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

May 29-30, 2014 Meeting Summary

The Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (Committee) was convened at 9:30 a.m. EDT on Thursday, May 29, 2014. The meeting was adjourned at 1:53 p.m. EDT on Friday, May 30, 2014. 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: May 29, 2014

A. Welcome and Roll Call

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

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

Dr. Joseph Bocchini welcomed everyone to the May 2014 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 79 attendees and 87 individuals participating by webinar. Ms. Debi Sarkar, the Health Resources and Services Administration's (HRSA) Designated Federal Official (DFO), also greeted the participants and reviewed the rules concerning lobbying for Committee members.

Dr. Bocchini took the roll for the first day of the meeting. Voting members present were: Dr. Bocchini, Dr. Jeffrey Botkin, Dr. Colleen Boyle (CDC), Ms. Mia DeSoto (AHRQ); Dr. Kellie Kelm (FDA), Dr. Fred Lorey, Dr. Michael Lu (HRSA), Dr. Dietrich Matern, Dr. Stephen McDonough, Dr. Melissa Parisi (NIH) Ms. Catherine Wicklund, and Ms. Andrea Williams.
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
- March of Dimes (MoD): Dr. Siobhan Dolan
- National Society of Genetic Counselors (NSGC): Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carole Greene

Dr. Bocchini announced that Dr. Homer will replace Dr. Greene as the Chair of the Follow-Up and Treatment Subcommittee and that Ms. Wicklund will replace Dr. Bailey as the Chair of the Education and Training Subcommittee. Both changes will become effective in September.

Dr. Bocchini reported that the House Energy and Commerce Committee passed the Newborn Screening Saves Lives Reauthorization Act of 2014 with only modest changes to the version agreed to in February. The bill proposes the amendment of the Public Health Service Act to expand and improve programs at the U.S. Department of Health and Human Services (HHS) related to newborn screening (NBS) and reauthorizes the Committee.

B. **Approval of January 2014 Meeting Minutes**

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

Dr. Bocchini indicated that a copy of the minutes for the January 2014 Committee meeting was provided in the briefing book for this meeting. The Committee members present unanimously approved the minutes with the adoption of minor changes recommended by Dr. McDonough and Dr. Matern.

II. Public Health Impact

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

Dr. Bocchini reviewed the history of the Committee's efforts concerning the assessment of the public health system impact (PHSI) of NBS for specific conditions. The development of a decision matrix for NBS expansion, including an evaluation of the PHSI, is one of the key responsibilities of the Committee. In 2011, when HHS Secretary Kathleen Sebelius accepted the Committee's recommendation concerning the addition of critical congenital heart disease (CCHD), she reminded the Committee of its requirement to determine the public health impact through collaboration with HRSA. Based on the Secretary's comments, the Committee made changes to the matrix it uses to evaluate conditions it is considering for addition to the Recommended Uniform Screening Panel (RUSP) by adding feasibility and readiness and decided that the PHSI could influence the outcome of the evaluation net benefit.

When the Committee reviewed Pompe disease, it expanded the condition review to include a survey of NBS program directors to assess the feasibility of implementation of Pompe screening and their readiness to screen for Pompe. Based on all of the information and data presented by the Condition Review Workgroup and deliberations, the Committee recommended inclusion of Pompe disease on the RUSP. The Secretary referred the recommendation to the Interagency Coordinating Committee.

Feedback from Committee members and stakeholders in the wake of the Pompe recommendation indicated that the PHSI analysis needed to be strengthened before allowing deliberations on nominated conditions to continue. To support the strengthening of the PHSI analysis, an Expert Advisory Panel (EAP), consisting of Committee members, stakeholders, and other experts, met in April to develop a systematic approach for the evaluation of the necessary PHSI information. The EAP concluded that the decision matrix did not need refinement and that the key elements of PHSI have been identified. A summary of the meeting findings was included in the meeting briefing book; once it has been reviewed by the Committee and feedback has been incorporated, it will be used to guide current and future condition reviews.

Alex Kemper. M.D., M.P.H., M.S.
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Dr. Alex Kemper reported more extensively on the April EAP meeting. The meeting participants represented a broad spectrum of experts, including public health laboratory representatives, newborn screening experts, ethicists, experts in public health assessments in other domains, state public health department representatives, genetic counselors, condition-specific specialists, primary care providers, and patient and family advocates as well as representatives from five federal agencies.

The meeting focused on *what* should be considered as part of the analysis of public health impact, *who* should provide these elements, and *how* the information should be gathered given the time and resource limitations of the Condition Review Workgroup (CRW).

The decision matrix focuses on the net benefits of implementing NBS and the certainty of that benefit. Most of the required information comes from the systematic evidence review and the decision analytic modeling. By the end of the meeting, the EAP had identified several key considerations the elements the PHSI should assess: NBS program organization, the ability to screen, issues related to short-term follow-up, and issues related to long-term follow-up. The EAP also identified several cross-cutting considerations related to data systems/information exchange, direct costs of adding a condition to NBS, opportunity costs, and leadership and motivation.

With regard to the NBS program organization, Dr. Kemper stressed the importance of understanding the process for adding a new condition, the process for securing the additional funds to expand the screening program, the role of public health in providing access to diagnostic and treatment services after a positive screen (e.g., genetic counseling), and contextual factors (e.g., motivation for change). Issues such as incidental findings, secondary conditions, carriers, genotypes of uncertain significance, and late-onset diseases are among the diagnostic and treatment considerations.

The EAP identified many considerations in the area of ability to screen. These considerations fall generally into either laboratory (dried blood spot [DBS]) or point-of-care (POC) considerations. Laboratory issues relate to the availability of an appropriate screening test/platform, the time needed to analyze a specimen and report results, the availability of quality control materials and standards, whether the test is new or an extension of one that is already used, the need for new equipment and supplies, and the implications for laboratory staff (e.g., more staff and/or training). POC considerations are similar and include the ability to incorporate screening into the patient flow and the need for additional training, equipment/supplies, and staff. Other POC considerations include data system requirements and the role of the NBS program (varies by state). Dr. Kemper indicated that the PHSI assessment should produce a description of the necessary laboratory technology, an evaluation of the resources required to implement the screen, an understanding of the short-term follow-up needs, an assessment of the effect of the new screening on laboratory process, and an estimate of the effect on costs, including NBS fees.

Short-term follow-up requires a defined process/algorithm and sufficient available public health personnel. Other issues related to short-term follow-up include a data structure and the ability to exchange health information within each state as well as the availability, accessibility, and cost of diagnostic testing and specialist services (e.g., whether services can be provided in state or through a new or existing collaboration). With regard to long-term follow-up, the availability of data systems, for either monitoring or service deliver is a key issue. Other issues of concern include availability and accessibility of treatment, including out-of-state services; the need to follow up with patients with disease variants, who are carriers, or who are pre-symptomatic or have late-onset conditions; and implications for state public health systems and Title V programs.

The EAP also identified potential sources for information on the impact of proposed screenings including NBS program and laboratory directors, state public health commissioners, laboratory and clinical specialists, and primary care providers. The EAP also identified ways to collect information for general

data that is not condition specific (e.g., existing infrastructure) as well as for condition-specific data (e.g., published data and surveys).

PHSI assessments that take all of these factors into account could be used by the Committee to determine feasibility and readiness to adopt new screens, identify related gaps, develop a roadmap for implementation for conditions to be added to the RUSP, and develop recommendations for conditions that lack feasibility or readiness.

Dr. Kemper described a multi-criteria/multi-perspective decision analysis model developed by EVIDEM (Evidence and Value: Impact on DEcision Making) that applies different weights to aspects of the decision and how it might apply to the PHSI process. The weighting helps facilitate the discussion of a particular issue. He anticipated that once a nominated condition has gone through the evidence review process, a list of PHSI questions would be developed (lists would be tailored to each condition) and weighted based on importance to the decision-making process. This would help those collecting data focus on the most important issues. The Centers for Disease Control and Prevention (CDC) also have a process for eliciting preferences.

The EAP proposed a six-step process for the PHSI assessment that would begin after the initial evidence review presentation:

1. The CRW identifies a list of PHSI questions
2. The Committee makes recommendations about the PHSI questions for each condition.
3. The CRW develops a final list of PHSI questions and surveys the Committee about the weighting of the questions.
4. The CRW prepares a report outlining the final PHSI questions and the relative weights.
5. The CRW prepares the PHSI report based on all PHSI questions, focusing on those with higher weight.
6. Using the decision matrix, the Committee makes recommendations based on all of the information and data available from the Condition Review Workgroup.

This process would streamline the PHSI process and allow for timely voting. It provides a transparent way to develop recommendations concerning readiness and feasibility. Dr. Kemper believed that the Committee should adopt this process on a trial basis for the consideration of mucopolysaccharidosis 1 (MPS1).

Next steps identified by Dr. Kemper were pilot testing the development of PHSI questions and weighting with the EAP, incorporating Committee feedback and finalizing the EAP summary report, and applying the approach to the consideration of MPS1. The Committee's final vote will take place after the completion of the systematic evidence review, the modeling component, and the PHSI assessment.

Committee Discussion

- In response to a question about the use of kits versus home brew, Dr. Kemper asked for more feedback from the Committee as it relates to state law. A Committee member suggested that the Committee look into advising states about whether they should require the use of Food and Drug Administration (FDA)-approved kits.
- With regard to POC considerations, a Committee member pointed out that the validated screen is complex because it is based on a validated screen algorithm, which minimizes the issue. Dr. Kemper noted that the Committee will need to determine how much evidence about the test characteristics of the algorithm would be sufficient to make a recommendation.
- A participant recommended that the POC considerations include quality control standards.
- There was a discussion of central reporting of POC results. The EAP emphasized the role of the public health system in providing care versus simply providing ways to track individuals. Meaningful exchange of health information is critical.
- There will be a need for new training and new employees for POC screening at both the hospital and the state health department level.

- An organizational representative noted that there is an issue of scope (i.e., public health system versus public health). With regard to long-term follow-up, Dr. Kemper noted that states cannot begin to screen for a condition if they cannot provide the follow-up services. He indicated that it would be helpful to have the Committee's input on how to evaluate these issues in a constrained time frame.
- An organizational representative noted the importance of having access to treatment as a key issue under long-term follow-up; treatment is part of the definition of long-term care. This was not adequately captured in the slides.
- Every aspect of POC screening places a greater burden on the public health system than laboratory screening (e.g., doing assessments at individual hospitals versus large laboratories).
- An organizational representative highlighted the integration of the public health system and the health care delivery system (i.e., discreet, overlapping, and shared responsibilities); this should be addressed in the assessments.
- Feasibility was a major concern of one participant who pointed out that it will depend on the case definitions recommended by the Committee. If the definitions are not clear, the burdens and responsibilities become greater for the public health system. Dr. Kemper envisioned that the first round of evidence review and case definitions would be completed before the decision analytic modeling could take place. Following the modeling, there would be a need to educate respondents about the surveys that will be completed concerning feasibility and readiness (e.g., describe the test, the expected outcomes, treatments, etc.).
- Dr. Kus pointed out that the ASTHO has policy statements concerning NBS and primary care that could influence the assessments. These should be considered in addition to any discussions with individual public health commissioners. Other professional societies and associations also have similar statements. Dr. Kemper indicated that the EAP was concerned that these statements do not represent the reality in the individual states. Dr. Kus indicated that these groups are supposed to reflect the overall sense of what is happening. He indicated that there should be some blending of the individual and group points of view. Mr. Jelili Ojodu indicated that APHL would look into taking this approach in the future.
- A recommendation was made to ensure that the clinical specialists who have expertise in the nominated condition, are interested in proving follow-up care, and have experience with NBS be included in the assessments as they are best able to assess the public health impact. They have felt left out of the process in the past.
- An organization representative stressed the importance of obtaining feedback from patients and families since they are the ones the system is supposed to serve.
- Messaging related to the assessments is very important, especially for groups that may be feeling left out. Dr. Kemper indicated that this would be something that the Committee would need to address.
- By asking for input from clinical specialists and pediatricians, the group is acknowledging that it is difficult to separate the public health system and health care system.
- An organizational representative indicated that the costs to labs and their ability to do a screening (public health system) is a separate question from that concerning whether there is a treatment and whether there are specialists who can treat those with a particular condition (health care system). Clinicians may not understand the impacts on the public health system. Dr. Kemper indicated that the goal of the EAP was to identify all of the issues. Each new topic will require slightly different methods, and the Committee will need to provide guidance on its priorities. Also, The Committee needs a transparent method for the weighing the various factors.
- A participant stressed that primary care providers are affected by the PHSI (e.g., children need follow-up testing, which requires testing by a hospital or public health lab). The hand-offs and notifications are especially important for primary care providers.
- A Committee member noted that there will be issues or gaps identified through the PHSI that may need to be addressed by bodies other than the Committee. She hoped that the Committee could raise the visibility of these issues.
- An organizational representative noted that the funding for some of the specialists and other professionals (e.g., nutritionists) that are not paid through fee-for-service comes from public health departments and HRSA.

- A Committee member voiced concerns about the timing of the PHSI assessment with regard to the voting on a nominated condition.
- It is important that someone pay attention to the weighting of the various questions, specifically the condition-specific questions. Weighting might need to vary from condition to condition, which could result in a degree of inconsistency over time. Dr. Kemper indicated that there are methods to help prevent any drifting in the weighting. He anticipated the PHSI would be used more for informative purposes.
- Concerning the process of gathering data from states, Dr. Kemper indicated that the issue is one of granularity. The questions developed will be the key to obtaining the level of detail necessary to make a good assessment of states' preparedness to begin screening. The bigger issue is how much the Committee will be willing to push for screening if a large number of states are not ready.
- A Committee member suggested separating net benefit from the implementation aspect. She found the overall decision matrix, the Committee Decision Matrix for Nominated Conditions for the RUSP, used by the Committee to be complicated. Dr. Bocchini indicated that the Committee originally intended to complete the net benefit analysis before the PHSI assessment. It became clear that these two were heavily intertwined and that the findings of each might inform the other and the Committee elected to conduct the two in parallel.
- A participant noted that the process for evaluating PHSI could become a circular argument with the same people talking to each other. It is essential that the Committee continue to have a public process that allows for the corrections to the data/interpretation to be made easily.
- There was a discussion on the effect of the process on the way the Committee does its work, especially with regard to the weighting. If the initial screen shows that there is a low likelihood of net benefit, the process could be stopped; however, having the initial screen come back to the Committee for evaluation and response would inform the next part of the process. This would fit within the overall matrix.
- A participant asked whether there is a way for the Committee to make recommendations for conditions that have a high net benefit but might be difficult for states to implement immediately that allows a window for implementation that will enable states to better prepare for screening. If there is a delay in implementation, there needs to be an easily understood explanation for the public on why a condition is on the RUSP but a particular state is not screening for it. Another participant stated that potential timelines for full state participation for each of the categories (A1 through A3) were defined when the matrix was created. With a better decision process for the elements needed to categorize screenings, he hoped that the categorization would be more accurate. There could be at tension between clear net benefit and the timelines necessary to achieve full implementation.
- In response to a question about the cost/benefit analysis and how it fits into the process, Dr. Kemper indicated that it is relatively easy to estimate the cost of new equipment. It is harder to estimate the opportunity costs within state public health departments (i.e., how equipment, training, and personnel costs for a new screening will affect the state's ability to provide services for something else of value). He anticipated that this would have to be done in a more qualitative manner. This approach will be tested during the MPS1 review, which will show how well the process works and how confident the Committee can be about the resulting estimate. The cost benefit analysis can be helpful in terms of predicting the number of cases and outcomes (e.g., years added to life).
- With regard to primary care providers as stakeholders, a participant stressed that they can be a resource, especially with regard to the public health system. Primary care providers coordinate care, interact with insurance companies, and create and maintain data. Public health initiatives often place new responsibilities on primary care providers; as a result, they should have input on the screening decisions.
- A participant stressed the importance of giving states an opportunity to voice their concerns even if the Committee will recommend a condition over all objections (i.e., a condition rated A1 in the matrix). It is also essential that the Committee take these concerns into account, and, possibly, modify its recommendations in response. If the Committee does not show respect for the states' point of view, the states will not participate in the process. Dr. Kemper indicated that the reports could highlight the states' concerns.

- An organizational representative noted that safety and quality issues will be pushed into the hospitals as the number of hospital-based tests increase. These processes should be integrated into the assessment and the implementation evaluation.
- A Committee member inquired whether the PHSI assessment could be revisited during the overall review process, especially if all of the other factors assessed by the CRW are positive. Dr. Bocchini replied that it would be part of the process, especially when the Committee provides feedback to the nominating groups about ways to move the nomination from a lower rating to an A1 or A2.
- With regard to the cost benefit analysis and primary care providers, the Committee needs to consider the costs of false positives and the resulting follow-up. Although it is difficult to obtain, the Committee needs to pay attention to the performance of the assay (i.e. false positive rate and positive predictive value). It is also important to define the acceptable false positive rate (these are condition-specific) and to assess the costs for long-term follow-up and treatment in a system that does not support it.
- Dr. Greene also emphasized the importance of considering the cost of not screening and of resources saved by testing. Costs for testing comes from different sources (public health) than costs for treatment (health care system); spending a dollar for testing to save $10 for treatment still means that resources need to be available in order to spend that testing dollar.
- Dr. Kemper stressed there are tight timelines associated with each condition. As a result, the Committee will need to identify the highest priority elements.
- The matrix assumes that there is a fairly high degree of uniformity regarding the determinations made by states concerning preparedness; however, there is likely to be more variation. Dr. Botkin indicated that the Committee needs to determine whether it will take an across the board view of this or take into consideration the various degrees of preparedness.
- A Committee member recommended highlighting states that do a good job of providing efficient and effective NBS to better inform states that do not do as well about ways they could improve their programs. A representative from a regional collaborative indicated that there is much interest in this type of information. A Committee member pointed out that a state that is working diligently toward implementing screening could also serve as a model.
- A participant stressed that states care very much about the Committee's recommendations since every addition to the RUSP is, essentially, an unfunded federal mandate. This has an unequal impact on small states with less resources.
- Dr. Tarini, organizational representative, stressed that states place great weight on the RUSP. She also noted that states use various models for funding screening and it is not always possible to rely on the NBS fee for additional resources for new screenings.
- Third-party payer representation was absent from the EAP meeting. This was because of the short turnaround time from the time the resources for the meeting became available and the meeting itself. This group is interested and their input will be sought.

III. Public Comments

Mr. Dean Suhr, President, MLD Foundation: Mr. Suhr advocated for a roundtable discussion concerning the Committee's requirement of a viable therapy for conditions nominated for inclusion on the RUSP. Such a discussion would provide feedback to the Committee. He anticipated that the roundtable would not take place until January 2015; it would take place in conjunction with the Committee's meeting. He added that the Newborn Screening Saves Lives Reauthorization Act is stalled in the Health Subcommittee of the House Energy and Commerce Committee. Mr. Suhr encouraged the various advocacy groups to support this bill.

Ms. Sandra LaPrad, Consumer Task Force Member, Baby's First Test, Genetic Alliance: Ms. LaPrad shared her family's experience with a diagnosis of phenylketonuria (PKU)in their 8-day old daughter and their lack of contact with any other PKU families for five months. Having contact with other PKU families helped reassure her and her family that her daughter could have a typical life despite her diet restrictions. Because the condition is rare, there may be only one child in a county with PKU and the treating primary

care physician might not have any experience treating a metabolic disorder. As a result, metabolic and specialty centers play a large role in care and should share information with the primary care doctor. Parents play an important role in observing the effects of the disease in their children and learning about treatments. They can also play an important role in educating their local birthing hospitals, pre-natal educators, nurse-midwives, local clinics, nursing schools, and medical schools about NBS.

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. There have been positive changes since her son's death, including standardization of policies and procedures for turning around NBS results. She looked forward to the changes included in the Newborn Screening Saves Lives Reauthorization Act. Ms. Wilkerson also expressed her appreciation of the Committee's work on refining best practices and researching timeliness. She encouraged the Committee to ensure that this information is made available to those who can put it use rather than simply being posted on a website. She also expressed her appreciation of the Committee's plan to engage the Joint Commission on these issues and encouraged the members to expand their efforts to include laboratories.

Ms. Joyce Wulf, Parent Advocate, Council for Bile Acid Deficiency Diseases: Ms. Wulf encouraged the Committee to directly establish screening for inborn errors of bile acid metabolism in newborns. There are nine often fatal congenital enzyme defects involving bile acid synthesis affecting approximately 500 newborns yearly. There is a group of approximately 20,000 newborns that should be screened for bile acid deficiency diseases. Undiagnosed and untreated children suffer from fat-soluble vitamin deficiency, failure to thrive, delayed growth, perspiration, build-up of toxins, and early death. Treatment is highly effective if started soon after birth. There are almost 500 children between the ages of one and five waiting for liver transplants; as many as one-fifths of these children would not need a transplant if there were an NBS mandate for bile acid deficiency disorders. She encouraged the Committee to take action to advocate for this screening.

IV. Impact of Electronic Health Records Implementation on the Early Hearing Detection and Intervention Programs

Coleen Boyle, Ph.D., M.S.Hyg.
Committee Member
Centers for Disease Control and Prevention
Atlanta, GA

John Eichwald, M.A.
Branch Chief, Child Development and Disability
Division of Human Development and Disability
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
Atlanta, GA

Dr. Boyle briefly described a demonstration of electronic health information sharing for Early Hearing Detection and Intervention (EHDI) that she witnessed at a recent CDC public health conference. The demonstration showed how NBS information could be transferred from system to system from the time of birth, through the state health department to the primary care provider and, ultimately, to the audiologist in real time. This provides the ability to track events from both a public health and a clinical systems perspective and evaluate the timeliness of the process.

Mr. John Eichwald stressed the importance of having the right information at the right time for the right person. Electronic health records (EHRs) are one format that could help make this possible. He reviewed the history of the Committee's work with CDC on EHRs. The Health Information Technology for Economic and Clinical Health (HITECH) Act, which was part of the American Recovery and Reinvestment

Act of 2009, provides almost $20 billion for hospitals and providers to adopt EHRs. In 2008, the CDC and the developed and the Committee approved a use case that followed both bloodspot and newborn hearing screening. Interoperability specifications were developed by the Health Information Technology Standards Panel in 2008 about the same time that the nonprofit Integrating the Healthcare Enterprise's (IHE) Quality, Research and Public Health (QRPH) Subcommittee published a white paper on NBS. The QRPH also developed a technical framework for EHDI in June 2010.

In basic communication, information is sent and received. From a technology perspective, the process starts with a content provider and relies on semantic interoperability (i.e., speaking the same language). The Newborn Screening Coding and Terminology Guide, which was created by the National Institutes of Health (NIH), is constantly updated and includes the coding and semantics that should be transmitted for NBS conditions. The same information is contained in NIH's Value Set Authority Center, which provides even more coding details. CDC's Public Health Information Network Vocabulary Access and Distribution System is another repository for this information. All of the information in these resources is the same as that being provided for purposes of standardization for newborn hearing screening.

Once the standards were in place, the emphasis shifted to the technical aspects of moving information from one place to another. HL7 is the primary way to do this. The EHDI HL7 Implementation Guide addresses the transmission of information from secure screening equipment to an information system to preclude the need for manual entry. This guidance is currently being tested in systems. This allows the capture of data such as patient demographics, risk indicators for late-onset hearing loss, length of test, who conducted the screening, and confirmation that the data has been sent without errors. Mr. Eichwald described the information that could be contained in an HL7 message for patient identification, which can include up to four patient identifiers. The guide indicates which information is required or optional. At the same time, a very similar standard for capturing pulse oximetry and demographic information for CCHD was published.

The HL7 Public Health Functional Profile provides guidance to EHR vendors concerning what should be contained in an EHR for the purposes of public health. The first version addressed EDHI, vital records, and cancer surveillance and identified that elements that must, should, or could be included. In 2013, the Profile was revised to include laboratory, health statistics, occupational disease, birth defects, and adverse events in hospitals.

Another important HL7 effort is the Clinical Document Architecture (CDA), which allows clinical documents to exist in an unaltered state for a period of time, to be maintained by a trusted organization, to be authenticated, to establish a default context for contents, and to be sent in a format that is readable by humans. The architecture has been tested in pilot projects in Oregon and North Dakota. The Oregon projects transmitted data from the EHR over a continuity of care document to a health systems information exchange, which then created a hearing screen document in the CDA format for use by the public health department. The North Dakota project took a similar approach to create a CDA early hearing care plan document that was submitted to a pediatrician's office.

The third aspect of interoperability is process interoperability, which relates to the processes needed to implement and comply with content and messaging standards. Additional profiles have been developed in addition to the EDHI profile; these profiles address quality measures for execution for EDHI, early hearing care plan/hearing plan of care, and EDHI workflow document. The National Quality Forum (NQF) endorsed three CDC quality measures, one HRSA measure, and one National Committee for Quality Assurance measure related to EHDI. The Centers for Medicare & Medicaid Services (CMS) included one measure, NQF#1354 – Hearing Screening Prior to Hospital Discharge, into Stage 2 of the EHR meaningful use incentive programs; it is one of 29 clinical quality measures that hospital can use (they must choose 16) to qualify for the incentives. Information on all 29 measures can be found at the Agency for Healthcare Research and Quality's U.S. Health Information Knowledge database. Mr. Eichwald reported that 22 EHR systems and modules have been certified as fulfilling the clinical quality measures domain requirements.

CDC's work with IHE is currently focused on a technical framework supplement that describes a hearing plan of care. It will be available at http://www.ihe.net/QRPH_Public_Comments for public comment for 30

days beginning on or before June 7, 2014. The plan is written so that jurisdictions can decide what goes into a care plan and provide it to physicians, audiologists, and other specialists.

The Newborn Admission Notification System (NANI) enables data to be sent to multiple locations without the need to recreate it. The system automatically captures information from the birthing hospital's patient discharge and transfer information and sends a message to the public system to inform it that a baby has been born. While this has been used specifically for EHDI, it could be used for any of the public health programs (e.g., blood spots, immunizations, etc.). The NANI manager can be installed in the EHR, in the health information exchange, or in the public health system.

All of the various CDC efforts—NANI, messaging devices, care plans, and quality measures—have been demonstrated at the Healthcare Information and Management Systems Society showcases and an multiple public health conferences.

Bi-directional exchange is also important to CDC. This allows the message consumer to be a creator and the message creator to be a consumer. Information can be used multiple times, in both directions. Information can be added along the way. CDC has conducted some demonstrations of this, including a recent demonstration in Orlando, Fla., that showed how the system would handle a 35-week neonatal patient. The demonstration showed how a child could be followed from birth and how hearing screening results could be captured. Another demonstration conducted at the IHE Interoperability Showcase showed how information from an EHR could be used to create an electronic birth certificate and to send NBS data to the public health system. CDC worked with multiple vendors and the Minnesota and Utah departments of health on the demonstration.

CDC is working with the Office of the National Coordinator on multiple initiatives:

- Standards and Interoperability
  - Public Health Reporting Initiative: To establish standards for information capture for public health.
  - Structured Data Capture: To agree upon common data elements for public health programs.
- Standards and Interoperability Cross-Initiative Workgroups
  - Clinical Quality Framework: To harmonize clinical decision support and electronic clinical quality measurement.
  - Public Health Tiger Teams – To place data in a state public health system through a new initiative that combines structured data capture, the data access framework, and Health eDecisions.

The next generation profile is the EHDI workflow document, which focuses on bi-directional data exchange and identifies where and how information needs to flow.

Concerning privacy and security, Mr. Eichwald explained that the Health Insurance Portability and Accountability Act (HIPAA) includes a security rule as well as the better known privacy rule. The security rules and standards go beyond what is required for paper-based records. HITECH added additional standards on top of those included in HIPAA, including those related to accidental disclosures. CMS also has its own privacy and security requirements for certified EHRs related to access control, authentication of users, encryption, information integrity, automatic log-off, and audit logs. The IHE Information Technology Infrastructure group developed the Audit Trail and Node Authentication integration profile that helps vendors understand how to meet confidentiality requirements and the Basic Patient Privacy Consents to record and report patient consent.

Mr. Eichwald concluded his remarks by encouraging the participants to follow the decision of the Health Information Technology Committee and identified several other committees that have input on EHRs and information transfer.

Committee Discussion:

- An organizational representative inquired how close the technology is to allowing providers to be able to look up NBS results for a child born outside of the practice. Mr. Eichwald indicated that

this is a moving target. Requirements are still in flux. He anticipated that the overall system is getting closer to this capability. There are incentives to adopting certified EHRs. CDC is also looking into ways to reimburse physicians for reporting to registries (it is not clear whether EHDI would be considered a registry).

- Concerning NANI, Ms. Terese Finitzo stated that an HL7 message that provides basic demographic information on a baby comes out of the EHR. As there is no newborn message, admissions messages had to be constrained to only newborns to create NANI. She encouraged the participants to participate in IHE activities and advocate for NBS issues.
- The genetics portion of EHRs are not standardized and each group adapts them to their own needs. Ms. Finitzo indicated that the admissions messages are the simplest messages hospitals produce; however, it is difficult for them to communicate such messages outside of the hospital.
- A participant expressed concerns about the timing of NANI, specifically about whether a message might go out before the blood spot card was sent out. It is essential that it be linked to the blood spots. Mr. Eichwald indicated that NANI is part of the admission, discharge, and transfer process, which means that any time the record is changed the information will be captured by public health. The patient identifier, which is part of the NANI profile, will allow for matching of records.
- EHDI, which is fairly simple, could be used as a basis for other screenings.
- A participant stressed the importance of linking the birth certificate file with the NBS record and asked how to obtain more information on which hospitals are using it. Mr. Eichwald indicate that IHE would be one way to get more involved.

Ms. Sarkar thanked the participants for their input and closed the first day of the Committee meeting on behalf of Dr. Bocchini.

V. Committee Business: May 30, 2014

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. Bocchini, Dr. Botkin, Dr. Boyle (CDC), Dr. Iris Mabry-Hernandez (AHRQ), Dr. Matern, Dr. McDonough, Dr. Parisi (NIH), Ms. Scott (HRSA), Ms. Wicklund, and Ms. Williams. Ms. Sarkar served as the DFO.
Nonvoting organizational representatives participating in the webinar were:

- AAFP: Dr. Chen
- AAP: Dr. Tarini
- ACMG: Dr. Watson
- ACOG: Dr. Rose
- AMCHP: Dr. Badawi
- APHL: Dr. Tanksley
- DoD: Dr. Kanis
- GA: Ms. Bonhomme
- MoD: Dr. Dolan
- NSGC: Ms. Vockley
- SIMD: Dr. Greene

Seventy-nine of attendees in-person and sixty-six additional attendees participated by webinar.

VI. Conducting Research on Population-Based Screening

Jeffrey Botkin, M.D., Ph.D.
Committee Member
University of Utah
Salt Lake City, UT

Dr. Botkin stated that the Committee conducts it work using an evidence-based system. However, screening programs outside of a research context do not provide adequate information for the Committee's decision making process. Efforts need to be made to develop an infrastructure that can support the acquisition of data to inform thoughtful and informed decision making. Evidence needed for the various conditions on which the Committee works includes the natural history of the condition, the range of clinical manifestations, the association between phenotypes and genotypes, the efficacy of early detection and intervention strategies, the adverse effects of detection and treatment alternative, and the cost effectiveness of analyses.

Over time, the NBS system has become more uniform from state to state; however, there is no system for evaluating screening tests and systems. When considering a new condition for the RUSP, Dr. Botkin indicated that the "test article" is the complete NBS system from blood spot acquisition to long-term follow-up and treatment. All nominated conditions should be evaluated through population-based pilot studies. Barriers to this type of evaluation include the state-based nature of NBS programs (states lack the funding, mission, and/or population for this sort of research); the system's reliance on investigator-initiated research, which results in substantial variation in research designs; the size and expense of the studies; the associated ethical concerns, and the limited commercial incentives, which makes public funding a virtual must.

Cystic fibrosis (CF) is the only RUSP condition that was evaluated through a randomized, controlled trial (RCT); in most cases, decisions are based on a small number of cases and outcomes assessed through comparison with historical control. Dr. Botkin's presentation focused on the second phase in a proposed research agenda for NBS consisting of four parts:

- Phase I – Evaluate clinical response to treatment/prevention
- Phase II – Assess benefits of population screening
- Phase III – Conduct economic analysis of the screening protocol
- Phase IV – Conduct post-implementation monitoring and evaluation.

One way to conduct population screening is through RCTs of screening versus clinical diagnosis with outcome tracking. Ascertainment bias for children identified clinically compared to those identified through screening is a challenge as screening will detect more children on the milder end of the spectrum. Other challenges associated with these types of trials is their large size, the need for long follow-up periods, and ethical issues. Cohort analysis is another possible method for population screening. It allows for comparison of screening in one or more states versus clinical diagnosis in comparable states and could include retrospective analysis of stored specimens (with outcome tracking) to avoid ascertainment bias. This method, although less valuable than RCTs, has fewer ethical concerns. Historical controls are the third method of population screening; this approach can be appropriate when the natural history of a disease is well-characterized and the available data is robust.

Dr. Botkin reported on an NIH-funded study of spinal muscular atrophy (SMA) designed to evaluate the feasibility of NBS for this condition. Based on an existing clinical research study, this effort planned to add an SMA pilot screening to the NBS panels in Colorado and Utah over a three-year period. Colorado withdrew from participation and the Utah institutional review board (IRB) required a full consent model, which limited the project's ability to recruit. The study is moving forward after the principal investigator was able to recruit large hospitals in both states. This study highlights the way in which state support can affect studies. It also highlights the need to develop an infrastructure in the states to enable them to help researchers conduct this type of research.

Dr. Botkin proposed the development of a multi-state network to support population-based research at the Phase II through Phase IV levels. Such a network would include a set of states familiar with NBS research, state department of health IRBs that are familiar with NBS issues, competitively awarded federal funding to support the state infrastructure, and, possibly, an established organization, such as the Newborn Screening Translational Research Network (NBSTRN), to coordinate projects. Advantages of this system include the potential to generate higher-quality data than currently available; the ability to recruit large populations, which would speed up the process by negating the need for international studies or state clinical program data; the ability to compare different elements of the system; the ability to be responsive to the needs of groups such as the Committee; and an increase in the quality of proposals resulting from the use of a national peer review system for federal funding. Challenges or disadvantages associated with this approach include the difficulty of establishing uniform approaches to pilot study designs, the potential burdens to NBS programs, a smaller number of families serving as research subjects for the much larger population of families, the limited number of participating states resulting in researchers being remote from study sites, and the possibility of delaying implementation of screenings that are clearly beneficial.

Dr. Botkin concluded by noting that there is an active request for proposals (RFPs) by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) concerning screening for Pompe disease. The RFP includes resources for screening and follow-up, not for state-level infrastructure.

Committee Discussion:

- Clinical utility would be a major outcome of the population-based research. Other outcomes could include test performance, spectrum of disease, and resource strategies for supporting affected children and providing access to treatment.
- With regard to calling these studies pilot studies, Dr. Botkin indicated that the studies would need to attempt to mimic the ways in which NBS would be conducted in order to be called a pilot study.
- Dr. Boyle noted that there are several networks that might be helpful in supporting NBS efforts, including a nine-state infectious disease platform that involves academics and public health systems and allows for ongoing surveillance and monitoring as well as special studies. Dr. Botkin added that the birth defects registry is another model of state/federal collaboration.
- Cost would be the limiting factor with regard to the number of studies that could be conducted. Additionally, studies of uncommon conditions would require the participation of larger states. State would probably only be able to handle one NBS study at a time.
- In response to a request for more information concerning NICHD's work, Dr. Tiina Urv indicated that NICHD, HRSA, and CDC began developing a pool of states that would be ready to pilot test screenings as the need arose several years ago. These states had the ability to follow children through the NBS system. Last year, NICHD issued a pre-solicitation notice. The sequester delayed this effort by one year. The Pompe disease solicitation is currently in the process of completion and NICHD anticipates releasing a pre-solicitation notice that describes groupings. The solicitation was written in such a way that funds from other partners can be added.
- The Committee could have an effect on the requirements federal agencies put in their RFPs, especially with regard to defining pilot studies.
- A Committee member questioned the need to contract out a new study of Pompe disease screening when one state, Missouri, and one country, Taiwan, have already implemented the screening. He also questioned why the Secretary would approve Pompe for inclusion on the RUSP and, at the same time, order a new pilot study. There was a discussion of the need to have results from more than one state in order to increase the number of births in a study. This allows studies to wrap up in shorter timeframes because they can obtain more data more quickly. Another issue is whether children identified by screening are receiving follow-up and treatment.
- In addition to providing information used to make a decision about condition nominations, the population screening approach could also reveal weaknesses in systems.
- In response to a question about the timing of the population-based studies within the nomination and review process, Dr. Botkin anticipated that it would be an iterative process and the timing would be dependent on the Committee's needs and the states' ability to conduct research. Dr. Bocchini recommended that the Committee consider how it might use population-based research to support its work.

- Conducting population studies on conditions that are already on the RUSP helps to add to the evidence base and to support economic (cost/benefit) analyses of screening protocols and post-implementation monitoring and evaluation. If these studies are going to collect cost/benefit information, they need to be designed with that in mind.
- A question arose regarding how pilot studies relate to the ability of the government to fund such an infrastructure.
- The severe combined immunodeficiency (SCID) study was conducted through the NBSTRN infrastructure for capturing data. Studies need to be able to capture state information, private provider information, and information on the state contracting process. These pieces are coming into place. SIMD would be interested in helping to develop such a consortium.
- A participant cautioned against calling projects pilots if they were not conducted prior to adoption; studies conducted after Secretarial approval should not be called pilot studies. Dr. Botkin noted that the Committee is in a similar position to that addressed by the orphan drug act, which overlays post-market surveillance onto earlier research. States are concerned that the mechanism that allows them to participate in a pilot study also gets a condition on the list. Once a condition is on the list, it is difficult to take off. The goal is to develop ways to do investigational research and to identify how many patients are needed to facilitate decision making. Post-market studies address issues such as condition variability.
- A participant from Massachusetts stressed that states are willing to share data and information. Massachusetts was one of the states that supported the initial SCID pilot (screening and follow-up) and shared its data with other groups. It is important to first provide the screening service then build research on top of the service through well-designed protocols. States should innovate and determine how to approach each topic but need a variety of funding mechanisms to develop research projects. Dr. Botkin indicated that the system has benefitted from several states that have conducted quality research over the years; however, it is not enough to rely on a few states for research. A new system is needed to support more robust development of data.
- In response to a request for more information about the consent issues, Dr. Botkin noted that a wide range of consent models have been used. Using signed consent models can collapse population-based screening research. An opt-out approach has been judged to be an appropriate model for this type of research and informs parents without requiring them to sign a form.

VII. Pilot Study Data Needed for Condition Reviews

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

Dr. Bocchini indicated that the Committee has an entire process to obtain the information it needs to evaluate conditions for possible inclusion on the RUSP. The Committee requests that a population-based pilot study be performed as part of the nomination process. Studies have come from many sources and have varied in the amount of data presented. Based on the discussion about PHSI, it is apparent that the Committee is not applying the pilot study requirement in the same way for every condition. He hoped that the Committee would reconsider what should be included in the pilot study at the nomination level and develop criteria to determine whether the included study is sufficient or if more data is required.

Dr. Bocchini proposed forming a work group led by Dr. Botkin to address this issue. The work group would have three goals:

- Recognize and support current efforts of translational NBS research to establish a research network
- Identify other resources that could support pilot programs and evaluation

- Identify the information required by the Committee to move a nominated condition into the evidence review process

This approach would help those nominating conditions determine if they have the appropriate data. It would also help them identify potential resources for obtaining the required data.

VIII. Public Comments

Mr. Gary Pyner, Parent Advocate: Mr. Pyner advocated on behalf of infants with inborn errors of bile acid metabolism, specifically the approximately 20,000 children born each year with inborn errors of bile acid metabolism, many of whom are diagnosed with idiopathic neonatal cholestasis. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition is writing new guidelines for the evaluation of cholestatic jaundice in infants, which will address inborn errors of bile acid metabolism. Quick diagnosis will lead to better quality of life for these children and their families.

Dr. Amber Salzman, President, The Stop ALD Foundation: Dr. Salzman advocated for the acceleration of NBS for adrenoleukodystrophy (ALD). In January 2014, the Committee gave its support for a full evidence review of ALD. Since then, the Committee decided to re-examine the methodology used for the PHSI analysis portion of the condition review process. She was concerned that the decision concerning the PHSI analysis would delay the consideration of ALD by the Committee and expressed her hope that the ALD review be conducted in parallel with the PHSI analysis re-examination. ALD screening has already begun in New York and has identified eight affected infants and several family members. She requested a timeline for the ALD review activities.

Ms. Jana Monaco, Organic Acidemia Association: Ms. Monaco, who previously served as a member of the Committee, shared her experience with the diagnosis of her son and daughter with isovaleric acidemia and their very different outcomes based on their age at diagnosis. She stated that the matrix should not become a way to avoid dealing with hereditary conditions, especially those that receive a rating of A3 or A4. While the solutions might not be perfect, the children need treatments. She encouraged the Committee to continue to support state efforts to remove barriers to NBS, to make better use of the research efforts begun at the state level, and to continue to push for the addition of more conditions to the RUSP.

IX. New CPT Codes Established for Molecular Diagnostics and Their Impact on Genetic Testing Laboratories and Patient Access

Michael S. Watson, Ph.D., M.S., F.A.C.M.G.
Organizational Representative
American College of Medical Genetics
Bethesda, MD

Dr. Watson reviewed the history and current status of Current Procedural Terminology (CPT) codes for molecular testing. CPTs describe the clinical or laboratory services provided and the International Classification of Diseases code describes the clinical indication for the provided service.

Once a service has a CPT code, including those in molecular diagnostics, pricing must be determined. CMS either finds a similar service and crosswalks the price to the new service or conducts an interactive negotiation with local billing sites to establish a price (gap fill). Medicare tends to lead pricing efforts and other payers take their guidance from CMS concerning reimbursement rates. Genetic testing tends to be billed through Medicaid, instead of Medicare, because it is a pediatric service. As a result, Medicare has a limited history regarding the pricing of these services. Pricing for molecular diagnostics began with

Medicare using a gap fill method, but payers wanted more transparency, especially with regard to the gene being tested.

In cases where there is high complexity in the testing and interpretation of information, CMS will categorize a service as a physician service instead of a laboratory service. CMS determined that molecular testing would be placed on the clinical laboratory reimbursement schedule. Because of antitrust laws, it is difficult for ACMG and other professional organizations to help their laboratory members with price setting activities.

Currently, CMS coverage policy is determined primarily by local coverage determinations involving Medicare Administrative Contractors (MACs) and Medicaid programs acting independently, although statutes cover some of the pricing determination processes. Coverage decisions concerning screening are difficult as Medicare does not cover screenings unless specifically directed by statute. Genetic testing is particularly difficult because the same test can be used for screening, carrier screening, and diagnostic screening. Non-coverage determinations can be either statutory exclusions (there is no appeal or reconsideration) or exclusions pending determination of necessity and medical reasonableness (physicians can argue for the necessity of the test).

Molecular diagnostic codes are methodology based. To address the limited capacity of the coding system, two tiers of molecular diagnostics were established. Tier 1 includes the most common individual molecular tests (approximately 85 to 90 percent of molecular testing). The remaining 2,000 to 3,000 genes for which testing is conducted fall into Tier 2. Tier 2 is complexity-based and includes nine levels of complexity (each level includes multiple tests). If Tier 1 includes a code for the test being done, codes from Tier 2 should not be used. The goal is to align indications with diagnostic tests.

In 2012, the American Medical Association approved the first set of new CPT codes for molecular testing and recommended them to CMS for placement on the physician fee schedule. In 2013, the codes were placed on the CMS Clinical Laboratory Fee Schedule, and CMS used the gap fill method to set reimbursement rates. This effort overwhelmed the MACs. Dr. Watson explained the process used by the MACs to determine the costs to do a particular test and how that is then used to develop gap fill pricing. Because of the latitude allowed in setting prices, some of the MACs have determined certain tests to be research, for which they will not pay, and others have identified certain tests as carrier screening, which is not a covered service.

The decision to use the Physician Fee Schedule versus the Clinical Laboratory Fee Schedule has implications for the types of individuals who interpret test results. Many of those who interpret molecular tests do not bill within the physician fee schedule and cannot, therefore bill for the interpretation of tests. Dr. Watson cited the example of the MAC for California and North Carolina claiming a statutory exemption for payment for Fragile X because it maintained that it did not need to pay for screenings in the absence of signs or symptoms of illness or injury.

There are several ways in which MACs and carriers are not following the required process with regard to CPTs, including not publishing coverage policies on the Medicare Coverage Database page, avoiding the requirements concerning public notices and comments, employing the statutory exclusion extensively (this is moving toward case-by-case preapproval), and lack of Carrier Advisory Committee input. Dr. Watson indicated that a large percentage of the statutory exemptions were claimed on the basis of insufficient medical evidence for a test; other reasons for claiming the exemption included testing in asymptomatic individuals, tests having both screening and diagnostic uses, and the availability of alternate tests.

By the middle of 2013, many molecular tests had not yet been priced, which created problems for laboratories. One large reference laboratory billed Medicare for $1 million and were paid less than $60,000. Signature Genomics, a cytogenomic array testing company, recently closed because the reimbursement rates made its business model unsustainable. More laboratories are closing and others are discontinuing certain tests in response to the lack of pricing. A survey conducted by an ACMG contractor found that the gap fill rates proposed by the MACs for several common molecular tests was significantly below the actual cost (45 percent to 93 percent below). MACs are also classifying all Tier 2 tests as research tests and are

not reimbursing for them. They are also requiring physicians to directly request preauthorization, which places a significant burden on physicians. Another effect of the lack of pricing is the threat to training programs resulting from the closure of laboratories. Dr. Watson anticipated that access to testing will be the next major problem to arise. Further complicating matters are the ongoing appeals of statutory exemption decisions and the adoption of Medicare pricing by Medicaid and private payers.

Dr. Watson stated that the emphasis is currently on the definition of outcomes. In its meeting with ACMG, Medicare and Medicaid have indicated that there is no inherent utility to obtaining a diagnosis of a condition; CMS wants to see how a diagnosis or results of additional testing change the outcome for patients. This type of information is difficult to obtain for rare diseases because it is hard to achieve the required statistical power. Registry systems will need to be built to provide the needed data. Additionally, few genetic tests are approved by the FDA. Because insurers are giving preference to FDA-approved tests, there is no incentive for laboratories to develop new ones.

The Protecting Access to Medicare Act 2014 included regulations that define how billing codes are developed, define the coverage guideline and price setting process, and require clinical laboratories to report what they were paid for every test in order to set the payment standard based on the lowest payment. This will further exacerbate the difficulties faced by small laboratories and could deliver a lethal blow to local testing. A coalition of professional organizations with a laboratory orientation have been discussing these issues with carriers and payers. Most of the cytogenomic testing conducted in the United States is for intellectual disability, developmental disability, and autism spectrum disorders, which fall into the pediatric arena. This means that Medicaid, not Medicare, is the main payer. As a result, work is ongoing with the various state Medicaid programs to secure coverage for these tests. So far, Wisconsin and Oklahoma have made changes to their programs, even though the emphasis is on preauthorization.

The Committee should look into whether access to testing that is considered medically necessary is becoming a problem and whether there is value in the diagnosis of rare diseases (diagnostic odyssey costs can be extremely expensive). It should also look into ways that the Orphan Drug Act could be used as a model for rare disease testing. Finally, the Committee should investigate whether the closing of laboratories and the shift toward older technologies with less clinical sensitivity is resulting in problems with access to testing.

Committee Discussion:

- In response to a comment about the way the codes and price lists are being affected by the shift from fee-for-service to capitated and Accountable Care Organization models, Dr. Watson indicated that the situation is chaotic. There is a wide range of payers and payment models. Genetics have been swept up into this and have had to do a lot of work to educate the MACs and payers. A Committee member noted the role of the evidence-based movement; lack of evidence fuels the arguments about clinical utility. Now the emphasis is on value-based pricing and higher efficiency. Moving forward, it is important to develop arguments for the value of avoiding diagnostic odyssey and for using developmental delay panels.
- Dr. Watson noted that in some cases, the diagnostic and therapy aspects have been linked (a positive result results in use of a particular therapy). While the system is in flux, thought needs to be given to how to best manage the changes.
- A participant expressed concern about access to reproductive genetics. Dr. Watson indicated that there are some issues, especially with regard to new tests such as free fetal DNA. Most of these tests are done in private laboratories, which makes for a very different situation for clinical trials.
- One participant reported receiving a large number of denials for carrier screening. Dr. Watson noted that there is no recognition of the genetic family of affected individuals; this will be problematic with regard to establishing risks within a family.
- There was a concern that the current payment climate will stifle research, innovation, and new testing. New CPT codes essentially mean that the reimbursement is zero until the appeal process can be completed. Developing new tests is costly. CMS reimbursement rates are often lower than costs, and the rates offered by the Blues and the Aetnas are lower than the CMS rates. Laboratories try to reduce costs as much as possible, but it is not possible to reduce them enough.

X. Subcommittee Reports

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

A. Subcommittee on Laboratory Standards and Procedures

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

Dr. Tanksley reviewed the Laboratory Standards and Procedures Subcommittee's three main priorities:

- Priority A: Review new enabling/disruptive technologies. Dr. Matern will report on the succinylacetone (SUAC) implementation survey.
- Priority B: Provide guidance for state NBS programs about decision making concerning implementation, integration, follow up, and quality assurance. The report will include an update on the SCID slide deck and on the timeliness of specimen transport and NBS.
- Priority C: Establish processes for regular review and revision of the RUSP. There are no updates related to this priority.

Priority B: SCID Slide Deck and Timeliness Report
Dr. Amy Brower presented an update on the SCID slide deck. The slide deck is meant to serve as a template for conditions newly added to the RUSP. The content was developed by a work group made up of Subcommittee members and is targeted toward administrators and laboratory personnel. The goal of this effort is provide information that state laboratories would need to support discussions with stakeholders (e.g., legislatures, hospitals, etc.) concerning implementing conditions that have been added to the RUSP. The slides would be available to the states to use at stakeholder presentations; users could choose which slides to use. Topics covered include background information on SCID, the SCID NBS pilot, efforts of federal partners regarding state implementations, tools and resources (e.g., SCID monthly conference calls), and publications. The Subcommittee discussed adding references for the work done under the initial CDC grants and for the algorithms for screening. The Subcommittee will provide feedback to the work group.

The Subcommittee also discussed the timeliness of NBS. A public comment made during the September 2013 Committee meeting raised the issue of timely NBS. This led the Committee to review the current policies and practices related to the timeliness of NBS in the United States. Based on a survey conducted by APHL and a literature review, the Committee made four recommendations related to NBS concerning to the timelines for collection and transportation of samples and for reporting results. The Laboratory Standards and Procedures Subcommittee is responsible for outlining the NBS system in the United States and the processes involved, identifying gaps and barriers within the NBS system, identifying best practices for achieving the timelines outlined in the recommendations, developing a list of critical conditions that require urgent follow-up, reviewing the recommendations in light of new technologies, and suggesting revisions, if needed.

Since its last meeting, the Subcommittee established a work group to study timeliness of NBS, which meets every other week, submitted an abstract to the APHL's Newborn Screening and Genetic Testing Symposium in an effort to share the outcomes of the group's work, worked with SIMD to assess metabolic disorders with the most urgent NBS timelines, and worked with APHL to develop a survey and webinars to collect information on gaps, barriers, and best practices related to timeliness of NBS from as many stakeholders as possible. Next steps in this process include conducting the survey (the webinars will provide an opportunity to clarify any questions concerning the survey questions), identifying additional stakeholders that should receive the survey (e.g., genetic counselors, hospitals), and identifying ways to

collect information on the non-metabolic conditions that require urgent follow-up. Dr. Tanksley anticipated completing the draft report on NBS timeliness prior to the Committee's September 2014 meeting.

Priority A: SUAC Implementation Study

Dietrich Matern, M.D., Ph.D.
Committee Member
Mayo Clinic.
Rochester, MN

Dr. Matern stated that an elevated level of tyrosine is not a specific marker for tryrosinemia type 1 (TYR1). SUAC is a better marker for the condition as it is specific to TYR1. Currently, 50 of 51 state NBS programs screen for TYR1, but only 38 NBS programs screen using SUAC. Tandem mass spectrometry (MS/MS) is used in the United States to test for SUAC. The tests are laboratory-developed tests that are fully validated by the laboratories but have not been approved by the FDA. There is also a new FDA-approved non-derivatized MS/MS kit available; however, it has poor extraction efficiency for SUAC. Based on the screening method used, some states will miss cases or have a high rate of false positives if their tyrosine cut-offs are not set at an appropriate level. Other states require the use of FDA-approved kits. There is a perception that these kits do not work well (this perception is not substantiated by data produced by a Region 4 Collaborative study).

The Subcommittee believes that TYR1 should remain on the NBS panel as early treatment can make a major difference in the health of those affected. SUAC is the best marker for TYR1 screening currently available and produces few false positives and no false negatives. CDC provides quality assurance, quality control, and efficiency testing for TRY1, including SUAC.

Next steps for this effort include Committee review of a draft article concerning the study findings, obtaining input from the Committee concerning future actions/recommendation resulting from the findings, and, possibly, reaching out to the programs that do not use SUAC to educate them about its benefits.

Committee Discussion:

- With regard to the SUAC education efforts, CDC has ongoing opportunities to educate state NBS programs. Since there are still 13 programs that do not use SUAC, additional efforts need to be made. It is not clear whether the issue is with 13 programs or with a smaller number of laboratories that serve multiple states.
- In response to a question about barriers to adoption of SUAC screening, Dr. Victor de Jesus, from CDC and a co-author, indicated that barriers included lack of funding and lack of space for new instrumentation. CDC has been working with several of these programs, but the agency does not have influence over state-level decisions. There is general agreement that SUAC is the preferred marker.
- A participant explained that a MS/MS system is very expensive ($400,000 used) and that the SUAC assay is a different assay from that used for tyrosine.
- Some laboratories that tested the new kits, found problems with it, and decided against making the transition to SUAC screening. The CDC data indicates that the kit works well. There needs to be more efforts made to ensure that the laboratories have this information.
- Concerning the possible use of performance measures to standardize the handling of samples as a way to address timeliness, Dr. Tanksley indicated that the Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) has proposed quality indicators. APHL attempted to collect this type of data, but because states did not provide it in a uniform manner, it could not be aggregated and compared. It might not be possible to obtain enough of this type of data in the short time available to establish a baseline. Lack of courier access, particularly in Alaska and Hawaii, is a major barrier to timeliness. Work processes can also be barriers, but are easier to change. Moving forward, collecting the data on the time points in the process could be a best practice and would support the development of performance measures.

- NewSTEPs has developed quality indicators that have been vetted by the NBS community. A statement from the Committee might help encourage states to enter this data into the system.

Following the discussion, Dr. Tanksley indicated that the Subcommittee members favored pursuing the educational effort over making a formal recommendation to the Secretary. The APHL's Quality Assurance/Quality Control Subcommittee could possibly take on this work and incorporate it into one of its webinars, which are broadcast to all states. NewSTEPs could also work this into its site evaluation tools. Another alternative could be to incorporate SUAC TYR1 screening into MS/MS courses.

Dr. Botkin indicated that some of the resistance might relate to kits fees. He indicated that the Committee should obtain a better understanding of the effect of these fees before it makes a decision on a course of action. Dr. Matern did not believe that there was much expense in adding SUAC to its screens based on the experience of his laboratory.

Dr. Bocchini suggested that the Committee accept the report on SUAC from the Subcommittee and that the Subcommittee move forward with the educational activities. He also suggested that the Committee schedule a vote for September about sending a formal recommendation concerning SUAC to the Secretary. The Committee reached consensus and accepted the suggestions.

B. Subcommittee on Follow-Up and Treatment

Carol Greene, M.D.
Subcommittee Chair
Organizational Representative
Society for Inherited Metabolic Disorders
Baltimore, MD

Dr. Bocchini corrected his statement made on the first day of the meeting and clarified that Dr. Greene will transition out of the role of Chair immediately following this meeting, not in September.

Dr. Greene reviewed the Subcommittee's charge, which calls for it to:

- Identify barriers to post-screening implementation and short- and long-term follow-up, including treatment, relevant to NBS results;
- Develop recommendations for overcoming identified barriers to improve implementation and short- and long-term follow-up, including treatment, relevant to NBS results; and
- Offer guidance on the responsibility for post-screening implementation and short- and long-term follow-up, including treatment, relevant to NBS.

The Subcommittee has organized its work into three priority areas:

- Priority A: Screening program implementation – The Subcommittee recently completed its work on lessons learned from EDHI that could be applied to CCHD. The Subcommittee is making the final changes identified by the Committee and looking for a place to publish the article.
- Priority B: Closing gaps in systems of care – The Subcommittee has identified possible tasks under this area for Committee input.
- Priority C: Real world impacts and outcomes – The Subcommittee has been exploring whether the promise of NBS is being realized by looking at ways to document outcomes and relate them to variables in the NBS system. This effort includes the development of a framework for assessing the outcomes related to screened conditions.

Priority C: A Framework for Assessing Outcomes from NBS: Do We Know If We Are Achieving the Promise of NBS?
Dr. Greene reported that the Subcommittee has been holding monthly conference calls in support of this effort, which is titled "*A Framework for Assessing Outcomes for Newborn Screening: Do We Know if We Are Achieving the Promise of Newborn Screening?*" The Subcommittee established a writing group, which

has been meeting by teleconference. The focus of this effort is to develop key questions and understand data sources and gaps in data in order to determine whether outcomes are improving as a result of NBS. The Committee tasked the Subcommittee with developing a framework for making these assessments. The framework and a preliminary version of the paper were shared with the Committee during the January 2014 meeting. Based on the Committee's approval of those initial documents, the Subcommittee added PKU as an additional exemplar condition (sickle cell disease was the initial example). Use of the example conditions helped the Subcommittee test the effectiveness of the framework in including essential data types, mapping data sources, understanding outcomes, and identifying data gaps.

The draft of the manuscript (included in the revised briefing book) describes the basic framework. After much discussion, it became clear that including the frameworks for both sickle cell and PKU would show how the framework could be used for any condition, not just a specific disorder. Dr. Greene indicated that the text provided to Committee members is essentially complete, but the table headers need to be changed. The manuscript also includes a new element, the Driver Diagram. This diagram is a model that is currently used for quality improvement purposes to identify the elements in the system that drive outcomes. Once the headings in the table are changed to match those in the Driver Diagram, work on this effort will be complete.

Changes recommended by the Subcommittee were:

- Add an explanation of the reason both sickle cell disease and PKU were used as examples
- Remove references to secondary drivers and add a definition for primary drivers
- Add references to the papers from which the primary drivers were identified
- Rewrite part of the summary to provide a better explanation of the content of the paper

Potential Projects/Next Steps

The Subcommittee discussed several possible options for new projects. One proposed project would be to apply the framework to several conditions to see how well it works for quality assurance purposes. A second possible project would focus on the public health/clinical interface, and the third would look at ways to build program improvement capacity. Because it is not possible to improve a program if it is not well understood, the Subcommittee was very interested in exploring the public health/clinical interface. This work would relate to Category B and would allow the Subcommittee to use some of the work it has already completed. This project could describe the current public health/clinical interface as it relates to follow-up by profiling the way the interface works and how the public health and the health care systems provide care in several states. Dr. Greene anticipated that the Subcommittee would use its monthly conference calls to more clearly define this project and present the project proposal to the Committee during the next meeting.

Committee Discussion:

- In response to a participant question about whether the proposed project would focus on one or multiple public health/clinical interfaces, Dr. Greene indicated that the Subcommittee was interested in the whole system and the complex interactions within it. The project would be more descriptive and would focus on access issues and roles and responsibilities.
- A participant suggested that the Subcommittee consider looking into loss of access to specialty care, which is not included in the essential benefit packages, and into the reduction in readmission rates incentivized under the Patient Protection and Affordable Care Act and the resulting loss of access for patients with heritable disorders (other than CF, which has an exclusion). The latter is particularly important for patients with sickle cell.
- Dr. Greene indicated that the Subcommittee would also reach out to those individuals in the regional genetic collaboratives who are working on these types of issues. Sickle cell is one of the conditions on which they are working. Some of these projects are being conducted in a coordinated fashion.
- Two of the goals of the study would be to look into access and to determine whether there is enough data available to be able to judge whether people have access to and receive good care.

Dr. Bocchini indicated that since there were no comments from the Committee members concerning the draft manuscript, *A Framework for Assessing Outcomes for Newborn Screening: Do We Know if We Are Achieving the Promise of Newborn Screening?*, the Committee could accept the document for publication pending final review of the version incorporating the changes identified by Dr. Greene. The Committee reached consensus and agreed to approve the manuscript for publication.

Dr. Bocchini also indicated that the Committee seemed to generally approve of the proposed project on the public health/clinical interface and encouraged the Subcommittee to continue to refine its plan.

C. Subcommittee on Education and Training

Beth Tarini, M.D., M.S., F.A.A.P
Subcommittee Co-Chair
Organizational Representative
American Academy of Pediatrics
Ann Arbor, MI

Dr. Tarini briefly reviewed each of the Subcommittee's three priority areas.

Priority A: Track, provide input on, and facilitate integration of national education and training initiatives
The Subcommittee is finishing up a project that identified three heritable conditions—Fragile X syndrome, Long QT syndrome, and Wilson's disease—that are not on the RUSP and for which screening and treatment would likely take place at a later point in child development. The Subcommittee identified major education and training needs for each condition. The group used six questions to guide its assessment:

- What is the typical pattern of identification of children with this condition?
- What problems exist with the current pattern of identification?
- Would population screening outside of the newborn period be at all feasible or desirable?
- In the absence of population screening, what is the best-case screening for early identification?
- What effort would be required to substantially change the current paradigm?
- Which stakeholders would need to be engaged in discussions about altering current practice?

Dr. Tarini summarized the findings for each of the three conditions for each of the six questions. She emphasized that the purpose of this effort was not to identify conditions that should be nominated for inclusion on the RUSP; instead, it was to develop a paradigm for discussion of screenings outside of the newborn period.

Priority B: Promote NBS awareness among the public and professionals
The Subcommittee provided input and support to APHL and CDC concerning the celebrations of the 50th anniversary of NBS.

Priority C: Provide better guidance for advocacy groups and other regarding the nomination and review process
Previous efforts in this area included efforts to revise the Committee's website to make it more user-friendly for the lay public and to develop a public-friendly document describing the Committee process. The latter effort is still in progress.

Dr. Jeremy Penn, a Subcommittee member, is helping the Subcommittee develop a glossary of terms. Dr. Tarini indicated that the Subcommittee would like to incorporate the glossary into the Committee website. If it is not possible to include a full glossary, the Subcommittee hopes to be able to define individuals terms as they appear on the website. The Subcommittee has developed a draft glossary, which is currently under review; is seeking feedback on the readability of the document; will revise the glossary to match the appropriate reading level; and will work on implementation logistics (e.g., identify a home for the glossary).

Next Steps
Next steps for the Subcommittee consist of completing the objectives under each priority and working with the Committee to identify future projects.

Committee Discussion:

- Concerning the final product for Priority A, Dr. Tarini indicated that the slides that were developed to summarize the findings were the final product. Dr. Bocchini indicated that the Committee was interested in identifying barriers that exist for all stakeholders and that might be different from those associated with NBS. Dr. Tarini indicated that the results could be reframed in a short summary.
- A Committee member suggested that it might be helpful to have input from a stakeholder from the payer side, such as CMS, to help explain payment-related barriers.
- A Subcommittee member noted that one unique question concerning screening outside of the newborn period is that of mandatory screening.
- The project did not map directly to the nomination criteria or framework. The Subcommittee did not address the specificity and sensitivity of each test for these conditions or whether they would support population-based screening. The Subcommittee took this course so that there was could be no impression that any one condition was gaining an advantage with regard to future consideration for the RUSP. Also, the scope of a project that delves deeply into each of the RUSP criteria is beyond the scope of the Subcommittee. The project was meant to be a very high-level review.
- The original goal of the effort was to develop a sense of the issues the Committee might face if it considered a condition for which screening would take place outside of the newborn period and to provide a high-level overview of the barriers associated with the various stakeholder groups. Dr. Tarini indicated that the Subcommittee could collect opinions for stakeholders and review the literature for identified barriers.
- A participant suggested including prenatal screening in the effort, especially with regard to how it could be connected in the pediatric record. Dr. Tarini indicated that the Subcommittee had discussed this issue and had concerns that it was beyond the scope of the Subcommittee. The issue is bringing tests into the public health realm rather than keeping them in the clinical setting and how to address the challenges of doing so.

XI. Future Topics

Journal Partnership
A participant suggested looking into ways to more widely disseminate to the public the PHSI work done by the Committee. Dr. Bocchini indicated that the Committee would develop a publication that could be posted on the Committee's website. The group could also investigate additional ways of distributing the document.

Dr. Bocchini reminded the Committee members that there had been some discussion of developing a formal relationship with a scientific journal under which the journal would publish all of the Committee's reports. In the past, many of the articles and reports have been published in a single journal. Two participants described similar relationships of which they were aware and highlighted the benefits of these relationships. Another participant stressed the need to be able to simultaneously publish information on the Committee website.

Dr. Bocchini asked the Committee members to recommend possible journals with which the Committee could partner.

Removing Conditions from the RUSP
A participant suggested looking into the process that would be used to remove conditions from the RUSP. The question is whether this would fit within the Committee's portfolio.

XII. Adjournment

Dr. Bocchini thanked all of the attendees for their participation in the meeting and for all of the work done between meetings.

With no additional business to address, Dr. Bocchini adjourned the meeting at 1:53 p.m.