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

February 12-13, 2015 Meeting Summary

The Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (Committee) was convened at 8:30 a.m. EDT on Thursday, February 12, 2015. The meeting was adjourned at 3:00 p.m. EDT on Friday, February 13, 2015. In accordance with the provisions of Public Law 92-463, the meeting was open to the public and was held as in-person meeting and via webinar.

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I. Administrative Business: February 12, 2015

A. Welcome and Roll Call

Joseph A. Bocchini, Jr. M.D.
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Professor and Chairman
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Louisiana State University
Shreveport, LA

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

Dr. Joseph Bocchini welcomed everyone to the February 2015 meeting of the Secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (Committee), which was held primarily as an in-person meeting, with 83 attendees and 110 individuals participating by webinar. Ms. Debi Sarkar from the Health Resources and Services Administration's (HRSA) was the Designated Federal Official (DFO).

Dr. Bocchini took the roll for the first day of the meeting. Voting members present were: Dr. Don Bailey, Dr. Joseph Bocchini, Dr. Coleen Boyle (CDC), Dr. Jeffrey Botkin, Dr. Denise Dougherty (AHRQ), Dr. Charlie Homer, Dr. Kellie Kelm (FDA), Dr. Fred Lorey, Dr. Michael Lu (HRSA), Dr. Dietrich Matern, Dr. Stephen McDonough, Dr. Melissa Parisi (NIH), Dr. Alexis Thompson, Ms. Andrea Williams, and Ms. Cathy Wicklund. Debi Sarkar, the Designated Federal Official (DFO), was also present.

Nonvoting organizational representatives participating included:

- American Academy of Family Physicians (AAFP): Dr. Frederick Chen
- American Academy of Pediatrics (AAP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- American College of Obstetricians and Gynecologists (ACOG): Dr. Nancy Rose
- Association of Maternal and Child Health (AMCHP): Dr. Debbie Badawi
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Association of State and Territorial Health Officials (ASTHO): Dr. Christopher Kus
- Department of Defense (DoD): Dr. Adam Kanis
- Genetic Alliance (GA): Ms. Natasha Bonhomme
- National Society of Genetic Counselors (NSGC) Cate Walsh Vockley
- Society for Inherited Metabolic Disorders (SIMD**)** Carol Greene
- March of Dimes (MoD): Dr. Siobhan Dolan

Dr. Bocchini informed participants that the bill to reauthorize the Committee had passed. It was signed into law on December 18, 2014. There are changes to the bill that will impact the Committee's work. The charter will be amended to reflect the new legislation and to allow the Committee's work to continue uninterrupted. A copy of all the amendments made by Congress was included in the participants' packets.

Dr. Bocchini discussed the Committee's additional roles and responsibilities. One of the most important new responsibilities is to review and vote on nominated conditions within nine months of the date on which the Committee referred the nominated condition to the Condition Review Workgroup. Dr. Bocchini reviewed the changes needed to address all new responsibilities including meeting four times a year instead of three.
This will be the last meeting of the Discretionary Committee. For the May meeting the group will convene as the SACHDNC. With this change the group will now return to rolling term limits for Committee members and organizational representatives. More details will be provided at the next meeting in May.

Dr. Bocchini also explained that they received a response from the Secretary to the letter of support for the National Committee on Vital and Health Statistics and its efforts to advance health informatics within public health. The letter was included in the participants' packets.

B. Approval of September 2014 Meeting Minutes

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

Dr. Bocchini informed participants that a copy of the minutes for the September 2014 Committee meeting was provided in the briefing book for this meeting. Committee members present voted to approve the minutes with the adoption of minor recommended changes.

II. U.S. Preventive Services Task Force – Overview and the Transfer of Newborn Screening Topics to the DACHDNC

Iris R. Mabry-Hernandez, M.D., M.P.H.
Medical Officer
U.S. Preventive Services Task Force Program
Center for Evidence and Practice Improvement
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Rockville, MD

Dr. Mabry-Hernandez's presentation explained the connection between the U.S. Preventive Services Task Force (USPSTF or Task Force) and the Agency for Healthcare Research and Quality (AHRQ) and described how the Task Force develops recommendations. She also discussed the process for topic referrals to other organizations.

The Task Force makes recommendations on clinical preventive services for primary care clinicians. The Task Force's scope for clinical preventive services includes screening tests, counseling, and preventive medications. The recommendations address only services offered in the primary care setting or services that can be referred by a primary care clinician. Recommendations apply to adults and children with no signs or symptoms (i.e. asymptomatic).

The Task Force uses a rigorous review of the existing peer-reviewed evidence to make its recommendations. The Task Force does not conduct research studies, but rather reviews and assesses existing research. It evaluates the benefits and harms of each service based on various factors such as age and sex.

The Task Force is an independent panel of nonfederal experts in prevention and evidence-based medicine. It is made up 16 volunteer members who represent various disciplines including family medicine, internal medicine, nursing, OB/GYN, pediatrics, and behavioral medicine. The Task Force is led by a Chair and two Vice Chairs, which serve four-year terms. Task Force members are appointed by the AHRQ director with guidance from the Chair and Vice Chairs. Current members include deans, medical directors, practicing clinicians, and professors.

While AHRQ provides support to the Task Force, it is important to note that the Task Force itself is an independent entity. It was created in 1984 by the Public Health Service. In the mid to late 1990s, AHRQ was tasked with providing support to the Task Force.

Topics to be addressed by the Task Force can be nominated by anyone via the Task Force's website. The public can suggest a new preventive service topic or recommend a topic for reconsideration due to new evidence, changes in the public health burden of the condition, or availability of new screening tests supported by new evidence. Topic nominations are accepted year-round and are considered by the Task Force during its three annual meetings.

Dr. Mabry-Hernandez walked participants through the steps the Task Force takes to solicit public input and make recommendations. Topics are ranked by priority. Once a topic has been decided to be high-priority, a research plan is created. Task Force members work with AHRQ staff and the Evidence-Based Center (EPC) to conduct a literature review. This process usually takes 9-15 months from the date the research plan is approved to the date the review of the peer-reviewed evidence is performed by the EPC. The draft recommendation statement is presented to the Task Force for a vote.

After the development of a research plan there is opportunity for public comment. The research plan is posted on the Task Force's website for public comment for four weeks. After this period, the Task Force and the EPC review all comments, address them appropriately, and create a final research plan. The Task Force then reviews the evidence and creates a draft recommendation statement.

The draft recommendation statement and evidence review are posted simultaneously on the website for public comment. The EPC reviews the comments on the draft, addresses them appropriately, and creates the final evidence review. The Task Force then discusses the final evidence review and any new evidence and develops a final recommendation statement. The final recommendation statement and supporting final evidence are posted on the Task Force's website and disseminated through various channels.

Letter grades are assigned to each recommendation statement. The grades are based on the strength of the evidence on the harms and benefits of a specific preventive service. Each of these letter grades is described below.

- A - The USPSTF recommends the service. There is high certainty that the net benefit is substantial
- B - The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial
- C - The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small
- D - The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits
- I Statement - The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined

Topics are also sometimes referred to other organizations. Topics may be referred to another organization if the Task Force believes such organization is in a better position to make an accurate and timely evidence-based recommendation. This practice avoids redundancy of resource use by the Task Force. The criteria for referring topics to another organization's recommendation are:

- The organization has been identified by the USPSTF as an appropriate source

- The organization has a process for updating recommendations in a timely manner
- The organization has a written and available evidence-based methodology, including the use of systematic reviews that assess benefits and harms that the Task Force judges to be adequate for the topic being considered

Committee Discussion

- Dr. Bailey explained that this Committee also considers feasibility; does the Task Force focus on net benefit? Also, is the Task Force reviewing screening tests obtained through dried blood spots?
- Dr. Mabry-Hernandez said that was the criteria they decided upon was looking at the balance between benefit and harm. For the second question that Dr. Bailey asked, the Task Force will decide to define a condition for newborn screening via blood spot or another way such as the screening for newborn hearing.
- Dr. Homer said he was a member of the U.S. Preventive Task Force. During that time, the issue of feasibility came up. When the Task Force recommend depression screening there was substantial discussion that the capacity or competency in primary care or behavioral health wasn't there yet. The conversation at the time was that the evidence supported it and therefore the Task Force should recommend it and the field should follow and create the necessary systems. Dr. Homer encouraged the Task Force to consider this Committee as an appropriate body for referral of any topic related to systematic newborn screening which involves the interface between medical practice and public health systems.
- Dr. Parisi asked a question about the time frame. She asked how long it usually takes to go from the time a condition is accepted, to the creation of a research plan, to the development of the evidence review by the EPC, and to a final recommendation.
- Dr. Mabry-Hernandez said that for that part of the process it would take between 1.5 to 2 years.
- Ms. Wicklund asked Dr. Mabry-Hernandez to discuss, from the point of view of the person nominating a condition, about any overlap among the conditions being nominated to the Task Force and this Committee.
- Dr. Mabry-Hernandez said she hasn't seen a lot of overlap in newborn screening, but offered the caveat that she hasn't seen all the nominations.
- Dr. Kemper, who is currently a member of the Task Force, said the Task Force hasn't addressed many conditions that can be identified through dried blood spots. He added that the topics of congenital hypothyroidism, PKU, and sickle cell disease are coming up again for reevaluation. The Task Force has recognized that it did not make sense for it to weigh in on those topics because this Committee is already doing that. Dr. Kemper said the Task Force only addresses a handful of topics at a time and he does not believe the Task Force has the desire to move far into the newborn screening world beyond of what it has already done.
- Dr. McDonough said it might be difficult to take on the Task Force's recommendations for review under a nine month time frame. He added that the group usually conducts one evidence review per year. He said he was concerned it would create a backlog and people might get frustrated by not getting a timely response. He asked if the Task Force had any resources that could assist the Committee with such requests.
- Dr. Kemper said that the Task Force will not be sending a specific request to look at any particular condition. The idea was that this Committee had already made recommendations about screening for congenital hypothyroidism, PKU, and sickle cell disease so they would not go back and consider it again. They assume that if something changes this Committee would be on top of it.
- Dr. Thompson asked if Dr. Mabry-Hernandez could provide more detail on the dissemination and implementation of the Task Force's recommendations.

- Dr. Mabry-Hernandez explained that the Task Force uses several different tools to disseminate its information. The final recommendation statement and the final evidence review are two documents that usually appear simultaneously in a peer-reviewed journal. Also, a consumer guide is simultaneously made available through the website. The Electronic Preventive Services Selector (ePSS) is also updated. This is an electronic tool that clinicians can use to search Task Force recommendations. A one-page summary of the recommendation is also posted on the website for the general public.
- Dr. Thompson asked if the Task Force interfaces with stakeholders such as medical societies or insurance companies/payers.
- Dr. Mabry-Hernandez replied that the Task Force does have partner organizations that represent professional societies and other groups. They attend the meetings and also provide comments during the public comment period. Dr. Chen said he supported the idea of the Task Force deferring a topic because the worst thing that could happen for their members is to have differing opinions on the evidence, such as a contradictory rating. The interesting nuance is that with the Affordable Care Act the recommendations from the Task Force are required to be covered by insurance.
- Dr. Dougherty said she wanted to follow up on a previous comment regarding feasibility. She explained that the latest recommendation states that primary care providers should screen for depression for 12 to 17-year-olds only if there is capacity either in the provider's office or in the community to do follow up. This addresses the feasibility issue, but in a different way.
- Dr. Bailey said that they should consider asking the Task Force to refer all newborn screening questions to this Committee.

III. Pilot Study Workgroup Update

Jeff Botkin, M.D.
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Dr. Botkin provided some introductory comments about the Pilot Study Workgroup. The workgroup's charges are to:

- 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)

Dr. Botkin informed participants about a new amendment added to the Newborn Screening Saves Lives Reauthorization Act of 2014. The amendment states that research on newborn dried blood spots will be considered research carried out on human subjects and will require IRB oversight. Subsections 46.116 (c) and (d) of title 45 of the Code of Federal Regulations will not apply. These subsections allow alteration or waiver of informed consent under certain circumstances. This means that informed consent of parents will need to be obtained for research using dried blood spots. This provision will only apply to dried blood spots used for purposes of federally funded or HHS research. This provision would not impact legacy spots collected in the past.

Dr. Mankoff, Director of the Office for Human Research Protections, explained that they did not have a lot of notice ahead of time about the changes prior to the provision being passed. The Secretary's Advisory Committee on Human Research Protection will also examine the issue and provide advice to the Secretary. In addition, the agency will develop further guidance on this topic.

Dr. Botkin said that Kathryn Swoboda, from Harvard, is the PI of the Prospective Evaluation of Newborn Infants with Spinal Muscular Atrophy Identified via Newborn Screening (SPOT SMA) study. This is an NIH study and has as a specific aim to assess public attitudes on parental permission for pilot studies for SMA. Parents and the general public are not the only stakeholders involved in the decision-making process around pilot studies. For this reason, there have been discussions about the feasibility of re-orienting the grant to address the attitudes of other stakeholders.

Carla Cuthbert, Ph.D., FACMG, FCCMG
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Dr. Cuthbert spoke about CDC's role in the implementation of newborn screening pilot programs. CDC's Newborn Screening and Molecular Biology Branch (NSMBB) has the only laboratory in the world devoted to ensuring the accuracy of newborn screening tests in every state as well as several countries. The branch is composed of about 40 to 45 scientists engaged in laboratory work. They also have oversight of the production of quality assurance material. The branch is composed of the Newborn Screening Quality Assurance Program, The Newborn Screening Translation Research Initiative, the Biochemical Mass Spectrometry Laboratory, and the Molecular Quality Improvement Program.

CDC funded the first public health pilot studies of newborn screening. Funding has been provided since 2008 and the first recipients were Massachusetts and Wisconsin. In subsequent years, funding was expanded to Michigan, Minnesota, Oklahoma, Virginia, and Georgia. In addition, CDC has funded the first newborn screening pilot study among Native Americans. Dr. Cuthbert presented the early research pilot objectives.

The programs were charged to: develop and evaluate testing in a high-throughput environment, develop secondary tests, look at novel approaches for data analysis and statistical algorithms, disseminate the knowledge and skills to other laboratory scientists within the newborn screening community, and train other public health community members.

Other CDC activities also support the sustainability of pilot programs and the implementation of screening for newborn conditions. For example, the Newborn Screening Quality Assurance Program supports quality testing. It is the only comprehensive quality assurance program using dried-blood spots in the world. The program develops quality control materials for new programs. These materials provide a high degree of confidence that testing results are accurate for the batch of samples being tested. Trends in method performance are documented and problems are identified so that corrective actions can be taken quickly. Quality Control data is evaluated twice a year.

The branch is also involved in proficiency testing of dried blood spot materials for newborn screening. A laboratory can be evaluated for its ability to obtain the same results on a set of samples. CDC has been involved with newborn programs for about 35 years. In 1978 it rolled out the first program for congenital hypothyroidism.

Dr. Cuthbert explained that it is critical that CDC be involved in the early stages of any newborn screening condition that is being considered for nationwide implementation. The development of robust quality assurance materials is not trivial and requires iterative evaluation with early adopting programs to assess performance and to document the proper certification of materials.

The branch is also involved in method development and opportunities for training state program lab personnel. Each laboratory within the branch is engaged in method development using dried blood spots for anticipated conditions. The branch also provides technical program support. That is, training and support to maintain technical expertise within the newborn screening labs. This is done through a variety of strategies including sharing best practices through national meetings, offering laboratory-based training, providing one-on-one consultations and laboratory data review, site visits, and website resources.

The branch also supports new born screening laboratory practice through partnerships. For example, CDC has a cooperative agreement with the Association of Public Health Laboratories. These and other partnerships facilitate training opportunities through courses, workshops, webinars, one-on-one training, and the development of online resources.

Tiina Urv, Ph.D.
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Eunice Kennedy Shriver National Institute of Child
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Bethesda, MD

Dr. Urv's presentation focused on Newborn Screening Pilots at NICHD. She also discussed the NIH's Hunter Kelly Newborn Research Program. The program focuses specifically on newborn screening disorders. It is authorized to carry out, coordinate, and expand research in newborn screening. The goal is to increase the number of conditions that can be diagnosed at birth, to understand the long-term effects of living with such conditions, and to foster the development of new treatments.

NIH also supports natural history studies and population studies to identify the prevalence of disorders. Investigators make use of these studies to determine when the best time to treat individuals is and how to treat some specific disorders. The NIH works closely with CDC, HRSA, and other organizations involved in newborn screening.

Dr. Urv provided an overview of funded studies and explained that Dr. Watson would provide more details about his study which is funded by NICHD. NIH has a model for newborn screening pilot studies. Once a disorder is targeted, the NIH then identifies states or small businesses that are able to screen a lot of babies in a short period of time. Children identified through screening are then followed through either short- or long-term studies.

NIH will soon be putting out an RFP for states that are capable of testing a large number of samples. The goal is to have a pool of contractors so that when pilots come up the implementation can be done quickly.

Michael Watson, Ph.D., FACMG
Organizational Representative
American College of Medical Genetics
Bethesda, MD

Dr. Watson's presentation discussed the Newborn Screening Translational Research Network (NBSTRN). He explained that Section 6 authorizes the Secretary to expand the Hunter Kelly Newborn Screening Research Program to provide research and data for newborn conditions under review by the advisory Committee to be added to the Recommended Uniform Screening Panel (RUSP). It also allows for support of pilot studies on conditions recommended by the Committee to ensure that screening is ready for nationwide implementation.

The three major tools the NBSTRN has are the Virtual Repository of Dried Blood Spots (VRDBS), the Longitudinal Pediatric Data Resource (LPDR), and the Region 4 Stork tool (R4S). The Virtual Repository of Dried Blood Spots is an open-source, web-based tool that enables NBS researchers to search over 2 million DBS from participating states.

The Longitudinal Pediatric Data Resource (LPDR) is a secure informatics system designed to enable enhanced data collection, sharing, and management, as well as analysis for conditions identified as part of newborn screening or for conditions that may benefit from newborn screening. The R4S tool is a web-based application for the collection and reporting of analytical results. It has been widely adopted into the routine practice of newborn screening by laboratories worldwide.

Dr. Watson explained that close to 2 million babies were screened for SCID in California during the 2010-2014 pilot period. NICHD has also funded a Pompe pilot that will screen approximately 400,000 babies. States funded thus far for this pilot are Georgia, New York, and Wisconsin. Two other states, Illinois and Missouri, are also screening for Pompe.

As of 2015, the RUSP includes a total of 57 conditions. This includes screening for 31 primary conditions and 26 secondary targets. There are various other conditions that could be considered for addition to the panel including ALD (X-Linked), CMV, HIV, Fragile X Syndrome, SMA, Toxoplasmosis and others. In all, there are potentially close to 100 conditions that could be considered in the future.

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Dr. Comeau's presentation highlighted a variety of state pilot studies. She began by defining a pilot study as an evaluation of the clinical merits of a particular newborn screen. This type of study aims to answer the following two questions: Does the test or strategy find the infants who have the condition? and What is the window of opportunity? She defined a pilot phase as the evaluation of the laboratory screening test. This type of study aims to answer two different questions: Can the test detect the marker? and If so, is the test scalable?

Dr. Comeau discussed some of the early pilot studies that eventually became expanded nationally. In 1982, Colorado began newborn screening for cystic fibrosis (CF NBS). Wisconsin joined the effort in 1985 and Massachusetts in 1999. These efforts led to the 2005 recommendation that CF be added to the RUSP.

Dr. Comeau explained that these studies took time and collaborative effort. It took a continuation and expansion of initial efforts by other states to bring in more numbers. She explained that when things needed to be fixed, the states helped each other. State activities included state-to-state information sharing, training courses, and kit development. Funding was sometimes a challenge and in the early days some pilot continuations were compounded by unfounded publicized criticisms.

Pilot phase technology evaluations have taken place consistently from 1994 to 2015 by various states including Massachusetts, Texas, Wisconsin, Missouri, Florida, and Washington. Through these efforts a wide range of markers have been studied. Some of these activities have resulted in implementation, evaluation of technology, or FDA clearance of specific kits.

Dr. Comeau said one of the biggest challenges is the absence of experience with specific newborn screening by other states. Also, funding can often be tight, which makes it difficult to hire staff with proper expertise in the design and implementation of pilot studies.

IV. Public Comments

Sarah Wilkerson, Board Member, Save Babies through Screening Foundation: Ms. Wilkerson shared the story of her son's death from undiagnosed medium chain acyl-CoA dehydrogenase deficiency due to a laboratory being closed on a weekend. She thanked the Laboratory Standards and Procedures Subcommittee for their hard work over the last year in researching the issue of timeliness. Ms. Wilkerson said that many states across the country have preemptively stepped up and done tremendous things to clean up policies on their own. Nonetheless, she continues to hear stories from other families and states across the country about existing delays that could put children at risk. A best practice guideline could help those hospitals and labs.

Elisa Seeger, Founder, Aidan Jack Seeger Foundation: Ms. Seeger said that on March 29, 2013 New York State signed a law in honor of her son who lost his life to ALD in 2012. She explained that on December 30, 2013 New York started testing all newborns for ALD. The first year of ALD testing ended on December 31, 2014. During that time, nine boys and six girls were identified with zero false positives giving these children and their families the information necessary to save their lives. With approximately 250,000 babies tested in 2014, one can safely say that ALD newborn screening works and should be added to every state. She said the ALD newborn screening manuscript has been published and is readily available for review. She added that every 36 hours another baby is born with ALD. This is an epidemic that can be stopped with a simple test. She said that everyone in the Committee today has the power to add ALD to the RUSP. She asked for the evidence review process to be expedited and make a decision to add ALD to the RUSP.

Dr. Amber Salzman, President, STOP ALD Foundation: Dr. Salzman said she supports adding ALD to the uniform screening panel. She said that Oliver, her nephew, was diagnosed with ALD at the age of 7 when it was too late to intervene. He continued to decline and lost ability after ability until he finally succumbed to the disease. Her son Spencer was one year old at the time of her nephew's diagnosis and thanks to the early warning the family was able to intervene. Today, Spencer is a healthy and charming 15-year-old taking honors biology, advanced math, and participating on the school's swim team. She has been attending Committee meetings since they submitted the nomination to add ALD in mid-2012. She added that she was encouraged that the process has moved forward, but also was saddened and alarmed by the knowledge that so many children have been born with ALD since that time and have not been given the opportunity to avoid a devastating outcome. It is important to find a way to accelerate the implementation of screening in the rest of the United States. Based on the new duties of the committee as outlined this morning, a decision needs to be made within nine months of the condition going to the Condition Review Group.

V. Laboratory Procedures and Standards Subcommittee Update – Timely Newborn Screening Project and other projects

Kellie Kelm, Ph.D.
Chair
Ex-Officio Committee Member
Food and Drug Administration
Silver Spring, MD

Susan Tanksley, Ph.D.
Co-Chair
Organizational Representative
Association of Public Health Laboratories
Austin, TX

Dr. Kelm explained that timeliness is important. In order to effectively reduce disability, morbidity, and mortality, screening must happen before the onset of symptoms. Some conditions may manifest with acute symptoms in the first days of life and require immediate treatment to reduce the risk of mortality and morbidity.

This Subcommittee was tasked with the following: outline the NBS system, investigate existing gaps and barriers in NBS systems, identify strategies to achieve these goals, develop a list of critical conditions that require urgent follow-up, review the recommendations in light of new technologies, and suggest revisions to the recommendations, if needed.

A total of 16 disorders were identified as being "time critical." The group also determined that many states were not meeting the first set of recommendations made by the DACHDNC. The group identified the following gaps and barriers:

- Lack of awareness of the urgency of NBS
- Lack of training/high turnover of staff performing dried blood specimen collection
- Batching by birthing facilities
- Geographic distance from birthing facility to NBS laboratory
- Lack of availability of courier/overnight delivery services
- Operating hours of the courier
- Operating hours of the NBS Program
- Lengthy testing algorithms to avoid high false positive rate
- Lack of ability to collect complete data

Several strategies for improvement were also identified:

- Utilizing courier or overnight delivery services
- Expanding the NBS program operating hours (laboratory & follow-up)
- Providing educational activities to birthing facility staff, laboratory staff & parents
- Improving reporting and communications mechanisms
- Improving Electronic ordering and resulting
- Focusing on continuous quality improvement activities
- Batching by birthing facilities/submitters
- Decreasing time from receipt in the lab to reporting
- Improving data collection to allow for evaluation
- Carrying out performance monitoring and feedback

The group also presented three areas that deserve further investigation:

- Continue/expand collaboration with American Hospital Association and possibly the Joint Commission to work on collection and transport inefficiencies at hospitals
- Develop recommendations based on communication of NBS results, whether presumptive positive for or normal, to the family of the affected infant
- Continued need for improved standardization of reporting procedures/statements

Based on the sum of all of the above work and extensive discussion, the Subcommittee suggested the following recommendations for timely newborn screening:

A. To achieve the goals of timely diagnosis and treatment of screened conditions and to avoid associated disability, morbidity and mortality, the following time frames should be achieved by NBS Programs:

    1. Presumptive positive results for time-critical conditions should be communicated immediately to the newborn's healthcare provider but no later than five days of life.

    2. Presumptive positive results for all other conditions should be communicated to the newborn's healthcare provider and soon as possible but no later than seven days of life.

3. All NBS tests should be completed within seven days of life.

B. In order to achieve the above goals:

1. Initial NBS specimens should be collected in the appropriate time frame for the newborn's condition but no later than 48 hours after birth, and

2. NBS specimens should be received at the laboratory as soon as possible; ideally within 24 hours of collection.

Committee Discussion

- Dr. Botkin said he was concerned about potential delays between the call made to the primary care provider and the time it takes to get the family in for testing, as some providers may not be adequately informed to understand the urgency. He asked if there is an opportunity to speak to some primary care organization groups to enhance education about the urgency.
- Dr. Kelm said they did hear from experts about issues surrounding missing communication. This topic was not touched on the presentation but it is something that needs to be followed up on. It was made clear that one of the items that needs to be addressed is to improve communication.
- Ms. Williams asked whose responsibility it was to do education at the hospital. Also, if it falls outside this guideline, who enforces it?
- Dr. Tanksley said that there are some hospitals that have good education programs, which could be a model for nationwide education. It might be useful to reach into the AHA to do this. Perhaps there should also be some JACHO measures. In terms of enforcement, since it is a state program enforcement will vary by state.
- Dr. Matern said that for time-critical conditions the laboratory should include information that the primary care physician should act immediately. It should be clear that immediate action is required.
- Ms. Bonhomme said that the recommendations are set at a national level and education and newborn screening happens at the local level. She suggested reaching out to nursing groups. There are also advocacy organizations that are working to increase awareness about newborn screening. She suggested looking for partners at the grassroots level.
- Dr. Tanksley suggested that point number three above be reworded to "All initial NBS tests…" to avoid confusion or to add it to A since it applies to points 1, 2, and 3.
- Dr. Matern said he concerned about the definition of "initial screen."
- Dr. Tanksley said it would be the initial specimen.
- Dr. McDonough moved that the Committee make the recommendation with the additional language changes to clarify the issue around the initial specimen. He also recommended that each newborn screening program adopt the following objectives for points 1, 2, 3 under "A": by 2017 at least 95 percent or more of newborn screening programs will have achieved these goals. He further recommended that by 2017 all newborn screening programs report annually to the Maternal Child Health Bureau about their progress in meeting these objectives and make available to the public the timeliness performance of hospitals and birthing centers in their state. In addition, he also recommended that the Committee recommend to the Secretary that she develop a grant program to assist all state newborn screening programs in implementing the above objectives or to assist in covering costs for state newborn screening programs in implementing new recommendations from this Committee once they have achieved their timeliness objectives.
- Dr. Bocchini seconded the motion and suggested having two separate parts. The first part would be the recommendations with the indicated modifications about the initial specimen. The second part would include Dr. McDonough's recommendations.

- Dr. Homer asked what would be the Secretary's authority to enforce these recommendations. For example, for Medicaid the Secretary can encourage states to report on a variety of issues but does not have the authority to [enforce them]. He suggested voting on the first recommendations, reviewing the language of [Dr. McDonough's recommendations], and holding further discussion and a vote tomorrow.

VOTE

The Committee voted on the suggested recommendations for timely newborn screening. The Committee approved the recommendations unanimously. The language for the second part was be worked on and presented the next day for discussion and vote.

The final recommendations are:

A. To achieve the goals of timely diagnosis and treatment of screened conditions and to avoid associated disability, morbidity and mortality, the following time frames should be achieved by NBS systems for the initial newborn screening specimen:
    1. Presumptive positive results for time-critical conditions should be communicated immediately to the newborn's healthcare provider but no later than five days of life.
    2. Presumptive positive results for all other conditions should be communicated to the newborn's healthcare provider as soon as possible but no later than seven days of life.
    3. All NBS tests should be completed within seven days of life with results reported to the healthcare provider as soon as possible.

B. In order to achieve the above goals:
    1. Initial NBS specimens should be collected in the appropriate time frame for the newborn's condition but no later than 48 hours after birth, and
    2. NBS specimens should be received at the laboratory as soon as possible; ideally within 24 hours of collection.

Further Committee Discussion

The Committee convened the next day to discuss the following additions to the recommendation that would be included in the letter to the Secretary:

- The Committee encourages States to track their progress in achieving each recommendation and support strategies that show progress in a transparent way.

- In order to support States with limited budgets, the Committee also encourages the Secretary to develop a grant program to further assist States in meeting the Committee's recommendations.

- States are encouraged to have 95 progress or more of newborns meeting the timeliness goals by 2017 and to communicate their progress to a national data resource to be determined by DHHS.

- Dr. McDonough made a motion to vote on the above recommendations and Dr. Bailey seconded it.
- Dr. Bailey explained that grant programs are time-limited. The problem is that laboratories have to be open over the weekend and samples need to be submitted overnight. Also, what would happen after [the grant ends in] five years?

- Ms. Wicklund wondered how the recommendation would affect states that have geographical challenges. Money will not be enough to overcome some of the obstacles they have in trying to get the samples to a laboratory if it is truly a geographical problem.
- Dr. Homer wondered if the recommendation could be made the stronger. Perhaps the Secretary could convene the Interagency Task Force on Newborn Screening and charge it with emphasizing the variety of mechanisms that the federal government could use as well as identifying appropriate vehicles to encourage public reporting. He believed the grants were more about technical assistance as opposed to ongoing maintenance of the state's infrastructure.
- Dr. Parisi said it would be a bit prescriptive to say a grant program is specifically the best strategy to encourage states to be able to comply with this recommendation. Dr. Parisi added that she's had experience in providing genetic services to some of the more remote regions of Alaska and other states that have geographical challenges. The Committee may be setting some of these states up for failure if they are not able to comply with very real barriers.
- Dr. Botkin said that perhaps there may be resources available to start mailing [samples] in a prompt manner without batching, so that the costs are covered in some way without the need for federal grants. He added that there may be other mechanisms that are more state-centric to cover costs.
- Ms. Williams suggested adding the language "developing mechanisms" to the recommendation.
- Dr. Bailey suggested that the second bullet read as follows: "In order to support States with limited budgets, the Committee also encourages the Secretary to develop a comprehensive program to further assist States in meeting the Committee's recommendations."

VOTE

- Dr. Bocchini asked if there were any other comments. Hearing none, the group proceeded to vote on accepting the additions so they would be included in the letter to the Secretary.
- The Committee voted to include the additions in the letter to the Secretary.

VI. Evaluating Harms in the Assessment of Net Benefits: A Framework for Newborn Screening Condition Review

Nancy Green, M.D.
Condition Review Workgroup
Columbia University Medical Center
New York, NY

Dr. Green explained that the task of the workgroup was to examine the balance of harms and benefits in order to arrive at a net benefit. Three decisions were made in the analysis of harms. The first was to define "harms." Harms was defined as any adverse impact such as adverse events, burdens, or risks. The second decision was to define the child as the *primary* consideration (family and social considerations were also included). The third decision was that harms considered would go beyond those just arising from standard clinical presentation and care including, for example, children who derived no clinical benefit.

Harms consider for the child included the physical burden to infants, increased risk of medical treatment (e.g. earlier Rx), delayed diagnosis from false negative results, and uncertainty of clinical diagnosis or clinical spectrum disparities in access. For the family harms included psychosocial and logistical burdens (e.g. false positives).

The challenges considered were both generic and those that are particular to newborn screening. One of the challenges is that trials are generally designed to focus on medical benefits. There is also limited data on harms and challenges related to subject recruitment and sampling selectivity (e.g. a child being diagnosed as a result of a sibling).

Dr. Green explained that pilot studies could help by gathering systematic data on harms as well as benefits. Pilots can also help to identify areas of research to focus on.

The group's finding on harms and recommendations were incorporated into the methodology of the Evidence Review Workgroup. The next steps are to receive the Committee's final comments on the manuscript and then to submit it for peer-reviewed publication.

Committee Discussion

- Dr. Botkin said that it is sometimes challenging for a pilot process to collect data on high risk problems such as, for example, inappropriate interventions (e.g. questions such as "How many children had inappropriate interventions based on their clinical conditions?")
- Dr. Bailey said there is a very high standard for benefits. Speculative benefits are not usually taken as evidence, so one should also not take speculative harm as evidence. The Fragile X pilot project was not only trying to prove benefit but also to determine if there were adverse events as a function of screening (e.g. depression, anxiety, etc.). It is important to think about pilot studies such as these while moving forward [and frame future pilots] in ways that can explicitly address harm.
- Dr. Boyle asked if this was something new that was being added to the evidence review process. Also, how might this have influenced prior reviews?
- Dr. Green said she did not believe the issue was ignored, but rather that it hadn't been systematically addressed. She said she did not believe they had to look back at missed opportunities for evaluation.
- Dr. Kemper said they reviewed the harms all along the process, but recognized that while there was a systematic approach to look at benefits, there wasn't the same approach to presenting harms.
- Dr. Homer said that, while the vulnerable child syndrome data are overstated and not consistently substantiated, he believes the evidence around the benefit probably needs to be higher than the evidence of net harm.

VII. Condition Review Update (ALD)

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

Dr. Kemper's presentation focused on the preliminary report of newborn screening for X-linked adrenoleukodystrophy (X-ALD). The group undertook a systematic review of the published literature through November 2014. This systematic review of the evidence included the selection of 170 studies.

X-ALD is a peroxisomal disorder affecting the adrenal cortex and the central nervous system. It has a broad phenotype spectrum ranging in onset and severity from childhood through adulthood. The conditionprimarily affects males although female heterozygous carriers can develop symptom onset in adulthood. X-ALD is the most common peroxisomal disorder with an estimated incidence in the U.S. of 1 in 21,000 newborn males. Studies also show that 1 in every 14,000 newborn females will be a carrier.

Newborn screening involves measurement of C26:0 lysophosphatidylcholine (26:0-lyso-PC) as detected in dried blood spots. Small pilot and validation studies have suggested low false-positive rates, high-throughput feasibility, and unknown sensitivity. Also, the clinical validity with confirmation has not been established. The primary screening method is tandem mass spectrometry. About 205,000 dried blood spots were screened in 2014.

Currently, X-ALD newborn screening is being carried out in New York, New Jersey, and Connecticut based on legislation approved in 2013. California has legislation in process to mandate ALD screening as does Maryland. A definitive X-ALD diagnosis can be obtained through a DNA diagnostic test for X-ALD involving non-nested genomic amplication of the ABDC1 gene, followed by sequencing and analysis with fluorescence. Neuroimaging will always be abnormal in neurologically symptomatic males. Clinical diagnosis in in severe cases (boys) includes the presence of symptoms of ADD, with signs of dementia, progressive disturbance in behavior, coordination, handwriting, vision, other neurological disturbances.

A variety of treatment strategies exist including hematopoietic stem cell transplantation, which may reduce the risk or progression of neurological degeneration in early stage CCALD. Adrenal cortisol replacement therapy is necessary for adrenocortical insufficiency ("Addison's disease") to prevent adrenal crisis, although it has no effect on neurological symptoms.

There are two cases of successful genetic therapy in France of boys with early CALD in which cerebral disease progression was halted after 14-16 months. Lorenzo's oil, another treatment strategy, aims to normalize saturated VLCFA plasma levels. It is considered controversial with mixed results. Lovastatin used for X-ALD aims to lower VLCFA although there are also mixed findings—a 2010 NEJM study showed a small decrease in plasma, but not red and white blood cells when using this strategy.

A 2007 study published in *Lancet* included survival outcomes with clinical detection for boys with early stage CALD. The study included both boys that received a stem cell transplant (n=19) and those who did not (n=283). The mean age at symptom onset among the non-transplanted group was 7 years old.

A total of 131 (46 percent) patients died during the mean follow-up period of 5.9 years at a mean age of 12.3 years. The 5-year survival was 66 percent. When comparing both groups, the 5-year survival probability of 54 percent in the early stage group was significantly poorer (p=0.006) than the 5-year survival of 95 percent in the transplanted group with early stage cerebral disease.

Committee Discussion

- Dr. Green said that the patients that did well in the study had sibling matched transplants. Not every child has this option, so this is something that has to be considered.
- Dr. Kemper said the purpose of the slide was to show that the primary outcome they will look at for childhood ALD will be mortality. Some open questions remain such as "What were the unique features that allowed them to have a successful transplant?" There are some nice data coming out about screening, but there are also various other issues that need to be explored.
- Dr. McDonough asked if there were data looking at the timing of the stem cell transplant and cognitive outcome.
- Dr. Kemper said they are still looking at the studies. There is information about cognitive outcomes and the ability to participate in activities.
- Dr. Greene said the committee should consider not only survival, but the cognitive and neurologic quality of life in survivors. Also, with respect to early intervention—especially intervention like a bone marrow transplant—the Committee will want to know percentages because some of the children with the disorder may become normal 40-year-old men who then develop Addison's and live to be 80 years old and never have neurologic disease. In such cases, would one want to transplant such a person as a newborn, if the transplant itself carried a risk of death? Dr. Greene said that DNA for ALD can be 99 percent definitive, but blood tests provide the definitive diagnosis.

- Dr. Matern said the role of the ABCD 1 gene is a little murky when it comes to newborn screening. From a screening perspective, one does not needs to consider molecular testing as part of the screening, but it should be included in the follow-up after the Very Long Chain Fatty Acid test. He added that some of tests have not yet been approved by the FDA.
- Dr. Botkin asked if the New York and New Jersey programs are collecting data in a comprehensive way that would help the Committee get a better understanding within a reasonable period of time.
- Dr. Kemper said he has not spoken to them directly, but based on publications he is hopeful that it would indeed be the case.
- Dr. Homer asked whether the screening test can differentiate [within the spectrum].
- Dr. Kemper said the screening test will identify the whole spectrum. One of the questions that arises, for example, is "If the screening test identifies the carrier females, how much information does the advisory Committee want back based on the benefit of detecting those carrier females?" There are several approaches one could take. One could argue there is no particular benefit to the carrier in infancy. Or one could say that down the line there would be a benefit to the individual's own health or their children. Dr. Kemper said it would be important to know where to focus their efforts.
- Dr. Lorey said that he believes that in Europe they are not screening girls.
- Dr. Greene added that outcome cannot be predicted solely by DNA. One also has to do an MRI. But doing an MRI may require sedation in young children, which carries some risk. Such risk needs to be considered to determine the net benefit.
- Anne Moser, a clinician, said she would put adrenal cortisol replacement therapy as the top treatment strategy, as it is lifesaving. She said that boys with ALD can die of Addison's disease from a simple fever. She added that there are a number of transplants that have been done and the data for those is being followed up. Also, it is important to remember that one does not always need a perfect match for a bone marrow transplant. She said that it is extremely important to identify females. Not all will be identified as some will be missed, but if a baby girl is a carrier for ALD one could do genetic testing in the family to possibly identify males.
- Dr. Bailey said he would like to know the percentage of babies that need to have treatment within the first year or two of life.
- Dr. Matern said that looking at the follow-up algorithm and what happens with the identified patients will be extremely important independently of whether X-ALD is detected or another peroxisomal disorder.

VIII. Cost and Cost-Effectiveness Analysis

Scott Grosse, Ph.D.
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Dr. Grosse's presentation focused on cost and cost-effectiveness for newborn screening applications. He explained that cost means different things to different people. For an economist, cost refers to resources that have been used up or were foregone. A cost-effectiveness analysis is a full economic evaluation in which costs and health are counted separately.

Dr. Grosse walked participants through definitions of various terms and then proceeded to highlight an analysis about Washington State and their addition of SCID to newborn screening. Washington State had 86,600 births and performed two screens per infant. The cost of T-Cell Receptor Excision Circles (TREC) assays (TREC amplification and a control gene, *beta-actin*) was calculated by the Washington Department of Health to be $8.08 per infant. Other costs considered included follow-up. NBS short-term follow-up for was determined to be $50 per positive screen. In addition, 0.029% of all infants were referred for confirmatory flow cytometry testing, which costs $250 per confirmatory tests (this includes costs for phlebotomy and clinical interpretation). Based on these figures, Washington State estimated the screening cost to be $8.17 per infant. As a result of this study, the newborn screening fee in that state was raised by $8.17 when SCID was added.

It is important to note that such costs may vary from state to state. There are many factors that play into determining costs. For example, the average variable cost of laboratory testing may be higher with lower testing volume, states may attribute a share of fixed costs to new tests, states may pay for the cost of confirmatory and diagnostic testing, and states may offer contracts to specialty centers. As an example, the Florida Department of Health estimated that adding SCID would cost $16.67 per infant. However, this cost included staff time, equipment, reagents, colocation, and referral center contracts.

When estimating costs one should also consider the cost to the clinical system for managing the disorders when they are identified via newborn screening as compared to not identifying the disorder through screening. In other words, costs need to go beyond the costs associated with laboratory testing. Dr. Grosse walked participants on the calculation of costs from a wide variety of perspectives.

Washington State used cost-benefit analysis as well as cost-effectiveness analysis in their newborn screening estimation. Washington state law requires cost-benefit analysis for new regulations, including additions to the newborn screening panel. Since 2002, the Washington Department of Health has developed spreadsheet economic models before each newborn screening expansion. Washington State's cost-benefit analysis calculated the dollar value of deaths averted using an estimate of Value of Statistical Life of $7.7 million in their 2012 SCID analysis.

They also used a cost-effectiveness analysis to calculate the direct cost per life-year saved. The cost-effectiveness of newborn screening for SCID in Washington State resulted in a base case estimate of $32,970 per life-year saved. They also calculated the net direct cost to be $343,070 per year based on the cost of screening ($756,961) and the cost offset ($413,888).

The Washington Department of Health, APHL, and CDC are working collaboratively to develop an updated model based on the adaptation of Washington's SCID cost-benefit model. Once completed, this model will be disseminated so that other states may customize it for other conditions using their own state parameters.

There were two major lessons learned from doing the modeling. The first was that modeling the cost-effectiveness or cost-benefit of expanding newborn screening can be resource intensive. For example, a cost-effective analysis of screening for CCHD conducted by CDC took two years. The APHL cost-effectiveness analysis of screening for SCID has taken nine months to adapt an existing model. These analyses were done for conditions where a good evidence base already existed. The second lesson learned is that economic evaluations of screening for candidate disorders may be even more challenging. Dr. Grosse said that Dr. Prosser estimated that it takes a minimum of 18 months to do a decent cost-effectiveness analysis.

Committee Discussion

- Dr. McDonough asked about information related to costs to society, families, and disability if the result was moderate or mild disability. Also, are there any figures about impact on siblings or divorce rates?
- Dr. Grosse said the usual approach is to look at the medical and educational costs of disability as well as the detriment in quality adjusted life years. He added that they published an article with quantified estimates of the loss of quality-adjusted life-years (QALY) for different types of developmental disabilities associated with newborn screening conditions or infectious diseases. There is a lot of variability in the estimates, rather than a single true number, so their conclusion was that any analysis should use a range to reflect the uncertainty rather than delivering a single point estimate. In terms of spillover effects on other family members—that is growing and there have been some papers published on those issues, but it is often hard to determine it due to the lack of good evidence. He said that he worked with another colleague on a survey of families with children with spina bifida and tried to quantify some of those items but the problem was inconsistent estimates from different studies. He added that families of children with the disabling condition don't always have a higher rate of divorce. There are some studies involving Down's syndrome which show lower rates of divorce.
- Dr. Botkin asked how often analyses will provide fundamentally different perspectives on an issue. Are there circumstances in which this sort of additional analysis would have perhaps led the Committee to a different decision about a condition? Also, should this become part of the Committee's workflow?
- Dr. Grosse said that as an economist his job is not necessarily to make a decision, but rather to provide information to the decision makers. The ACIP has wrestled with this issue. The meningococcal immunization was delayed in part because of cost issues. He said that often the economic analysis will help by providing evidence supporting an expansion. Modeling SCID screening is helpful because there still are lot of states that are not screening for SCID. Showing that it is highly cost-effective compared to other public health expenditures can help provide a justification for the investments and resources for those states to add SCID. Dr. Grosse added that economic evaluation can also be helpful in prioritization.
- Dr. Homer asked Dr. Grosse to contrast the figure of $1 million for treating some rare diseases with the old and arbitrary standard of $50,000 to $100,000?
- Dr. Grosse said there isn't a single value. If it is a screening test, which is easy to do, low costs may be sufficient [to make a decision]. When presented with the cost of $1 per infant to screen for conditions using existing instruments, existing staff, etc. people usually say "Why not?" He said he wasn't recommending this but rather saying that this is typically how people respond. For new processes or technology that requires investing, the bar is going to be higher and so a cost-effectiveness analysis will be more influential.
- Dr. Boyle referred to the SCID example that was presented. When one looks at the cost of early vs. late treatment it seems like a "no-brainer." [Such an analysis] could really help accelerate implementation. She added that having a model that states can modify by plugging in their own data is terrific.
- Dr. Lu made a comment with respect to the 18 month time frame to do a good cost-effective analysis. If the Committee is given nine months to get from nomination to decision, what can really be done during that period?
- Dr. Grosse said that what can be done is a partial economic evaluation, which is calculating the cost of implementation from a budget perspective. That is, not doing a global economic analysis that takes into consideration the health care system. In other words, determine how much will it cost the state to implement screening for a certain condition—not just the reagent cost, which is often a relatively small part of the total, but the whole cost including, for example, recruiting staff, training staff, making sure there are staff for follow-up, etc. This can be done within a nine month time frame.
- [audio was cutoff]

- Dr. Tanksley said that people often ask about the cost of implementation, but from a public health lab's perspective they found it much more beneficial to be able to determine the cost avoidance of performing screening. This approach was very successful for SCID implementation in Texas. They were able to get the test implemented because a Medicaid cost-benefit analysis showed that it was more beneficial to screen than not to screen. And this was looking at only about 50 percent of their population.
- Dr. Grosse asked if this was calculated using charges rather than cost.
- Dr. Tanksley said it was calculated using charges.
- Dr. Grosse added that the 18 month time frame assumes doing a systematic evidence review to find the parameters to include in the model. This would result in a model that can be published in a peer-reviewed journal. If one is interested in doing a quick, back-of-the-envelope calculation for internal purposes without publication, it can take less time. However, he did not believe the Committee could use that type of analysis for its work. He suggested considering doing a cost of implementation analysis within the nine month time frame. A full economic evaluation could be done concurrently which would not necessarily inform the Committee's decision, but could help inform the state implementation process which would take place after the condition was added to the RUSP.
- Dr. Botkin asked, with respect to pilots, if there was a way to develop a better evidence base for making these sorts of decisions. Should the Committee be thinking about routinely incorporating economic considerations in the data collection so these sorts of analyses can be promoted?
- Dr. Grosse agreed this would be a good idea.
- Dr. Badawi asked if states would be able plug in their own costs in the cost-benefit analyses done for conditions that are nominated to the workgroup.
- Dr. Grosse concurred and explained that this is exactly what happened with the SCID model.
- Dr. Grosse said the estimates he presented were conservative. The actual difference in cost is likely to be larger because the cost estimates do not necessarily include the cost of hospitalizations for infections before an infant is diagnosed. Also, the number of deaths avoided is probably understated because it is based primarily on post-transplant deaths. However, there are infants with SCID who died without a diagnosis or died of infections before they were eligible for a transplant. However, even with relatively conservative assumptions screening was still highly cost effective. Dr. Grosse emphasized that the figures presented today were in draft form and asked participants to please refrain from citing the figures in the presentation.

IX. Committee Business: February 13, 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. Bailey, Dr. Bocchini, Dr. Botkin, Dr. Boyle, Dr. Homer, Dr. Kelm, Dr. Lorey, Dr. Lu, Dr. Mabry-Hernandez, Dr. Matern, Dr. McDonough, Dr. Parisi, Dr. Thompson, Ms. Wicklund, and Ms. Williams. Ms. Sarkar served as the DFO.

Nonvoting organizational representatives participating were:

- AAFP: Dr. Chen
- AAP: Dr. Tarini
- AMCHP: Dr. Badawi
- APHL: Dr. Tanksley
- DoD: Dr. Kanis

- GA: Ms. Bonhomme
- MoD: Dr. Dolan
- SIMD: Dr. Greene
- ACOG: Dr. Rose
- ACMG: Dr. Watson
- NSGC: Ms. Vockley

X. Public Comments

Jenny Bailey, Parent, Representing cCMV Families: Ms. Bailey said she is a CMV mom. CMV causes a child to become disabled every hour in the United States. If a newborn is not tested for CMV at birth, the only option is to retrieve the newborn blood spot from the state lab, if it has not already been destroyed, and have it tested. Medical practitioners often lack basic CMV prevention, diagnosis, and treatment knowledge. Hearing loss and other disabilities caused by cCMV are often late onset. While cCMV is not rare, timely diagnosis and intervention are indeed rare. Ms. Bailey commended the committee for adopting recommendations on shortening the time between a baby's birth and when the baby's screening results are returned. This will save lives. In 2004, when the screening panel was devised by a contractor, CMV was deferred for inclusion in the panel. After more than a decade, it is long past time to move congenital CVM from the deferred category to inclusion on the RUSP as a core condition. Absence of CVM from the RUSP creates the perception that CVM is not the common and devastating congenital illness that it is. Immediate inclusion of CVM on the RUSP will save lives and the abilities of babies and signal obstetricians that prevention for pregnant women is imperative.

Mr. Stephen Holland, Parent, Representing MPS I families and the National MPS Society: Mr. Holland is a board member of the MPS Society which represents 800 families touched by MPS and related diseases. He is also the father of three MPS I children, one of which passed away seven years ago at the age of 18. Once a child receives a diagnosis like MPS, a parent feels a desire to make things right by the child and to create an equal playing field for a child who was born with a huge disadvantage of having a terminal genetic syndrome through no fault of their own. One of the most important ways of doing this is by providing them with medical treatment that will help prevent further damage for the condition and help sustain their life. The problem is that parents cannot begin treatment until they know their child has the disease. Yet often it takes many months and sometimes even years between noticing there is a problem to getting a diagnosis. During this time irreparable harm is done to the child that a future treatment will not be able to reverse. This delay in diagnosis and treatment often creates parental guilt and regret. However, with newborn screening all of this regret, guilt, and conflict with the medical community over a delayed diagnosis is eliminated. Treatment can start immediately. The evidence conclusively shows that the long-term clinical, life-limiting, and life-ending effects of MPS I can virtually be eliminated with early treatment. There are concerns over false positives and resulting parental anxiety these can create. However such anxiety is short-lived as compared to the permanent damage caused by the untreated disease in the months and often years following birth. Another important benefit for newborn screening would be reducing the births of affected siblings. In Mr. Holland's family all three children were affected. Because they were born close together and had an attenuated form of the disease, the parents did not realize there was a problem while they were having children. If newborn screening had indicated his son had MPS I, he would have used the benefits of genetic counseling to prevent his daughters from being affected. The ability to prevent most, if not all, of the permanent damage caused by MPS I by providing parents with treatment options at birth currently exists. His family along with other MPS families thanked the Committee for its service.

Mr. Bill Morris, NBS Education: Mr. Morris is the father of four boys, two of which were affected by two separate genetic recessive disorders. In 2007, he lost his youngest son. He said there is a chronic lack of grassroots education of not only for expecting parents but also for health care providers. All in attendance know the importance of newborn screening, but for the most part only those parents and clinicians directly affected by identification (or lack of identification) of a disorder have any knowledge of the existence of newborn screening. This body suggested in 2010 that education should happen during the prenatal period. Some work has been done through wonderful websites and organizations that were created. However, his experience indicates that only parents that hear the term "newborn screening" search out these websites. The majority of parents aren't hearing about it. He suggested that more should be done through the education and training subcommittee to strategize around this issue. He strongly cautioned against removing this important subcommittee during the restructure. He suggested partnering with many eager advocacy parent groups to create a uniform education plan.

XI. Final Condition Review of Mucopolysaccharidosis I (MPS I)

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

Lisa Prosser, Ph.D., M.S.
Condition Review Workgroup
Child Health Evaluation and Research Unit University of Michigan
Ann Arbor, MI

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

Dr. Kemper's presentation focused on highlighting the key findings from the systematic evidence review, describing the bounds of benefit and harm based on findings from the evidence review, and summarizing the capability of state newborn screening programs to offer comprehensive screening for MPS I.

MPSI is an autosomal recessive Lysosomal Storage Disorder (LSD) caused by deficiency of α-L-iduronidase (IDUA) enzyme. It is a progressive and multisystem disorder with variable clinical symptoms. It presents a continuum of disease severity. The estimated MPS I incidence is 0.54 to 1.15 per 100,000 individuals.

MSP I can be classified as either "severe" or "attenuated." Based on currently known prevalence estimates, the severe form predominates and the disease spectrum is skewed towards this form. The severe form (also referred to as "Hurler's Syndrome") typically has onset by the first year of life, is rapidly progressive, and has multisystem organ involvement. It presents significant involvement of the central nervous system (CNS) as opposed to the attenuated forms which have less CNS involvement.

The untreated severe form is associated with death in early childhood (<10 years). In contrast, the moderate attenuated version (also referred to as "Hurler/Scheie" syndrome) has a typical life expectancy of less than 20 years, while most individuals with the milder attenuated version ("Scheie" syndrome) have a normal life span.

A 2014 study based on a registry of patients (n=987) showed that for the severe version the median age of onset is at 6 months and diagnosis at year one. For the attenuated Hurler/Scheie version, median age of onset is at 1.8 years and diagnosis at 4 years. The attenuated Scheie version showed a median age of onset of 5.3 years and diagnosis at 9.4 years.

Screening is based on the detection of low IDUA enzyme activity in dried blood spots. The two main key screening methods are tandem mass spectrometry (MS/MS) and flourometry by digital microfluidics. Different protocols are used for MS/MS.

To establish an MPS I diagnosis one needs to confirm low IDUA enzyme activity—typically less than 1 percent of normal. However, enzyme activity alone does not predict the condition's phenotype. Glycosaminoglycan (GAG) levels may also be measured in urine to rule out pseudodeficiency of IDUA. While GAG levels are measured babies will also generally be genotyped. Genotyping can help predict the course if it reveals a known mutation. However, most mutations are "private." In addition to these tests, a clinical assessment is required to confirm diagnosis and begin treatment. There are more than 100 known MPS I-specific IDUA mutations, and many are unique to specific individuals. There are also 7 to 9 commonly recurring mutations that are known at present.

Treatment strategies include hematopoietic stem cell transplantation (HSCT), HSCT + Enzyme Replacement Therapy (ERT), and ERT alone. HSCT allows individuals to produce endogenous enzyme. ERT is proposed as a bridge prior to HSCT as it may augment enzyme availability after transplantation. Increasingly, standard regimens include ERT before and after HSCT. Enzyme replacement therapy may benefit patients with all forms of disease, though because intravenously administered ERT does not cross the blood-brain barrier, it is typically used with MPS I patients with mild and attenuated forms who do not present with central nervous system involvement. There is a case report of intrathecal ERT administration that suggests improved motor control and stability and normal CSF GAG levels, though this approach is not currently considered standard of care.

Dr. Kemper walked participants through the process for conducting a systematic literature review of the published literature from 2003 to January 2015. A total of 170 studies were selected for review, data extraction, and synthesis. Experts in the field were also interviewed to inform the evidence review process. Dr. Kemper reviewed screening strategies and results for Missouri and Illinois NBS programs, along with key studies such as the MS/MS LSD Screening Study conducted by the University of Washington. Pilot studies in Taiwan and Italy were also discussed.

The evidence showed that recent advances in transplant regimens seem to improve survival. It also showed that mortality is similar in cases detected through screening compared to those detected clinically. There is no evidence regarding transplantation in "asymptomatic" infants. The review also showed that, with respect to cognitive outcomes, ERT along with transplantation seems to be potentially better than transplantation alone. Evidence suggests that transplantation at an earlier age (before nine months) is better than transplantation after nine months with respect to normal developmental trajectories. However, potential bias in the methods of these studies limits certainty of the findings.

For the attenuated version of MPS I, the evidence suggested that ERT leads to improved outcomes in symptomatic individuals. This includes mobility improvements as well as improvements in the disability index.

Two case reports of sibling sets suggested that early detection and identification of individuals with MPS I who are treated early ERT (before five months) in asymptomatic individuals with MPS I who were detected early show halted or limited disease progression. However, there is no other published evidence to corroborate this finding. It is important to note that ERT treatment does present some harms. It is associated with the need for weekly infusions which creates the possibility of developing antibodies to the therapy.

Dr. Kemper presented Dr. Prosser's work, "Population-Level Outcomes for Newborn Screening of MPS I." This decision analysis study used simulation modeling to estimate population-level health benefits. Dr. Prosser used a computation simulation model to evaluate outcomes for universal newborn screening for MPS I (NBS) vs. the clinical identification of MPS I (CI). The study's key endpoints were the number of cases identified, the number of deaths averted by five years of age, and the number of cases with improvement in cognitive outcomes.

The study assumed that the number of severe cases identified by 36 months would be the same under NBS or CI. Another assumption was that all severe cases of MPS I identified through NBS would be eligible for HSCT. Results of the modeling study showed that 44 cases would be identified via NBS vs. 40 cases through CI.

The potential benefits of newborn screening could include earlier identification and initiation of treatment (HSCT) for severe cases of MPS I as well as earlier identification and initiation of treatment (ERT) for attenuated cases of MPS I. The decision analysis process highlighted lack of evidence to reliably model cognitive outcomes and morbidity for severe cases as well as outcomes for attenuated cases and those of unknown phenotype.

Mr. Ojodu's presentation focused on the assessment of the public health impact for MPS I. The assessment presented opportunities to understand "real-world" barriers as well as facilitators related to: screening, identifying research gaps, evaluating opportunity costs, and sharing practices that can ultimately improve implementation.

A survey of newborn screening programs of 50 US states, three territories, and the District of Columbia was undertaken. Three states (Illinois, Missouri, and New Jersey) were selected for interviews about their screening programs. A factsheet regarding background information on MPS I was developed and provided to state newborn screening programs involved in the survey. Outreach was conducted through webinars to those in the newborn screening community. The response rate for the survey was 74 percent.

The three states interviewed were asked about considerations for implementation, barriers to implementation, facilitators to implementation, and implementation challenges. Results for each of these areas are presented below.

With respect to considerations during the implementation process, states cited the following:

- Meeting with state Advisory boards
- Obtaining needed equipment
- Choosing and validating a screening method
- Developing clinical protocols
- Resolving database/LIMS issues
- Collaborating with medical specialists
- Conducting pre-pilots

The states listed a variety of potential barriers to implementation including:

- Cost/time involved with obtaining new equipment and making laboratory upgrades
- Hiring staff for testing
- Dealing with a high number of false positives and cases of pseudo-deficiency
- Low incidence of the disorder
- Difficulty in creating treatment algorithms
- Uncertainty regarding the age of onset and how to handle cases of unknown phenotypes
- Broad burden on the medical system
- Method validation process

The states identified five factors that either had helped or would help implementation:

- Multiplexing MPS I with other LSDs
- Conducting a pilot

- Having the infrastructure in place
- Developing well-defined protocols
- Having strong relationships, communication, and expertise from staff, medical professionals, and partners

States identified the following challenges related to implementation:

- Time required to validate it
- Adjusting cutoffs to reduce false positives
- Not having quality control or proficiency testing materials available by CDC
- Not having an FDA-approved kit

In terms of a timeline, NBS program directors interviewed believed it would take two to three years (or more than three years) to complete the entire implementation process from obtaining equipment to conducting statewide screening.

The survey showed that states classified providing the screening test as the major funding challenge (81 percent thought this was a major challenge). Other major funding challenges included: long-term follow-up for those with late-onset disease or who are carriers (74 percent), having to increase the NBS fee (56 percent), support to treatment for MPS I (51 percent), and support to specialists in MPS I (47 percent).

Nearly 50 percent of the states noted that it would take approximately one year to get the new tandem mass spectrometry procedures into the laboratory for screening purposes for MPS-1 and 39 percent of the states said that it would take approximately a year for the advanced liquid logic methodology. Survey results showed that the cost per specimen was the number one factor that would hinder implementation.

Of the states responding to the survey, 50 percent of the programs agreed that funding and costs associated with implementation were the most significant implementation barriers. Other barriers included:

- Not having MPS I on the RUSP
- Condition not meeting criteria for screening
- Limited ERT capabilities
- High number of false positives
- Uncertainty with mild cases of the disorder

With respect to facilitators, 25 percent of programs listed having treatment and clinical and outcome evidence showing the utility of screening as a facilitator. Having funding associated with implementation was noted as a facilitator by 22 percent of the programs. Other facilitators included having an FDA approved kit and having MPS I added to the RUSP. Nearly 80 percent of programs believed it would take between one and three years to implement screening for MPS I after the approval and allocation of funds.

Mr. Ojodu said that a lot was learned from the two states that have begun screening. One of the most important lessons is that detecting a large number of false positive and cases of pseudo-deficiency remain important challenges.

Dr. Kemper summarized some take-away points from the presentation:

- The birth prevalence seems to be about 1/100,000, with most cases being severe
- Screening can identify newborns with MPS I and has been implemented in Missouri and Illinois
- It is unclear from published or available newborn screening data which screening method is best. Also, all require adoption of new methods for states not screening for lysosomal storage disorders
- The expected number of false-positives related to pseudo-deficiency is greater than anticipated
- Early identification of MPS I compared to clinical detection may not improve survival in young children
- Early treatment (<9-16 months) may lead to improved developmental trajectories for cognitive outcomes
- For the attenuated version of MPSI, the age at which symptoms develop cannot be predicted. There is also no evidence that pre-symptomatic treatment leads to better outcomes.

Committee Discussion

- Dr. Tarini asked Dr. Kemper to explain the term "pseudodeficiency."
- Dr. Kemper said he considered pseudo-deficiency to be a false positive. Although in the assay it looks like the baby has low enzyme activity, for all intents and purposes, it is fine. So it is an artifact of how it is measured.
- With respect to the MSP I Registry, Dr. Parisi asked if Dr. Kemper had any information about cognitive outcomes or relative physical disability.
- Dr. Kemper said the registry does collect standardized data on developmental outcome. The problem is that there is probably a lot of error in the database in terms of how those numbers are reported and what particular tests were used in the evaluation. He added that as the registry stands now, he would feel uncomfortable drawing certain conclusions from it.
- Dr. Botkin asked if it was the case that children would not be transplanted prior to the development of symptoms. He added that it might be likely that children transplanted at the youngest age would be biased towards being the more severely affected children, so that in fact better outcomes might be more impressive because of the negative bias of the early onset point.
- Dr. Kemper agreed that there is a spectrum bias and that the babies being detected clinically usually are the ones more likely to have a more severe presentation. The transplant could affect issues of cognitive development. The natural history shows a significant and rapid involvement of the CNS in severe cases. These are children that are on the downward curve in terms of what one would expect with respect to their ultimate cognitive outcomes. If one could get them earlier, it may be possible to preserve more of their cognitive outcome so that they don't have that decline.
- Ms. Wicklund asked to clarify who needs to be transplanted and who does not.
- Dr. Kemper said the experts feel comfortable in moving babies to transplantation if they have confirmed low enzyme activity level, elevated urine GAGs, a mutation associated with what they think would be severe disease, and if there is an early sign or symptom of severe MPS I.
- Dr. Kemper said a few individuals asked him questions during the break that he wanted to answer. The first question dealt with a bias in the spectrum. He said that in terms of the spectrum of the disorder, most cases will likely be the severe form. The other question was about the different screening modalities. There are systems that are based on tandem mass spec platforms and then there are the digital microfluidics "lab-on-a-chip." The tandem mass spec platforms and the digital microfluidics are all designed to test multiple LSDs.
- Dr. Homer asked, with respect to Dr. Prosser's presentation, what was the median age of diagnosis in the clinical identification of severe cases. Also, how much earlier would newborn screening lead to detection compared to clinical detection?
- Dr. Prosser replied that the median age from the study they used was 16.7 months of age for a clinical diagnosis. She added that, assuming the same number of cases would be identified within the first three years of life, for newborn screening those would all be identified within the first six months or so of life.
- Dr. Botkin said he had not thought about the prospect of newborn screening identifying children who would never become symptomatic. He asked if this would mean creating certain classes of children who carry the diagnosis when they were never destined to be symptomatic.
- Dr. Prosser said that is partly an artifact of the timeline for the decision modeling due to modeling at two- to three-year endpoints. The assumption is that there would be some children that would be identified within that period under newborn screening that would not be picked up until after the three-year period under clinical identification.
- Ms. Wicklund asked Mr. Ojodu a question about coverage for the genetic test and access to the treatment. She asked if those issues were discussed with the state programs.
- Mr. Ojodu said it was an interesting question. If the child is detected clinically rather than through newborn screening and has the severe form, the treatment will be a transplant. So in a sense, it is not creating a service need that was not there already.
- Dr. Botkin asked if the data showed whether the majority of programs could implement within one to three years.

- Mr. Ojodu said this was the case, with a nuance. They also need the authority to screen and allocation of funds to actually implement the screening.
- Dr. Boyle made a comment concerning CDC's quality assurance materials. She said that in the past couple of months, they have been able to develop specific MPS I materials that have been scientifically evaluated and tested both on the digital microfluidics and the tandem mass spec platforms and they perform well. They have had informal evaluations by some of their laboratories and are now moving towards having a round of formal evaluations of the materials.

XII. Committee Review of Mucopolysaccharidosis I

Jeff Botkin, M.D., M.P.H.
Committee Member
University of Utah
Salt Lake City, UT

Stephen McDonough, M.D.
Committee Member
Sanford Health Bismarck
Bismarck, ND

Dr. Botkin provided a summary of screening benefits, feasibility, and readiness. He then presented the recommendation. He explained that this disease presents some dimensions of uncertainty. As with many a rare conditions, there aren't many data points and this is also a condition with a fair amount of variability. Also, the disease has different treatment modalities that have evolved overtime. In addition, the outcomes examined are developmental which require periodic assessments over a period of time.

In terms of mortality outcomes, the data do not demonstrate a reduction in mortality from early intervention from NBS compared to treatment following clinical detection. With respect to outcomes for cognitive function for severe MPS I, the report states that overall, it is difficult to quantify the effect of early HSCT on cognitive outcomes in severe MPS I cases. Although earlier treatment may improve developmental outcomes, based on the results of one study by Poe *et al*., quantifying the magnitude of the benefit is difficult. Two recent analyses reported that transplantation at less than 8-16 months is associated with significantly better cognitive outcomes and lower risk of cognitive impairments among affected children.

For the attenuated version of MPS I there are reports that mild cognitive impairment is common among children with attenuated MPS I (Shapiro *et al.* 2012)—in particular for a subset of the condition associated with the L238Q missense mutation (Ahmed *et al.* 2014). Cognitive outcomes in attenuated MPS I merit further attention by researchers. He explained that no data are available regarding whether early detection through newborn screening will improve cognitive outcomes for children with attenuated MPS I.

Dr. Botkin also reviewed the risks associated with newborn screening for MPS I. He explained that the consensus is that the positive predictive values with current test technologies are low (<5 percent). There are also a relatively high number of false positive results requiring re-testing and confirmation. There is also the phenomenon of pseudo-deficiency. Dr. Botkin believes that this terminology will be damaging to some children and families and it might be helpful to come up with a better term. In terms of treatment, HSCT does carry a risk of morbidity and mortality. The risk associated with HSCT also will be present for children identified clinically. There is uncertainty about whether there might be inappropriate transplants in children who don't require a transplant (i.e. those having the attenuated form).

Dr. Botkin concluded that the benefits of early detection via newborn screening for children with severe MPS I are not definitive due to the lack of data from newborn screening systems. However, in terms of cognitive outcomes, the results of studies in other clinical contexts strongly suggest that significant benefits can be anticipated. Cognitive benefits of early intervention on children with attenuated MPS I remain to be determined, although the level of certainty about cognitive benefits for children with severe MPS I has been determined as "high."

Feasibility of newborn screening for MPS I was determined to be "High or Moderate." In terms of readiness, the survey of public health impact indicates that "Although most respondents reported that screening for MPS I could be implemented between 1 and 3 years after funding was made available (79 percent), it is critical to recognize that obtaining funding for the screening test was seen as a major challenge by 81 percent [of them]." As a result, most public health departments are unprepared for screening.

Dr. Botkin concluded his presentation by offering the following recommendations:

- DACHDNC recommends that newborn screening for MPS I be approved under matrix category A3
- Substantial work will need to be done in most states to fund, develop, and implement screening for MPS I
    - States should be encouraged to implement screening within 3-5 years of approval for inclusion of MPS I on the RUSP
    - Early adopters of newborn screening for MPS I are encouraged to obtain data in a rigorous fashion to promote continuous improvement of the evidence base regarding the risks and benefits of screening

Committee Discussion

- Dr. McDonough said he asked the Heartland Regional Collaborative their opinion about adding MPS I to the RUSP. Of the 24 responders, 75 percent were in favor of adding it to the RUSP.
- With respect to the matrix, Dr. Homer said he would feel more comfortable moving from an "A" category of certainty to a "B" category. He said he preferred the language in this category which states there is "moderate certainty that screening would have a significant benefit."
- Dr. Bocchini said he wasn't opposed to a change in category. He thought it would be helpful to determine what would be the implications of a change. For example, a categorization into a B4 would preclude including it on the RUSP.
- Dr. Bailey said the agreed the categorization should be a "B" because there isn't high certainty. Also, if there is a change in category, what would the implication be for other conditions that reviewed in the future?
- Dr. Kelm said she believed that the group had agreed not to designate certain categories as "being included the RUSP" but rather that the decision would be left up to the Committee. She said that in her opinion she leaned towards a "B" although she is hesitant whether a "B" should be recommended for screening.
- Ms. Wicklund said she also thought the correct category should be "B."
- Dr. Bailey said he wanted clarification as to whether a "B" category could be recommended and the Committee could still make the decision to include it in the RUSP.
- Dr. Bocchini said that was his understanding.
- Dr. Boyle said this is a perfect condition where a state pilot rollout would be appropriate to clarify all the unknowns. Maybe not even the certainty around the evidence, but just in terms of harms.
- Dr. Bocchini said that [a pilot] could be included in the recommendation to the Secretary.
- Dr. Matern said that if the group had applied the matrix to all of the conditions that came before this one they probably would never reach an "A" level. For example, for Galactosemia, which is a condition where a lot is still unknown, if one wanted to categorize as an "A" it would take a significant amount of time.
- Dr. Tarini said it would be inappropriate to use the disorders discussed prior to the formation of this committee to make current judgments. What stood prior to the committee should stay separate and not influence current decisions which are based on the structure that was created. She added that in addition to harms, multi-state pilots could add the ability to determine the effectiveness of treatment.

- Dr. Bocchini said that back when the matrix was proposed, in 2012, the general approach was that conditions categorized as A1 and A2 would recommended to the RUSP while conditions categorized as A3, A4, and B would have expedited review. And for C, D, and L resubmission would be required for consideration to the RUSP. However, this was proposed two and a half years ago.
- Dr. Botkin said he would feel more comfortable, at least in the context of this disease, if the group would consider perhaps a more nuanced approach. He said that if it is added to the RUSP it would be part of various state public health systems. Perhaps there is a way that a "B" categorization would imply that this should be implemented in a way in which more data would be collected.
- Dr. Bocchini said he agreed with Dr. Tarini's previous comment. SCID today is somewhere in the "A" category but at first it was not approved because they wanted to see more pilots.
- Dr. Chen said this committee has no control over evidence. It comes to consensus around how the evidence is graded, but has control over consistency, both with past decisions and moving forward on future decisions.
- Dr. McDonough said he did not know how long it would take to obtain enough data and how many kids would end up brain-damaged because they were not treated in time. A longer delay in adding MSP I and getting states to move forward would result in more kids suffering. He added that "Bs"—individually considered—could be added to the RUSP.
- Dr. Bocchini said the matrix was designed to provide a framework for the group. However, the Committee has latitude to make a decision that would incorporate suggestions such as the one made by Dr. McDonough.
- Dr. Parisi said that, in response to the comment about continuing to do research for this condition, there is a track record both with SCID and Pompe disease. If a condition is accepted for addition to the RUSP, the Newborn Screening Translational Research Network and other systems are in place to continue to study outcomes for the symptoms that are screened in the states willing to start the adoption.
- Dr. Bailey made the motion to recommend that the condition be categorized as a "B3" and added to the RUSP. He also urged to have extensive pilot studies to document efficacy and help reduce false positives.
- A participant seconded the motion.
- Dr. Boyle asked if there was a record of the language used for Pompe.
- Dr. Bocchini said the recommendation was made before the matrix was developed.
- Dr. Homer said that as the Chair of the Long-Term Follow-Up Committee and one of the authors of a paper focusing on establishing mechanisms to monitor and determine whether newborn screening achieves its purpose, monitoring should be in place for newborn screening anyway. He added that if a recommendation is made one should be monitoring to determine if it is achieving its promise.
- Dr. Kus agreed with Dr. Homer. When the Committee makes recommendations it also says they need to be studied, but all newborn screenings should have long-term follow-up to collect information. That should be part of the project.
- Dr. Thompson asked for clarification on the most recent recommendation, as to whether a "B" should be approved.
- Dr. Bailey said that was correct. He felt that the costs of not screening outweigh the costs of screening. He added that this shouldn't create a precedent and that everything classified as a "B" in the future moves forward.
- Dr. Boyle said that what makes this case different from others is the rarity of the condition and the ability to be able to obtain new data.
- Dr. Bocchini agreed. He said it would be helpful to add the specifics related to this condition to the letter going to the Secretary along with information as to why the decision was made. He also agreed it shouldn't be a precedent-setting decision.

MOTION AND VOTE

- Dr. Lu moved to have two votes instead of one. The first vote would decide on the categorization and the second on whether it should be added to the RUSP. Dr. Lu moved that the group categorize MPS I as a B3.
- Dr. Botkin seconded the motion.
- The committee unanimously agreed to categorize MSP I as a B3.
- The second vote was on moving forward to recommend that the Secretary add MPS I to the RUSP. The letter to the Secretary would include additional information providing a rationale as to why the group made the decision to move it forward.
- Dr. Botkin suggested speaking more directly to the Secretary by encouraging her to support additional data collection perhaps through large-scale pilot studies. These data could be used to help inform additional recommendations.
- Dr. Greene said that stating that it should be on the RUSP and at the same time saying that pilot studies are needed could be a red flag to someone reading the recommendation. He suggested not using the word "pilot studies" but rather saying that there needs to be more work on implementation and quality improvement, as some challenges still exist.
- Dr. Thompson asked how long it would take to obtain additional information to move MSP I from a B to an A. In other words, how long would it take to accumulate the needed information?
- A participant said it would be difficult to answer that, but some of the participants present thought it could take many years.
- Dr. Lorey asked if taking away the word "pilot" would decrease the probability of making funding available. This would be important because if the recommendation goes through, it is going to fall on the newborn screening programs and they will require funding. Perhaps there is a way to word the recommendation in a way that does not decrease the possibility for funding.
- Dr. Bailey suggested following up on all conditions to evaluate the long-term benefit once the screen has been implemented.
- Dr. Botkin asked if the B3 approval would send a message to the states about the timeframe in proceeding forward. If so, should the group include a provision that it would take some time to get it up and running?
- Dr. Bocchini agreed that such language could be added. He said that if states were unprepared, there would be a three- to five-year timeline for implementation.

VOTE

- The second vote was on moving forward to recommend that the Secretary add MPS I to the RUSP. The following individuals voted for the recommendation: Dr. Bailey, Dr. Bocchini, Dr. Botkin, Dr. Boyle, Dr. Homer, Dr. Lorey, Dr. Lu, Dr. Matern, Dr. McDonough, Dr. Parisi, and Ms. Williams. The following individuals voted against the recommendation: Dr. Kelm, Dr. Thompson, and Ms. Wicklund. The recommendation passed.

XIII. Subcommittee Reports

Representatives from each Subcommittee summarized their most recent meetings, which were held the previous day.

A. Education and Training Subcommittee Update

Beth Tarini, M.D., M.S., F.A.A.P
(for Cathy Wicklund, M.S., CGC)
Co-Chair
Organizational Representative
American Academy of Pediatrics
Ann Arbor, MI

Priority A: Identify heritable conditions that are not part of the RUSP and for which screening and treatment most likely would occur at a later point in child development.

- ***Write a white paper summarizing the work of this initiative and discuss the role of public health in childhood screening versus the role of practice guidelines.***

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

- ***Develop a glossary of terms to be incorporated into SACHDNC website.***

Dr. Tarini reviewed the Subcommittee's remaining priorities. Priority A was to identify heritable conditions that are not part of the RUSP and for which screening and treatment most likely would occur at a later point in child development. The assessment surrounding this priority has been completed and presented to the Committee as a whole. The next step is for Dr. Bailey to lead an effort to write a white paper summarizing the work of the initiatives and discussing the role of public health in child screening versus the role of practice guidelines. The first draft will be presented in May.

The next Subcommittee priority is to provide better guidance for advocacy groups and others regarding the nomination and review process (Priority C). The goal was to develop a public-friendly summary document of the SACHDNC Nominations process. Work has been carried in collaboration with Natasha Bonhomme of the Genetic Alliance. Ms. Bonhomme has presented an overview of the purpose of the proposed project including its target audience, key messages, key messages, and general suggested content. The information will be presented to the Committee in May for discussion. Once the content is finalized, the group will then determine the best way to package and present it to the public.

The Subcommittee is also working on the development of a glossary of terms to be added to the SACHDNC website. A revised glossary was presented to the Subcommittee for feedback. Members of the Subcommittee will work with staff from the Genetic Alliance to identify advocates to review the glossary and also provide feedback. Revisions will be made based on feedback provided and then presented during the May meeting.

B. Follow-Up and Treatment Subcommittee Update

Charlie Homer, M.D., M.P.H.
Chair
National Institute for Children's Health Quality
Boston, MA

Dr. Homer said the Subcommittee has two main areas of activity. The first is to identify barriers that impede access to high-quality counseling and treatment services required for effective long-term follow up and to propose policy solutions to address them. The second is to facilitate widespread implementation of the framework for assessing outcomes from newborn screening.

On the first area of activity, the Subcommittee needs to think about the unique and specific contribution the Committee can make compared to grantee organizations, such as the Catalyst Center that may be working in general in this area and perform on access to the quality of care.

In terms of improving access to quality LTFU, essential health benefits address the broad needs of children and youth with special health care needs and specifically those identified through newborn screening.

A potential policy action is to incorporate input from families, providers, and advocates in the upcoming mandated revision of the Essential Health Benefits (EHB). It is important to remember that coverage does not equal access. In other words, just having an insurance card does not necessarily mean that someone has access to necessary quality services. It would be helpful to examine if there are appropriate incentives and payment models. Such as, for example, adults who have dual Medicare and Medicaid eligibility due to the basis of their disability.

There could also be further exploration of provider incentives that could enhance access. There is also the broader question of whether there are mechanisms in place for prospective monitoring and what federal actions could facilitate widespread implementation of monitoring. In other words, could a monitoring system be implemented to assess the impact on this population? This could be a topic that is addressed by the full Committee and not necessarily contained within the Subcommittee. Next steps in this area would include to review focus and content with the full Committee, identify appropriate experts to refine approach and recommendations, and present background and recommendations to the full Committee.

C. Laboratory Procedures and Standards Subcommittee Update

Kellie Kelm, Ph.D.
Chair
Ex-Officio Committee Member
U.S. Food and Drug Administration
Silver Spring, MD

Dr. Kelm explained that the Subcommittee's three priorities are to: 1) Review new enabling/disrupting technologies; 2) Provide guidance for state NBS programs in making decisions about lab implementation, integration, follow-up, and quality assurance; and 3) Establish a process for regular review and revision of the Recommended Uniform Screening Panel.

Dr. Kelm proceeded to reviewed some of the Subcommittee's recent activities and discussions. The Subcommittee was provided with an update by Dr. Shapira of the CDC on a long-term project about the results and implications of single tests or routine second testing for primary CH and CAH. Also, the APHL and CDC hosted a meeting on MS/MS in Newborn screening (including SUAC). In addition, the Subcommittee discussed the next steps needed for the timeliness paper.

The long-term project examined single screen states and states that routinely perform second screening. The data was for 2005-2007 for California, Wisconsin, Alabama, Delaware, Maryland, Oregon, and Texas. The study showed that in two-screen states the characteristics predictive of cases detected on the first vs. the second screen for Primary Congenital Hypothyroidism was only race and ethnicity. It showed that, compared to White newborns, Black and Asian/Pacific Islander newborns were more likely to be detected on the second screen vs. the first screen. Based on mean serum TSH at time of screening, race/ethnicity differences are likely due to physiologic differences in biochemical presentation of Primary CH.

With respect to Primary Congenital Hypothyroidism detection rate, when comparing one- and two-screen states results showed that the rate was higher among White, female, or normal BW newborns, or those having been screened before 48 hours. Potential causes of detection rate differences could include screening methodologies, case misclassification, and the differential effects of genetic factors or environmental exposures between the populations in one-screen and two-screen states.

Dr. Kelm also provided data for a routine second testing study for CAH. The detection rate was statistically equivalent for first-screen cases for each type of CAH: salt-wasting, simple virilizing, and non-classical. Some of the questions arising from discussing this study were: What is the target screening for CAH? Is the purpose of screening for CAH actually salt wasters or additional cases beyond that?

Dr. Kelp said the APHL meeting hosted by CDC was titled "A National Conversation: Tandem Mass Spectrometry in Newborn Screening." The meeting was held in Atlanta on February 5-6. There were a total of 76 attendees and 40 states presented. There were interesting discussions about missed cases, SUAC conditions, and the experiences of using mass spec assays. The proceedings of the meeting will be available on the APHL website.

Committee Discussion

- Dr. Botkin said that in the future it would be helpful to put together a presentation on CAH and obtain feedback from the Committee.
- Dr. Boyle asked if Dr. Kelm could speak more about the CAH of congenital hypothyroidism as discussed by Dr. Shapira.
- Dr. Kelm said she believed Dr. Shapira was talking about the target for screening for CAH. Other issues that were discussed but not presented today included future topics and examining old methods that are known to cause issues. For example, the false positive rates for CH. This could be a potential area of discussion for the Subcommittee in the future.
- Dr. Tanksley said they have discussed looking at old technologies and the possibility of reevaluating some of them. With respect to CAH, one of the questions that arises is: We have case definitions now, but what are states screening for? In Texas, simple virilizing is considered to be classical CAH, but there is discussion about states screening for salt wasters. So what are we screening for and what are we supposed to be screening for? It may be interesting to perhaps survey states about what specifically they are looking for.
- Dr. Botkin agreed and said that a systematic review of individual states would be helpful. The review should be based on what the Subcommittee believes are the high priorities such as, for example, false positive rates or not using standard definitions.
- Dr. Boyle said that CDC is working on an MMWR on recommendations around the new case definitions.
- Dr. Greene said that such a discussion would be incredibly valuable, important, and useful, particularly relating to the issue of hypothyroidism—and to a large extent CAH. However, one should keep in mind that technology does not solve all problems, because the problem with CH is physiology.
- Dr. Kelm said there has been an evolution over the years where states were primarily using T4 as an initial screen. Now a lot of states are screening TSH as a primary screen. It would be interesting to look at that information.

XIV. Future Topics – Discussion

FDA Guidance on Lab Developed Tests

Dr. Greene said that SIMD would like to put forward for future discussion an issue related to lab developed test guidance, which will have profound implications for biochemical genetic testing, and therefore, for newborn screening follow up. The current definition as proposed by the FDA includes virtually all biochemical genetic tests. Even the largest laboratories currently do not feel they will be able to meet the bar that the FDA is proposing in the guidance. She said would be happy to provide the Committee with a copy of the document that the SIMD submitted to the FDA to demonstrate the problem. She respectfully requested that the Committee consider addressing this in a future meeting.

Dr. Kelm said she believed the comment period ended the first week of February but she could keep the Committee on the loop on further developments.

XV. Adjournment

Dr. Bocchini thanked all attendees for their participation in the meeting as well as Subcommittee members for their work. He memorialized the passing of Dr. Ken Poole, a friend of the newborn screening community and Chairman of Oz Systems, who died unexpectedly last month. Dr. Poole was a pioneer in developing technology that transformed health care. He worked tirelessly to integrate newborn screening into modern health information technology. Dr. Bocchini offered condolences to Dr. Poole's wife, his children, grandchildren, and extended family. Dr. Bocchini said he would be remembered not just for his tremendous contributions to newborn screening, but also for his generosity and warm spirit.

With no additional business to address, Dr. Bocchini adjourned the meeting at 2:49 p.m.