.
Associate Professor
Child Health Evaluation and Research
Division of General Pediatrics
University of Michigan Medical School
Ann Arbor, MI

Dr. Prosser reported that the Cost Analysis Workgroup (CAWG) met formally for the first time the previous afternoon after having met informally several times by telephone. The Workgroup is charged with considering methods to assess the cost of NBS expansion as required by the legislation that reauthorized the Committee. The resulting deliverable will be a report to the Committee making recommendations concerning ways to incorporate cost assessment into the evidence review.

The current evidence review process includes available economic valuation information; however there is often very little such information available. The CAWG anticipates developing an approach to the cost assessment that would enable it to be integrated into the evidence review similar to way the decision modeling was incorporated. Dr. Prosser stated that the CAWG would work with states, APHL, and NewSTEPs to identify ways to collect data on the cost of screening in order to inform the Committee's decisions.

The CAWG identified five questions that need to be addressed with regard to the cost analysis of NBS:

- What costs of NBS expansion should be included within a condition review to better inform the Committee?
- What are the critical data elements needed to address the cost of NBS expansion?
- What is the availability and feasibility of collecting data?
- What/who are the data sources and who will provide the data (e.g., the nominator, the CRW)?
- How will this impact the nomination and review process?

There are many types of economic evaluations, starting with the most comprehensive, either a cost-effectiveness analysis or a cost-benefit analysis that compares NBS with clinical identification. Creating and developing either type of analysis is not feasible within the nine-month evaluation timeframe. As a result, the CAWG is considering the use of a budget impact analysis (BIA) that would analyze the net change in financial expenditures for a health care system over a given timeframe. This approach only considers cost.

Costs to be considered as part of the BIA include costs to the public health departments (e.g., staff, equipment and reagent costs, and short-term follow-up and tracking); downstream costs to health care systems and families (e.g., clinical follow-up and long-term management, including treatment and monitoring for target and secondary conditions); and expansion costs, which are greater than the actual laboratory costs for the screen. There is substantial variability in the costs to the states when a new condition is added to a panel; these can be a result of the total volume of screens conducted, the number of screens performed on each sample (one versus two), and states contracting screening out to laboratories and specialty centers.

Factors that need to be considered when developing the cost analysis include the need to provide useful information that takes downstream costs into account, the variability of the costs across states, the feasibility of completing the analysis within the nine months allotted for condition review, the available resources for conducting the analysis, and the way in which the Committee plans to use the cost analysis.

The CAWG has determined that a BIA is the most feasible approach and that it should focus on the most common cost categories associated with NBS expansion. The group will focus on making any assumptions clear, identifying variability or ranges for cost inputs (e.g., states use different screening algorithms), and determining the scope of the analysis (e.g., cost categories, time horizon, etc.).

Next steps for the workgroup include reviewing the methods used for the MPS 1 cost estimates, developing a draft template for estimating the incremental costs of a new NBS condition, coordinating efforts with other groups, and preparing a retrospective cost estimate for X-ALD to determine the amount of time required and the feasibility of the proposed approach. The CAWG also discussed the possibility of developing a framework for preparing estimates for the Committee's evaluation that could also be translated into a tool to help states estimate their costs for implementing conditions.

Committee Discussion:

- A Committee member noted that the state of Washington is required to conduct a cost analysis before implementing a new condition. Dr. Prosser indicated that several of the CAWG members have been working on the state's analysis and the group will be looking at it to determine if there are aspects of the analysis that could be implemented for this effort.
- Regarding the role of cost in the decision to recommend conditions for the RUSP, a Committee member indicated that cost was not supposed to be a factor in determining whether or not a

condition should be added. Cost needs to be a separate conversation from the other factors addressed by the decision matrix.

XI. Workgroup Updates: Pilot Study Workgroup

Jeff Botkin, M.D., M.P.H.
Professor of Pediatrics and Medical Ethics
Associate Vice President for Research
University of Utah

Dr. Botkin stated that the Pilot Studies Workgroup (PSWG) has been in existence for about one year. It anticipates developing a formal set of recommendations for the Committee's consideration during the next in-person meeting.

The PSWG was set up to address the need for data that can be used in the evidence review process. The previous day's discussion highlighted the challenges of obtaining sufficient data for rare conditions and of funding costly population-based research. Additionally, Section 12 of the NBSSLRA requires informed consent for the use of DBS in federally-research.

Consent issues represent a significant challenge for pilot study research. NBSSLRA Section 12 eliminates the ability to conduct federally-funded research that involves adding a new screening test on a pilot basis either on an opt-out basis or with a simplified consent process. Research shows that parents generally want to know about these types of activities and want to have a choice regarding participation. The legislation sought to address these desires, but created unintended consequences for this type of research. It also sets up an ethical dilemma that pits the need for evidence for testing that potentially benefits children against the need for people to be adequately informed and have a choice about these activities. The primary challenge is identifying a way to implement consent processes that do not reduce substantially participation. The consent issue has the potential to make pilot studies more complicated, difficult, and expensive to conduct.

Dr. Botkin reported that HHS' Office of Human Research Protections will be releasing guidance about the NBSSLRA and that a Notice of Proposed Rule Making (NPRM) concerning human subject regulations will be coming out soon. The NPRM will require an additional comment period; it could be several years before these results in any actual regulatory changes. Until changes are made to the current set of rules, pilot studies will require consent, or they will have to be conducted through state-mandated systems (no federal funding). This produces a dilemma because things that are not known to be beneficial to children should not be part of mandated systems; on the other hand, not having the data upon which to make informed decisions for the welfare of children and families is an intolerable situation.

The PSWG's charge focused on three areas:

- Recognize and support current efforts regarding pilot studies and evaluation.
- Identify other resources that could support pilot studies and evaluation.
- Identify the information required by the Committee to move a nominated condition into the evidence review process (i.e., define the minimum pilot study data required for a condition to be accepted for evidence review).

Understanding the minimum level of data required is particularly important in light of the accelerated process for review required under the NBSSLRA. The minimum data would only apply to moving conditions from the nominated state to the evidence review state, not to the process of approving a condition for recommendation. Currently, the core requirements for moving into evidence review are having validation of the laboratory test, having widely available confirmatory testing with a sensitive and specific diagnostic test, and having a prospective population-based pilot study. The lack of a pilot study has been a consistent reason for not moving nominated conditions into the evidence review stage.

The definition of pilot study needs to be clarified. The term is generally used in the literature to describe several types of studies such as test validation studies and testing of anonymous DBS, but it is not specific. The PSWG believes that the focus should be on clarifying the type of study needed to move a condition forward rather than on redefining the term. The key factor in identifying the type of study needed is how well a screening test performs on a population-based sample with regard to clinical validity.

The PSWG proposes replacing the current requirement for a prospective population-based pilot study with one for a prospective population-based evaluation of NBS and patient identification. This gets away from a formal study, allows use of the experience gained from mandated state programs, and makes the actual screening of identifiable newborns a requirement. The PSWG proposed several stipulations to the requirement:

- Newborns screened should be identifiable and their clinical status evaluated to determine the clinical validity of the screening test result.
- At least one affected newborn should be detected through population screening.
- The evaluation need not demonstrate clinical utility as long as other data are submitted to address the utility of screening (e.g., the evidence for ALD came from small unpublished studies).
- The screening evaluation should be conducted in an appropriate population (i.e., one that adequately represents the U.S. population that would be screened for the condition under consideration).

Once the PSWG finalizes its recommendations, it will need to work with the Committee to determine whether the minimum criteria have been met to move a condition from the nomination stage into evidence review. Evidence reviews should not be used to justify evidence reviews. The decision concerning whether a condition has met the criteria to move into evidence review should be made by a person or group that has the knowledge to determine whether the evidence is sufficient and appropriate.

Committee Discussion:

- The way that research, feasibility, pilot testing, and formative and summative program evaluation fit together in the decision making model was highlighted by a Committee member. Now is a good time to consider how pilot studies fit into the broader sequence of decisions that need to be made.
- In response to a question about the difference between feasibility studies and pilot studies, Dr. Bailey indicated that feasibility studies are efforts to determine whether screening could be conducted on a smaller scale. Pilot studies should be larger in scale. Dr. Botkin added that feasibility studies could look at specific aspects (e.g., is it possible to ramp up to a high-throughput platform, can a particular state do the test given its specific considerations).
- A Committee member asked whether clinical studies done as part of a legislative mandate to conduct testing and research projects with informed consent could both produce pilot data for purposes of the evidence review. Dr. Botkin replied affirmatively.
- An organizational representative noted that many of the agencies represented on the Committee have defined ideas concerning what constitutes a pilot study. These definitions could help guide the Committee's definition. Dr. Botkin stressed the importance of the difference between pilot studies required to approve a condition and those needed to inform the decision to move a condition into evidence review.
- An organizational representative indicated that the focus should be on what questions need to be answered to move a condition forward rather than on how pilot studies are defined. A Workgroup member stated that the PSWG discussed avoiding the use of the term "pilot study" in order to focus on the parameters that should guide the decision to move forward with an evidence review.
- The wording used to describe the projects that the PSWG is focused on is important. An audience member noted studies are often equated with research when they could really be other things such as program evaluations.
- In response to a question about the role of pilot studies, Dr. Botkin confirmed that the PSWG's work on requirements for pilot studies is separate from the work associated with the matrix. The challenge will be ensuring that the CRW has the type of data it needs to move through its review in a timely manner. The goal should be to determine whether quality data exists for the nominated condition, not whether the data supports a recommendation.

- An audience member asked about how, under the stipulations, the Workgroup anticipated being able to find data that both establishes clinical validity and identifies at least one newborn. Dr. Botkin indicated that the Workgroup welcomed comments on these issues. Both SCID and ALD were cases in which the population data was not the critical factor in convincing the Committee that there was sufficient clinical utility to justify adding a condition on the RUSP. Population-based evaluations do not need to be of sufficient size and rigor to demonstrate utility.
- An audience member questioned the need for a single newborn to demonstrate clinical validity. A specimen from an affected newborn should be run through a high-throughput screen to demonstrate that affected newborns can be found. The laboratory needs to demonstrate that the analyte can be found. Dr. Botkin noted that by doing a population screen and finding 20 children for clinical evaluation who ultimately do not have the tested condition is very informative. Once an affected child is identified, the positive predictive value can be more accurately determined.
- A Committee member indicated that the population to be studied should be large enough to pick up one case based on the known prevalence of the disease in the population. It is acceptable to include samples from actual patients in the study to determine whether the testing will identify them as a means of validating the test. The samples should include disease variants to determine what can and cannot be identified.
- Based on the comments about the difference between validating a test and conducting population-based evaluation, Dr. Botkin indicated that the wording could be changed to focus on the validation of the screening paradigm rather than the validation of the test. The CRW would want to know how many false positives or variants were identified in the population regardless of whether a true positive is identified.
- An audience member pointed out that finding the false positives for some analytes would be more informative than finding the true positives. Knowing that a test is good enough to distinguish between a homozygote and a heterozygote will enable NBS programs to distinguish between the two. Clinical validity rests on being able to identify the affected newborn; having this should not necessarily be a criteria for moving a condition into evidence review. Including population-based screening in the criteria means that the process is controlled by the frequency of the condition in the population.
- An organizational member asked whether consent would be required in a special way (e.g., consent beyond opt-out or active, informed consent) if the pilot study process is conducted using a test that is not FDA approved. Dr. Botkin indicated that FDA -regulated trials do not have waiver criteria for informed consent. The Secretary's Advisory Committee on Human Research Protections recommended that there are certain circumstances that might benefit from waivers. Dr. Kelm stated that FDA has enforcement discretion with regard to retrospective studies. There is no problem with de-identified data. This could change for a variety of tests if the Common Rule changes.
- With regard to whether a pilot study for a test that is not FDA approved in the study population would require informed consent, Dr. Kelm indicated that the draft laboratory-based guidance indicates that investigational tests would require informed consent in cases where results are provided to the physician or patient until they are cleared by FDA. Using de-identified samples makes the process easier.

XII. Workgroup Updates: Timeliness Workgroup

Kellie B. Kelm, Ph.D.
Chief
Cardio-Renal Diagnostic Devices Branch
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostic Devices Evaluation and Safety
Food and Drug Administration
Silver Spring, MD

Cathy Wicklund, M.S., C.G.C.
Feinberg School of Medicine
Center for Genetic Medicine
Northwestern University
Chicago, IL

Dr. Kelm indicated that the Timeliness Workgroup (TWG) is in its second iteration. The original TWG developed a report, which is being edited for possible publication, as its final product. The new version was formed to respond to additional questions from the Committee. The TWG held its first meeting the previous afternoon; it membership is not yet complete. Currently, the Workgroup's membership includes representatives from the nursing, hospital administration, specialists, follow-up, and information technology/communication fields.

Dr. Kelm reviewed the recommendations for NBS timeliness developed by the TWG, and Ms. Wicklund reviewed the proposed charge for the Workgroup, which was based on the outcomes from the first timeliness report:

- Optimize successful strategies to address NBS specimen collection and transport.
  - Engage key stakeholders in these processes.
- Collect and disseminate timeliness-specific practices from state NBS programs including programs that have implemented efficiencies in collection, transport, screening, and follow-up. This may include:
  - Updates from states at NBSTRN Regional Collaborative meetings.
  - Updates from states participating in the NewSTEPs CoIIN program.
  - Updates from other timeliness efforts.
- Investigate strategies for improved standardization of communications of NBS results to providers and families.

Ms. Wicklund indicated that one of the Workgroup's responsibilities is to be aware of other ongoing projects in order to avoid duplication of effort, identify gaps, and identify ways in which the Committee could help move efforts forward. During the meeting, the TWG members received reports on recent activities under the CoIIN initiative, on the recently awarded NewSTEPs 360 grant, on Dr. Tarini's project on modeling and cost-analysis for NBS timeliness, and on the March of Dimes Quality Improvement Workgroup. With regard to the NewSTEPS 360 grant, the Workgroup learned that requests for proposals will focus on five areas and will be released in September.

Much of the Workgroup's discussion focused on brainstorming projects related to improved standardization of communication of NBS results to providers and families. Ms. Wicklund indicated that the group anticipates collecting data to determine if this is an area in which it could make contributions. The TWG also discussed potential projects related to specimen collection, specifically developing a better understanding of what happens in the hospital (e.g., blood draw, courier timing, etc.); determining whether there is sufficient data to describe the process; and formulating the Committee's role in regard to providing standardization guidelines, including potentially working with other groups with more authority in this area.

The Workgroup will begin holding monthly conference calls with an initial focus on possible projects.

Committee Discussion:

- A Workgroup member mentioned three best practices discussed during the meeting: localizing ACT sheets to include contact information, documenting who has been notified and when, and ensuring communications between the hospital and other individuals. There was also some discussion concerning whether point-of-care testing would fall under the purview of this group.
- A Committee member suggested that JCAHO be added as an organizational member since four million babies are born in hospitals annually and the organization has much influence over how hospitals operate.

XIII. New Business

With regard to the possibility of removing conditions from the RUSP, Dr. Matern suggested adding a link on the ACHDNC webpage that would allow for the nomination of conditions to be upgraded from secondary to primary targets, downgraded from primary to secondary targets, or removed.

With regard to the LSDs, he noted that Gaucher disease is always added in the states but never proposed to the Committee. The Committee should consider proposing it to determine whether it would succeed in the evidence review process and whether it should be added to the RUSP.

Dr. Bocchini indicated that these topics could be considered by the Committee; once the workgroups wrap up their efforts, the standing subcommittees will resume work and could possibly take them on. The PSWG anticipates delivering its final report in February 2016, which will complete its work. The TWG will likely continue on as a permanent workgroup; the others will sunset before the February 2015 meeting. In February, all of the subcommittees should be fully back in action.

Ms. Bonhomme pointed out that the Subcommittee, as a whole has not addressed educational issues since 2013. There has been much focus on this issue out in the field, and it should be reflected on the Committee's upcoming agendas. Specifically, the Committee should look at what is working, gaps, lessons learned, and how to communicate new ideas. Dr. Bocchini agreed that this topic could be considered for future discussion.

Dr. Botkin recommended that the Committee consider studying the ethics of multiplex screening platforms. Multiplexing for primary targets can also bring along a variety of conditions for which there is relatively little data. The questions concerning multiplexing relate to whether machines can be set to not generate the data for these other conditions and, if the data is generated, the possible ethical obligations for disclosure. This issue will become more significant in NBS as technology moves toward DNA-based platforms.

Dr. Greene recommended that the Committee to turn its attention to heritable disorders that are not on the RUSP.

Ms. Wicklund expressed her belief that the Committee should consider advances in the pre-natal aspects of heritable disorders, including non-invasive pre-natal testing. Ms. Williams agreed with Ms. Wicklund and tied this into the need for more education.

Concerning how to determine whether screens added to the RUSP are actually improving health outcomes for affected individuals, Dr. Parisi suggested that the Committee look into coordinating and integrating the various follow-up activities supported by multiple agencies and organizations. Dr. Bocchini indicated that now would be a good time to bring the various efforts being undertaken by NewSTEPs, the NBSTRN, and the data repository together to assess where gaps exist and identify ways to obtain data in a timely fashion.

An audience member with a family physician organization noted that outcomes issues were being addressed by the Follow-Up and Treatment Subcommittee before it went on hiatus. He looked forward to working with the Subcommittee again and indicated that looking at outcomes would be a reasonable charge for the group.

An audience member with the California Department of Public Health echoed Dr. Parisi's comments concerning the need for data to measure the impact of NBS. California has been collecting data in a systematic fashion and anticipates dissemination information about the data. She recommended that the Follow-Up and Treatment Subcommittee focus on data collection for conditions with late onset.

XIV. Adjournment

Dr. Bocchini thanked the Committee members for their contributions and adjourned the meeting.