Advisory Committee on Heritable Disorders in Newborns and Children

August 3-4, 2017

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) meeting was convened on Thursday, August 3, 2017 and adjourned on Friday, August 4, 2017. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

[Note: The information in bracketed text indicates clarification added by Committee members and HRSA staff upon review of the minutes. This information may not have been explicitly stated during the meeting.]

Committee Members

Mei Baker, MD
Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health
Co-Director, Newborn Screening Laboratory
Wisconsin State Laboratory of Hygiene

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

Jeffrey P. Brosco, MD, PhD
Professor of Clinical Pediatrics
University of Miami School of Medicine
Department of Pediatrics
Deputy Secretary, Children's Medical Services
Florida State Department of Health

Fred Lorey, Ph.D.
Genetic Disease Screening Program
California Department of Public Health (Emeritus)
International Society for Neonatal Screening
North American Council Representative

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

Annamarie Saarinen
Co-founder, CEO
Newborn Foundation

Beth Tarini, MD, MS, FAAP
Associate Professor and Division Director
General Pediatrics & Adolescent Medicine
University of Iowa Hospitals & Clinics

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

Ex-Officio Members –

Agency for Healthcare Research & Quality
Kamila B. Mistry, PhD, MPH
Senior Advisor
Child Health and Quality Improvement

Centers for Disease Control & Prevention
Carla Cuthbert, Ph.D.
Chief, Newborn Screening and Molecular Biology Branch
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Food and Drug Administration
Kellie B. Kelm, PhD
Chief, Cardio-Renal Diagnostic Devices Branch,
Division of Chemistry and Toxicology Devices,
Office of In Vitro Diagnostic Devices Evaluation & Safety

Health Resources & Services Administration
Michael Lu, MD, MPH
Associate Administrator
Maternal and Child Health Bureau

National Institutes of Health
Diana W. Bianchi, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Acting Designated Federal Official –

Catharine Riley, PhD, MPH
Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau

Organizational Representatives –

American Academy of Family Physicians
Robert Ostrander, M.D.
Valley View Family Practice

American Academy of Pediatrics
Pending Assignment

American College of Medical Genetics
Michael S. Watson, PhD, FACMG
Executive Director

American College of Obstetricians & Gynecologists
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March of Dimes
Siobhan Dolan, MD, MPH
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Albert Einstein College of Medicine and Montefiore Medical Center

National Society of Genetic Counselors
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Children's Hospital of Pittsburgh

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

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I. Administrative Business — August 3 -4, 2017

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

A. Welcome and Roll Call

Dr. Bocchini welcomed participants to the tenth meeting of the Advisory Committee on Heritable Disorders in Newborns and Children (Committee). He announced that Dr. Robert Saul, who had been the organizational representative for the American Academy of Pediatrics (AAP), stepped down from the Committee but the Academy has not selected a replacement and, therefore, would not be represented at the meeting. He thanked Dr. Saul for his work on the Committee and on the Education and Training Workgroup. He also announced that three new members of the Committee have not completed their clearance process yet and, in their absence, the Committee asked Dr. Fred Lorey who retired from the Committee during the May meeting, to extend his term for up to six months; Dr. Lorey agreed to do so.

Dr. Bocchini then took the roll call. The Committee members in attendance:

- Dr. Mei Baker
- Dr. Joseph Bocchini
- Dr. Jeffry Brosco*
- Dr. Carla Cuthbert* (ex-officio member, Centers for Disease Control and Prevention—CDC)
- Dr. Fred Lorey*
- Dr. Kelly Kelm (ex-officio member, Food and Drug Administration—FDA)
- Dr. Michael Lu** (ex-officio member, Health Resources and Services Administration—HRSA)
- Dr. Dieter Matern
- Dr. Kamila Mistry (ex-officio member, Agency for Healthcare Research and Quality (AHRQ)
- Dr. Melissa Parisi (attending for ex-officio member Dr. Diana Bianchi, National Institutes of Health-NIH)
- Annamarie Saarinen
- Dr. Beth Tarini
- Catherine Wicklund
- Dr. Catharine Riley (Acting Designated Federal Official)

* Dr. Brosco and Dr. Cuthbert joined the meeting on Day 1 after roll call. Dr. Lorey joined the meeting on Day 1 after the roll call and May minutes vote were taken.

**Joan Scott (HRSA) attended the afternoon portions of the meeting on Day 1 and Day 2 as Dr. Lu's alternate.

Organizational Representatives present were:

- American Academy of Family Physicians, Dr. Robert Ostrander

- American College of Medical Genetics, Dr. Michael Watson
- American College of Obstetricians & Gynecologists, Dr. Britton Rink
- Association of Maternal & Child Health Programs, Dr. Kate Tullis
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Chris Kus
- Department of Defense, Dr. Adam Kanis
- Genetic Alliance, Natasha Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Carol Greene

B. Vote on the May 2017 Meeting Minutes

A vote was taken on whether to accept the minutes for the May 2017 meeting, which Dr. Bocchini noted underwent several small changes submitted by Committee members, which were later amended to include edits Ms. Saarinen submitted that affect Ms. Gaviglio's presentation. (Amy Gaviglio was one of three speakers who presented on Identifying and Following Up on Out of Range and Borderline Results—State Perspectives—Panel Presentations). By roll call vote, the minutes were approved by all Committee members except for Dr. Lorey who was not present until later.

C. Opening Remarks

Dr. Bocchini explained that this meeting is the Committee's third for the year; the fourth and last meeting of 2017 will be Nov. 8-9, followed by meetings on Feb. 8-9 and May 10-11 of 2018. Meeting dates have been set through 2020; this information is available on the Committee's website.

Dr. Bocchini provided a brief update on medical foods; a draft report on this topic which was discussed during the May meeting. The Committee accepted the report, which has gone through several rounds of editing and final edits are being sent to the four primary authors. Once they are added, the final version will be distributed to the members of the Follow-Up and Treatment Workgroup and the Committee. Once the report is finalized, the Committee will send a cover letter to the Secretary of Health and Human Services expressing support for the document and is working to determine where it should be published.

Dr. Bocchini also listed the topics that would be covered during the first day of the meeting.

Dr. Riley provided a standard reminder on the Committee's advisory role and related ethics issues. She asked that Committee members check with either her or Dr. Bocchini before agreeing to media interviews and reminded Committee members that they must recuse themselves from issues on which they have conflicts of interest unless they have obtained a special waiver.

II. SMA Evidence Review—Phase I Report

Alex R. Kemper, *M.D., M.P.H. M.S.*
Division Chief, Ambulatory Pediatrics
Nationwide Children's Hospital

Dr. Bocchini introduced Dr. Kemper as the lead on the Evidence-based Review Workgroup and said that he recently became division chief of ambulatory pediatrics at Nationwide Children's Hospital and is professor of pediatrics at the Ohio State University College of Medicine.

Dr. Kemper acknowledged Dr. K.K. Lam, project leader, special populations at Duke University for her contributions to the project (she was present at the meeting).

Dr. Kemper explained that he would focus on spinal muscular atrophy (SMA), providing a description of the condition and screening-related issues, which have been informed by a very recent expert panel call on this topic. He noted he would not go over much about treatment today because they are still in the process of reviewing the evidence. Dr. Kemper noted that screening is a key part of the Workgroup's nine-month task, which will consist of a systematic evidence review, a decision analysis — through which the Workgroup will model expectations should newborn screening be implemented for SMA— and the public health impact. The first portion of the project, which is underway, involves fleshing out methods and data review and then building on this work. The Workgroup will report on its findings at the Committee's meeting in February.

Dr. Kemper defined SMA as an autosomal recessive disease that affects the motor neurons in the spinal cord and brainstem and causes progressive weakness and atrophy. The disease has a broad phenotypic spectrum with onset ranging from birth and early infancy to adulthood with variations in severity in clinical course. The condition affects from nine to 16 per 100,000 newborns and has a carrier frequency of one in 40 to one in 60 people—a relatively high carrier frequency in relation to its incidence.

The Workgroup is focusing on SMA type 1, which severely affects newborns and types 2, 3 and 4, which have later onset and less severe effects. All types develop due to mutations in the survival motor neuron 1 (SMN1) gene, which is located on the long arm of chromosome 5. This typically involves the deletion of exon 7, which prevents the production of a protein that is encoded by SMN1. In relatively rare cases, point mutations in the gene can occur that result in SMN1 deletion and point mutation compound heterozygotes, but most involve the homozygous loss of exon 7.

Disease progression is tied to age of onset with newborns being the most severely affected. Dr. Kemper warned that some conditions that are referred to as SMA do not fit this in category because they are not caused by SMN1 gene mutations and those conditions will not be covered in the evidence review project. These include X-linked SMA, SMA-LED and adult-onset SMA. Dr. Kemper also explained people with the highest number — up to eight — of another gene—SMN2—have a higher level of protection from late onset of SMA; this gene is a link to pharmacotherapy for SMN1 and SMA.

Newborn screening for SMA typically involves detecting homozygous deletion of exon 7 in the SMN1 gene through quantitative, real-time polymerase chain reaction (PCR) from a dried blood spot and for the number of copies of SMN2 gene that are present, which can predict the likely age of onset. These results are correlated with a clinical examination.

Treatment for SMA consists of nusinersen, an antisense oligonucleotide drug that alters SMN2, allowing more SMN protein to be produced, which the Food and Drug Administration (FDA) approved in December 2016; the evidence review will look at how well it works. Other treatments are in development, including gene replacement therapy and other targeted therapies that alter SMN2.

The Workgroup reviewed 2,447 articles that were published in PubMed, EMBASE, CINAHL and Cochrane from 2000 to 2017 and plans to conduct a full-text review of about 1,202 journal articles among 1,943 that were screened for relevance.

The Workgroup will follow a conceptual framework of adding newborn screening which compares the process followed under usual clinical case detection and clinical care to the process for newborn screening, which involves diagnosis and confirmation. Both processes call for long-term treatment and follow-up and outcomes. The review will also cover the benefits and harm both of screening and diagnosis (unrelated to treatment), including screening accuracy and of treatment and long-term follow-up care. The Workgroup will use the Public Health Systems Impact Assessment to determine the effects of these steps on the public health and the public health system.

Dr. Kemper went on to discuss the status of SMA newborn screening. New York is conducting screening through a research study, which requires parental consent for newborn screening. Missouri has approved such screening through legislation, but screening has not yet begun; Massachusetts, North Carolina and Wisconsin are considering it and others may be as well. He also noted that the Centers for Disease Control and Prevention (CDC) is developing materials states can use to test how well their screening tests perform and proficiency materials for SMA screening.

Dr. Kemper went on to describe two pilot evaluations of newborn screening for SMA, one in New York and one in Taiwan. The New York project was funded by Biogen with Dr. Wendy Chung as the primary investigator. Dr. Kemper noted that Biogen, which manufactures nusinersen, gave him permission to share these data but because they have not been published yet — they are included in an article that is in press in Genetics in Medicine — he asked those present be respectful of that fact.

The goal of the pilot study in New York, in which testing was conducted in a designated laboratory, was to determine whether parents would accept screening and the feasibility of screening for SMA, which was performed through dried blood spots using DNA amplification to detect SMN1. Tier 1 (initial) and Tier 2 (confirmatory) screening was done to distinguish positives from false positives but Dr. Kemper said that this type of tier nomenclature is somewhat artificial. The researchers began by looking for a homozygous SMN1 exon deletion with real-time quantitative PCR with a TaqMan probe and, as a second tier, examined SMN2 copy numbers, which is connected to phenotype and checking for a missing exon 7 which denotes an absence of copies of the SMN1 gene. Two copies of the SMN2 gene are likely to result in type 1 SMA, three to four copies will typically result in type 2 or type 3 SMA and four to eight copies are indicative of type 4 SMA. Based on results, the next steps are confirmatory testing and referral to a neuromuscular specialty treatment center or, in the case of carriers, follow up with genetic counselors. He noted that this is considered to be a laboratory-developed test, which has implications on programs' ability to conduct it. He pointed out that the baby who was identified as having SMA was followed up at the clinic at seven days old and began undergoing treatment eight days later. At a year old, the baby is reportedly asymptomatic and is meeting developmental milestones. He also noted that the testing can be multiplexed with severe combined immunodeficiency (SCID) screening to lower the amount of added work SMA testing imposes on newborn screening programs.

The Taiwan study was also conducted using real-time PCR. Dr. Kemper noted that a new test is being developed by Perkin Elmer. He also noted that there is an algorithm for SMA diagnosis that is compatible with the information he provided.

Dr. Kemper pointed out that the issue of what to do about carriers that are identified through newborn screening is not unique to SMA but creates challenges due to the high number of carriers. He chose not to discuss the number of false negative results which might occur because that issue will be examined through the evidence review process.

Dr. Kemper also noted that the mother of a child with SMA will be participating in the technical expert panel calls that will be held to discuss SMA.

A. Discussion

Dr. Matern expressed interest in learning how families are likely to react upon learning that they are carriers and added that some false negatives could be acceptable, provided this possibility was discussed transparently. Dr. Brosco agreed, saying it would be useful to know how families responded to this information. Dr. Kemper said this was a topic the Workgroup could raise with the New York research team.

Ms. Wicklund expressed concern about the repetitive nature of newborn screening for this type of condition, noting that this screening is typically offered in the prenatal setting and how beneficial this particular screening would be in the newborn period. She noted that many carriers may already have been identified — Dr. Lam said that many were already aware of their carrier status — while others may choose not to undergo testing. Dr. Kemper agreed but did not think he would be able to find data to answer that question.

Dr. Baker stressed the importance of identifying which type of SMA is involved because type 4 patients will not be tested if they do not exhibit symptoms. If only SMN1 is reported rather than the number of SMN2 gene copies, she believes families should be informed.

Dr. Tarini, while acknowledging that the goal of screening is primarily to avoid missing cases, asked what the comparative rate of false negatives is for other disorders and added that if a certain rate is acceptable this could represent a change in current standards and asked what gain would be realized. She added that, if it is accepted, then the false negative rate for all pending and existing disorders should be examined as well. Dr. Kemper agreed that no one wants cases to be missed but pointed out that it does happen — with critical congenital heart disease (CCHD), for example — and suggested that if most cases can be picked up through early detection, leading to benefits for newborns, this approach might be acceptable even if some cases are missed. He said that the review will indicate the expected number of cases that will be picked up, which will provide an estimate of the projected overall benefit of this screening.

Dr. Dolan pointed out that medical groups have not agreed on what guidelines to set for SMA; the American College of Obstetricians and Gynecologists (ACOG) said that, due to the difficulty obstetricians have in screening for it they shouldn't test for it unless genetic counseling was available but, in March 2017, issued new guidelines suggesting that screening for SMA, cystic fibrosis, fragile X and hemoglobinopathies should be offered to every pregnant woman. Meanwhile the American College of Medical Genetics and Genomics, citing carrier frequency, has said it should be a routine screen. Dr. Watson said that the public health system's capacity is already overwhelmed in trying to run newborn screening pilots and testing large numbers of potential carriers for X- adrenoleukodystrophy (X-ALD) and asked whether the ability of programs to add more screens is being examined. Dr. Kemper said that his

Workgroup does not have the resources or the time to determine screening capabilities on the clinical side that fall outside newborn screening.

III. Quality Measures in Newborn Screening to Promote Long-Term Follow-Up

***Jeffrey P. Brosco**, M.D., Ph.D.*
Professor of Clinical Pediatrics
University of Miami School of Medicine

***Alan Zuckerman**, M.D.*
Assistant Professor, Community and Family Medicine and Department of Pediatrics,
Georgetown University

Dr. Brosco is the chair and Dr. Zuckerman is a member of the Follow-Up and Treatment Workgroup. Dr. Brosco began by defining quality measures as standardized, quantitative assessment tools that are used for long-term follow up for various results, ranging from health outcomes to attitudes and achieve quality improvement and quality assurance. These measures are typically presented as ratios (e.g., percentage of children with sickle cell disease who are treated with penicillin) and can be used to track processes, such as the rate at which vaccines are administered, health outcomes, such as mortality or function rates, and attitudes — the extent to which providers communicate effectively. They are also being incorporated into clinical decision making such as electronic medical records, professional certification and payments to individual providers and managed care organizations. He warned, however, that some quality measures that have been developed do not reflect patients' and their families' priorities but are adopted on the basis of their availability.

Dr. Brosco pointed out that, for the past decade, the Committee, through efforts led by Cynthia Hinton and others in the Follow Up and Treatment Workgroup, has been examining what types of questions should be asked about long-term follow-up, e.g., care coordination, evidence-based treatment and quality improvement. A framework, which Dr. Brosco presented during the May meeting, provides a structure for looking at long-term outcomes. The Workgroup examined outcomes measures that work toward improving the survival and well-being of people with screened congenital conditions, the primary drivers that contribute to those outcomes and measures used to determine how effectively, in terms of percentages, long-term follow up is being conducted.

Dr. Brosco explained that about 15 months ago, the Committee asked the Long-Term Follow-Up and Treatment Workgroup to establish a subgroup to examine quality measures and their role in promoting long-term follow-up. He then turned the discussion over to Dr. Zuckerman.

Dr. Zuckerman began by explaining that most of the work the Workgroup has done on quality measures that affect newborn screening has focused on the types of conditions that have been screened for and what steps are taken after a positive result has been identified. Now, the group is focusing on long-term follow-up of children with conditions that were identified through newborn screening. The Agency for Healthcare Research and Quality (AHRQ) and the Centers for Medicare and Medicaid Services (CMS) entered into a partnership, which was mandated by the Children's Health Insurance Reauthorization Act of 2009 to address the lack of child health quality measures and find ways to improve the quality of care

for all children. The first phase, which launched in 2011, funded seven centers of excellence to increase the existing portfolio of evidence-based measures, one of which developed several measures for sickle cell disease that are being tested now. The second phase, which began last year, is supporting the work of six sites that are studying the feasibility of implementing these measures in the real world. Two sites are examining different measures for sickle cell.

This work revealed that evidence-based measures are difficult and costly to develop, validate and implement, even for a common condition that is well understood. The use of quality measures helped to identify deficiencies in care, such as immunizations, the use of prophylactic antibiotics and ultrasonography screening. However, individual intervention programs have resulted in improved outcomes and reductions in emergency room use have also been documented and Dr. Zuckerman stressed that it is important to encourage engagement and cooperation among primary care specialists and emergency physicians to improve care for children identified through newborn screening to address gaps in service delivery because starting the right treatment at the right time affects outcomes. For example, as a University of Maryland study showed, primary care providers can participate in and measure the quality of care in medical homes and sometimes even track children who have not been identified through newborn screening. He noted that the Cystic Fibrosis Foundation funds a nationwide network of centers of excellence that report and share outcome measures, which has led to new findings about which treatments are most effective. This in turn has led to improvements in care and long-term outcomes. Among the lessons learned are that privacy protection is necessary to increase cooperative data sharing while also limiting outside access to the data but yielding important findings; in this effort, national networks can be a valuable resource. He also noted that the Mountain States Regional Genetics Collaborative developed a medium-chain acyl-CoA dehydrogenase (MCAD) deficiency checklist and integrated it into its Epic electronic health record system to collect data on several measures. This effort revealed deficiencies in care and documentation and led to proposals for ways to improve communication during patient visits, including those involving physicians who were unfamiliar with the patient and for those who visited emergency rooms. The subgroup learned that integrating quality measures into routine care improves continuous quality improvement and eliminates the need to fund additional data collection through redundant databases.

Dr. Zuckerman also noted that the Centers for Disease Control and Prevention (CDC) has become the custodian for early hearing detection and intervention (EDHI) measures that were certified by the National Quality Forum (NQF). The existence of certified electronic measures has improved states' data reporting. Large numbers of infants who were screened before and after hospital discharge were compared to determine timing of audiological testing completion. He reported that NQF's process for developing electronic measure formats and obtaining certification is time-consuming and difficult but feasible for some conditions and that standardized measures can improve the completeness of data reporting. He hailed the California Department of Health's efforts to include in the state newborn screening fee necessary funding for long-term follow-up and data collection. He added, however, that many health departments lack a mission or the resources to replicate its success and noted that California ends its follow-up at five years of age, which is not long enough to follow some conditions. He also noted that long-term follow-up in some states may not be conducted by their newborn screening programs.

Dr. Zuckerman reported that the National Survey of Children's Health, which now incorporates the former National Survey of Children with Special Health Care Needs that HRSA conducts.
The survey covers consumer satisfaction issues and access to services, which align well with questions the Workgroup had developed previously. These surveys do not single out children identified with

conditions through newborn screening but are starting to collect data on whether a child's condition is heritable. These surveys provide key data on access to medical homes and services, the adequacy of insurance and even access to clinical trials, providing data that can be compared to national norms; they also ask standardized questions.

Dr. Zuckerman pointed out that many conditions have subtypes with a range of severity and the best treatment options are not always clear, making it hard to develop condition-specific measures; this is also true of conditions with late onset where evidence is limited. In addition, the NQF certification process requirements are difficult for newborn screening to meet, requiring 1,000 cases per measure, and the measure validation process is costly. He also called for a commitment to move beyond disease-specific measures, whether they cover a single disease, or those involving one lab test or other measure as a proxy for true outcomes. He called for adoption of public health or system measures, which track what services are available, ensure that patients are not lost to follow-up and that they transition into adult care. He also called on child-specific measures to focus on access to medical homes, available treatment, child well-being and parent satisfaction with the care process, which will require data sources that move beyond health care providers. Consumer perspectives on quality measures should also be conducted to reflect their definitions of quality and to capture needs and gaps that are not being captured, including the ability to participate in research studies, access to specialists and insurance coverage for expensive treatments. Several disease advocacy organizations have collected disease-specific data from patients and families through surveys and patient natural history registries.

Dr. Zuckerman noted that the Office of the National Coordinator for Health Information Technology, CMS and AHRQ maintain an electronic clinical quality improvement resource center, available at https://ECQI.HealthIT.gov, which provides access to new health IT standards for quality measures, definitions and reporting and a quality data model for extracting data from electronic health records. The data must be in the electronic medical record, however, and many relevant, portable measures do not work in them. He pointed out that the Association of Public Health Laboratories (APHL) Newborn Screening Technical Assistance and Evaluation (NewSTEPs) program has created case definitions and case reporting databases that can define the denominator for newborn screening quality measures and that the Newborn Screening Translational Research Network (NBSTRN) has a Longitudinal Pediatric Data Resource that contains data field definitions. Dr. Brosco finished the presentation by suggesting potential future steps for the Follow-up and Treatment Workgroup:

1. Develop strategies to encourage the development and validation of quality measures for long-term follow-up of newborn screening;
2. Identify a core set of long-term follow-up quality measures for state newborn screening programs, such as mortality at five years of age for all infants identified in a newborn screening program;
3. Address quality-measure-related gaps for newborn screening-related quality measures;
4. Develop strategies to educate and engage stakeholders in using these quality measures; and
5. Determine the feasibility of newborn screening in the National Survey of Children's Health and other consumer surveys.

A. Discussion

Ms. Wicklund asked to what extent the Workgroup had focused on implementation — how to obtain the data and implement their suggestions. Dr. Zuckerman explained that research projects designed to collect data and examine focused improvement cycles in connection with routine care are different from

long-term follow-up studies, which require consent, ambitious data collection and duplicate entry or even chart abstracting. Newborn screening is just beginning to go from the comprehensive research approach to the targeted indicator and improvement approach. Dr. Mistry said that, although measures exist, an understanding of what implementation — moving from measurement to improvement — involves is less clear. How does the information collected improve care? Dr. Matern suggested using the Epic electronic health record to put in notifications to the physician when follow-up visits or reminders to educate families are needed. Dr. Zuckerman pointed out that electronic record systems differ and that single plug-ins for each condition tend to be customized. However, an early phase of a Nationwide Interoperability 10-Year Roadmap project is under way, which could lead to such applications in these record systems. The challenge of inputting the data into these records and coding it properly remain, however. Dr. Brosco also pointed out that many electronic health record systems are geared more for adults than for pediatrics and many newborn screening conditions are so rare that they are not incorporated into them. Dr. Parisi suggested, as a starting place, using a core set of long-term follow-up measures to gather data on and develop possible implementation strategies, rather than focusing on less common ones, to develop a baseline of standard measures that could be used across various conditions. Dr. Brosco said the Workgroup welcomes guidance on what types of measures they should focus on and that this could be done working with APHL, state newborn screening programs and other stakeholders.

Ms. Saarinen pointed out that, in moving her child from one school to another, the Individualized Education Program (IEP) team that had been following her daughter for three years would no longer follow her because such teams are school-system-based. As a result, clinical and educational progress data would have to be transferred to and maintained by a whole new team. Dr. Tarini said that solving this issue is key to performing long-term follow-up. Dr. Greene suggested that it would be more valuable to focus on quality measures that encompass multiple rather than single diseases, which would require examining small patient subsets for which it would be difficult to collect data.

Ms. Bonhomme and Dr. Ostrander stressed the importance of including the parent and family perspective in developing quality measures to ensure that their priorities and needs are being met which would gauge accessibility, comprehension and their understanding and level of inclusion and comfort with the way health care is being delivered, including education. Dr. Ostrander discouraged the Workgroup from focusing on using electronic health records as a vehicle for implementing quality measures because they are developed for a patient-centered medical home world that focuses on chronic, expensive, adult diseases that affect whole populations. Dr. Greene and other commenters called for the use of patient registries to get diagnostic information that will inform quality measures.

IV. Public Comment

A. Megan Lenz, Director of Communications, Cure SMA

Ms. Lenz spoke on behalf of her organization, the Muscular Dystrophy Association, and the spinal muscular atrophy patient community regarding the nomination of SMA to the Recommended Uniform Screening Panel (RUSP); which is currently undergoing evidence review. She reported that SMA is the leading genetic cause of death for children younger than 2 years of age and reminded the Committee that the FDA-approved nusinersen, also called Spinraza, is the only treatment for SMA. Ms. Lenz also reminded the Committee that Biogen's open-label study (NURTURE) of pre-symptomatic infants who

received this treatment reached more motor development milestones than those in the ENDEAR study who received the drug after exhibiting symptoms. She reported that, as of October 31, 2016, no pre-symptomatic SMA infant who received Spinraza died or required permanent respiratory support, whereas 39 percent in the ENDEAR group had one of these outcomes. She also reported that her cousin had died of the condition one week after his fourth birthday. She noted that infants with type 1 SMA who do not receive early treatment suffer motor loss within the first 30 months of life and by 6 months of age, often suffer loss of 90 percent of motor units. She called for SMA to be added to the RUSP to ensure early treatment.

B. Ms. Jana Monaco, mother of children with ALD

Ms. Monaco's shared a story about a family she knows. This family had a second son, Alex, who had been incorrectly diagnosed with several conditions, including ADHD, autism and sensory integration over time until, after a severe fall at nine years of age, he was correctly diagnosed with ALD. At that time, he was given nine months to live. His older brother, Zack, was then tested and diagnosed with inactive ALD. Alex received a bone marrow transplant but succumbed to his disease at age 16. Zack remained asymptomatic but received treatment with Lorenzo's oil; he suffered from survivor's guilt, however, and ended his own life at age 20. Ms. Monaco said that families in these situations not only grieve but feel guilt over their inability to obtain early, correct diagnoses for their children and asked the Committee to consider this when attempting to identify conditions that "don't fit the desired criteria," and to include the effects of the families when considering outcomes.

V. Establishing and Revisiting Newborn Screening Cutoffs — Lessons Learned from the States

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

Dr. Bocchini explained that Dr. Tanksley would be presenting a summary of a survey APHL conducted among newborn screening programs. Dr. Tanksley reported that the APHL Newborn Screening, Genetics, and Public Health Committee developed a pilot version of the survey, for distribution to a few states in the wake of media stories about missed newborn screening cases. It was conducted over a two-month period, which ended two weeks ago. The survey collected information on how they set cutoffs, what results are reported and the tools they use to do so. Respondents consisted of newborn screening laboratory directors, follow-up managers, clinicians and others who might use the analytical tools. Thirty-eight of 53 newborn screening programs participated and about 97 percent of them have access to R4S or CLIR. The first part of the report focused on how states determine a not-normal result; the second part covered their use of Region 4 Stork (R4S) Laboratory Performance Database and Collaborative Laboratory Integrated Report (CLIR) tools.

Dr. Tanksley explained that some states reported using vendor recommendations — typically, a kit insert — to set a reference range for establishing cutoffs. Many use population data and screen dried blood spots using normal populations and incorporating affected babies when residual newborn screening specimens are available. These data were sometimes used to set age- or weight-specific

cutoffs as well. Other sources included consultants, clinical specialists, the state newborn screening advisory committee, published literature and advice from other state programs. The tools used to establish cutoffs included R4S, statistical analysis software, Excel and the Specimen Gate Laboratory Information Management System (LIMS) cutoff analyzer.

Most programs — 43.5 percent — conducted lookbacks of their cutoff values or of the process used to determine them for follow-up testing or referral based on a specific event — when a missed case or multiple false positives occurred or because of a change in instrumentation or new kit lots but some do so on a regular basis — monthly, quarterly or annually. Every program conducts lookbacks at least periodically. Most states have a process for communicating the information; two programs did not have a process and one state did not know whether one was in place. Almost 87 percent of state programs said their risk report includes a risk assessment (e.g., normal/abnormal, slightly/highly elevated or heterozygous/disease). Those that did not have a risk assessment mentioned challenges such as the fact that their LIMS reports abnormal analyte ranges, not disorders.

Of the 38 newborn screening programs that responded, 4 were unaware of R4S and CLIR, 23 (67.7 percent) had access to both, 29.4 percent had access to R4S only, and one state had no access to either one. About a third of the states use the tools at least monthly and some medical consultants do as well. Twenty-five programs reported that they had been trained on how to use one of these tools. Twenty-two percent said they use one of the tools to determine which analytes, markers or ratios to include in a risk assessment — in other words, whether a child is at risk for developing a disorder; 19.2 percent said they use it for managing cutoffs and 18.2 percent use it to determine risk for select diseases. Other uses included setting cutoffs (12.1 percent), determining normal/abnormal status (7.1 percent) or determining risk for all diseases included in R4S/CLIR (5.1 percent). One percent of programs do not use either tool. One program that does not use the tool said that R4S has not been peer reviewed with published results that support its use for risk determination and the algorithms have not been validated and are subject to change, which imposes a risk on the clinician. A second program argued that there is not enough evidence to indicate that the tools work better than cutoffs, that the tool risk determination changes every time data is added and cited a lack of knowledge on how the tools performed previously and poor integration with the state LIMS. When they were asked for examples of R4S or CLIR use that resulted in false negatives or false positives, of 32 programs that responded, 40 percent said no; 34.4 percent said yes and listed examples such as a false positive for maple syrup urine disease and a false negative, for both the state's cutoffs and CLIR for beta-ketothiolase. Dr. Tanksley said newborn screening disorders are rare and no approach will pick up every case. She also warned against equating screening with diagnosis; if a baby is symptomatic, diagnostic testing is needed independently of the screen.

When asked whether a program uses R4S or CLIR for every abnormal result, 12.5 percent responded affirmatively; of these, 21.1 percent were made in a clinical setting by specialists while 15.8 percent were made in the laboratory with results reported on newborn screening reports and 15.8 percent said in follow-up with the results used to decide what algorithm to use. Seven programs (almost 30 percent) reported, when using RS4 or CLIR to determine risk and said they re-ran values to obtain a new risk assessment on previously reported cases; in one case, the risk had changed over time.

When asked about the strengths of R4S or CLIR, programs reported that the programs validate newborn screening findings, are useful for rare disorders, support risk assessments, offer comparisons of results between states and help to rank cases' urgency. The ability to choose modules and ease of use were mentioned as well. Perceived weaknesses were the lack of algorithm validation, the need to customize

the algorithm for each state and lack of transparency. Programs also called for better integration with the LIMS, the fact that data and tools are not method- or instrument-specific, change in the tool when data are added, variability in case definitions and the lack or unavailability of training when needed. Only 34.4 percent actively submit data to R4S or CLIR and most do not do so regularly because of lack of staff time. Slightly more than 53.1 percent submit case data to R4S or CLIR, 28.1 percent said they used to do so and 18.8 percent do not; slightly less than 6 percent do so regularly. Programs that stopped submitting data cited the lack of staff time, difficulty collating data from the LIMS and department of health concern about data security issues or managing, storing or sharing data without parental consent. Benchmarks used to define a case before adding it to R4S or CLIR was typically a positive diagnosis confirmed by a clinical specialist, follow-up program, or genetic referral center. She noted that some respondents interpreted the questions differently, which would affect their responses.

Dr. Tanksley said that APHL has a quality assurance/quality control subcommittee that has been working on a guidance document newborn screening programs will be able to refer to when setting cutoffs. She indicated that the document will be discussed during the Laboratory Standards and Procedures Workgroup later in the day and that the survey results could prove useful in developing the document.

A. Discussion

Dr. Matern pointed out that R4S and CLIR are very different and that this fact should, perhaps, have been reflected in the types of questions that the survey asked. He also questioned the assertion that CLIR has not been validated or peer reviewed, alluding to several peer review papers that have been published, including one by Hall, et. al., in *Genetics in Medicine* that ran data for about 200,000 babies through CLIR that showed the false positive rate could be reduced by 90 percent. He also said that many states were trained in the tool's use. Dr. Tanksley confirmed that training is available online.

Dr. Cuthbert offered to obtain and test borderline cases from states and test them at CDC then recreate some of the materials and provide them as samples to states so that programs could see which ones might have yielded a positive result, which could provide more perspective on setting cutoffs. Dr. Tanksley said this would be educational for states. Dr. Tanksley and Dr. Matern pointed out that some conditions, such as cystic fibrosis and maple syrup urine disease, can be difficult or impossible to detect. Dr. Baker concurred, saying that other factors not linked to the disease can result in a false negative. The difficulty in defining cases, including what type a case falls into and each state's definition, influence results as well. Dr. Watson proposed conducting a comparative analysis of the cutoff systems that are used and the CLIR or R4S tool. He asked whether California and Georgia are the only states that have compared the tools. Dr. Matern said that several states are working on this in connection with congenital hypothyroidism and that every state can compare their data to that run through CLIR. Dr. Baker said that her state, Wisconsin, is running a parallel study of using both traditional cutoff method and CLIR, and so far they are agreeable. Dr. Watson noted that false positives, which can run from a 2 percent to 60 percent positive predictive value across states, are costly to the health care system and the work force.

Dr. Greene pointed out that state newborn screening programs change their cutoffs all the time in response to multiple false positives or changing conditions just as CLIR and R4S do. She also questioned whether it's possible for a federal committee or agency to require a state to use a particular method or tool or prevent them from doing so. Dr. Tanksley said that the concern expressed through the survey is that when more data are put into the system, they are not revalidated.

Ms. Bonhomme suggested that since news reports about missed true positives helped focus attention on cutoffs, there may be a need to bring an education or communications perspective on the discussion, in part to explain what happens when a missed case is identified. Dr. Tanksley said a better understanding of newborn screening in general is needed, not only for the public at large but for parents and primary care physicians, some of whom may rule out a disease based on the newborn screening result alone. She stressed that any symptoms should trigger diagnostic testing. Dr. Baker said that changing a cutoff to make it more conservative can trigger too many false positives but conducting second-tier testing after the cutoff has been changed can help to address that. Dr. Parisi said that North Carolina had success using CLIR by incorporating it into its algorithm while developing its screening protocol for MPS I and had reduced its false positive rate by 80 percent; this allowed the state to reduce costs, screen more newborns, and reduce the number that required secondary evaluation, which also reduced stress on families.

Ms. Saarinen asked what barriers exist to instituting standardized cutoffs from one state to another and some but not all run second- and third-tier tests. Dr. Cuthbert said that this is not possible because laboratories have different platforms and, therefore, do not get the same absolute values. However, the CDC is looking into an attempt at harmonization whereby the CDC would examine the cutoffs that states share with the agency and normalize them against quality control materials the CDC provides to arrive at a standardized way to look at test cutoffs. This is what the APHL quality control/quality assurance committee will be working on and it will incorporate CLIR and R4S tools. However, as a federal agency, the CDC cannot tell states what to do.

Dr. Brosco suggested that the issue is not as much about cutoffs as it is laboratory practices, which are becoming increasingly complex and are already diverse. He suggested moving toward use of regional labs rather than 50 different approaches. Dr. Cuthbert said it would be up to the states to decide whether to adopt that approach; some states already contract with others to do their testing.

Dr. Joe Schneider, a pediatrician with the University of Texas Southwestern Medical Center in Dallas and a retired pediatric informaticist agreed that the states' differing ways of establishing cutoffs makes screening difficult and perceives value in the Committee calling for efforts to identify more national best practices, from a scientific basis. He also said that, when calling for standardization, it is important to consider cultural issues and suggested changing the terms "positive" and "negative" when referring to a screen. He called for better ways to communicate such results.

Ms. Sabra Anckner, a nurse consultant with the state of Alaska, said that states have different populations that should be considered in terms of screening because the cutoffs her state uses in view of the Alaskan native population might not work for others; this applies to using a single cutoff for the C0/C16+C18 ratio and the different cutoffs the state uses for 17OHP for Alaska native children who have high rates of salt-wasting congenital adrenal hyperplasia.

NOTE: Dr. Bocchini did not deliver his complete presentation on "Establishing and Revisiting Newborn Screening Cutoffs—Summary and Next Steps," saying that most of it had been covered in Dr. Tanksley's presentation; however some of the remarks he had planned to make are included in the following discussion.

Dr. Tanksley and Dr. Bocchini said that the survey provides a map of the type of screening activities that are occurring through newborn screening programs that indicate where interventions might be helpful. Dr. Bocchini also said that potentially incorrect assumptions show where education needs to be done and that the Committee can provide guidance, including what would be termed best practices. He also

mentioned that the Education and Training Workgroup focuses on making health care provider education available regarding newborn screening results, which could involve representatives of various medical groups and education for residents as well as public education. He also acknowledged that states may lack the resources to add data into CLIR. Dr. Ostrander said that education on newborn screening should begin in the first year of medical school. Dr. Berry said that negative results are usually not explained adequately to families; an ongoing survey of families that is being conducted in Minnesota shows that families don't know that screening is being done or what the results mean. She promised to provide findings on this project.

Dr. Brosco called for more education on screening sensitivity and specificity. Dr. Greene, however, said that sensitivity and specificity can vary based on other factors, such as state of health and whether the child is fasting and some tests will not detect intermittent cases. In the end, what's important is whether a baby requires more testing. Dr. Watson pointed out that it can be difficult to collect large amounts of data on rare diseases after which it's still necessary to overlay population differences. Dr. Zuckerman pointed out positive and negative predictive value of a test depends on the prevalence of the disease among the population being screened even if sensitivity and specificity properties of the test do not change. He also said that he has trouble using the term "cutoff" in connection with R4S and CLIR because they are inherently multi-variate, multi-hypothesis tools that do not fit the traditional laboratory test cutoff model and it may be necessary to communicate how they're used and the fact that they examine different data parameters and not a single test.

Dr. Bocchini showed the final slide in his planned presentation calling on the Committee to think through how it could help APHL's efforts to develop newborn screening cutoffs and screening algorithm documents, either as a whole or through the Laboratory Standards and Procedures Workgroup. The Committee could also play a role, possibly through the Education and Training Workgroup in the effort to craft provider education on newborn screening results interpretation, including within-normal-range results, while helping to stress that screening results are not diagnostic. He also stressed the importance of thinking through state newborn screening programs' infrastructure needs.

Dr. Riley reminded the Committee that, as special government employees and federal employees, no one on the Committee can endorse products.

Workgroup meetings were held for the rest of the day.

VI. Administrative Business — August 4, 2017

A. Welcome and Roll Call

Dr. Bocchini welcomed the participants to the meeting and conducted roll call. Committee members in attendance:

- Dr. Mei Baker
- Dr. Joseph Bocchini
- Dr. Jeff Brosco
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention—CDC)
- Dr. Kellie Kelm (ex-officio member, Food and Drug Administration—FDA)

- Joan Scott (attending for ex-officio member Dr. Michael Lu [Health Resources and Services Administration—HRSA])
- Dr. Fred Lorey
- Dr. Dieter Matern
- Dr. Kamila Mistry (ex-officio member, Agency for Healthcare Research and Quality—AHRQ)
- Dr. Melissa Parisi (attending for ex-officio member Dr. Diana Bianchi, National Institutes of Health -NIH)
- Annamarie Saarinen
- Dr. Beth Tarini
- Catherine Wicklund
- Dr. Catharine Riley (Acting Designated Federal Official)

Organizational Representatives present were:

- American Academy of Family Physicians, Dr. Robert Ostrander
- American College of Medical Genetics, Dr. Michael Watson
- American College of Obstetricians & Gynecologists, Dr. Britton Rink
- Association of Maternal & Child Health Programs, Dr. Kate Tullis
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Chris Kus
- Department of Defense, Dr. Adam Kanis (afternoon only)
- Genetic Alliance, Natasha Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Carol Greene

B. Recognition of Service

Dr. Bocchini announced that Dr. Coleen Boyle, is rotating off the Committee after serving as a member since its inception in 2004. She served on the expert panel that developed the initial Uniform Screening Panel and co-authored the "Newborn Screening: Toward a Uniform Screening Panel and System" report in 2006. She also led the Follow-Up and Treatment Subcommittee for many years and was involved in the Workgroup's production of "Road Map to Implement Long-Term Follow-Up and Treatment in Newborn Screening. In 2008, Dr. Boyle co-authored the "Long-Term Follow-Up After Diagnosis" report. In 2012, she co-authored a manuscript on insurance coverage of medical foods for treatment of inherited metabolic disorders. Dr. Bocchini saluted her for her many contributions the advancement of newborn screening and presented her with a plaque for her service. Dr. Boyle thanked Dr. Bocchini and expressed appreciation for the honor, for the opportunity to learn about newborn screening during her time on the Committee and to serve with her colleagues. Dr. Bocchini also introduced Dr. Carla Cuthbert who will take Dr. Boyle's place, representing the CDC.

VII. Overview of Newborn Screening Technology

***Alex R. Kemper**, M.D., M.P.H., M.S.*
Division Chief, Ambulatory Pediatrics
Nationwide Children's Hospital

Dr. Kemper began by noting that technologies used in newborn screening are complex and changing rapidly and Committee decisions require an understanding of current advances and anticipating new ones. He explained that the Evidence-based Review Workgroup is working on a report to describe developments in screening, confirmatory and treatment methods that have occurred within the past five years and others that are on the horizon and how they can be applied to benefits, potential risks and the cost of newborn screening. The Workgroup convened a technical expert panel, which included expert representatives to cover clinical care, public health laboratory, research and regulatory issues.

The report will cover tandem mass spectrometry, digital microfluidics, molecular tests, PCR in targeted gene sequencing, next-generation sequencing and new instrumentation, such as the genetic screening processor, which permits high through-put batch analysis of quantitative or qualitative measures of neonatal screening samples, and point of care (POC) testing.

In terms of tandem mass spectrometry, Dr. Kemper explained that great work has been done on lysosomal storage disease (LSD) screening to detect potential markers for a wide range of disorders, including Pompe disease, Gaucher, adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency, Wilson disease, GAMT, Duchenne muscular dystrophy and others.

The Workgroup is also examining molecular tests such as DNA-based assays for screening and confirmatory testing, such as PCR for first-tier SCID and SMA screening. Many of these could be multi-plexed which would allow targeted gene sequencing, including traditional sequencing for second-tier confirmatory testing and next-gen sequencing panels that can examine an array of mutations on a panel. There is also near-future work on whole-exome or whole-genome sequencing.

In terms of treatment, the technical expert panel advised the Workgroup to review developments in hematopoietic cell therapy — the infusion of allogeneic or autologous stem cells from umbilical cord blood — to address deficient enzyme activity or replace a missing cell. This therapy could lower the risk of graft-versus-host disease or infection and, related to this, lead to specific gene editing technologies to repair genetic lesions. Enzyme replacement therapy is promising although patients can develop antibodies that neutralize the therapy. There is also the danger of the therapeutic agent crossing the blood-brain barrier for which one preventive measure is delivering it directly through intrathecal injection. This therapy can be combined with hematopoietic cell therapy as well. Dr. Kemper pointed out that oligonucleotide therapy — short, single stranded molecules that bind to mRNA and alter splicing, which affects the protein that is developed — could be relevant for SMA and other conditions that could be nominated soon for the Recommended Uniform Screening Panel (RUSP) along with other similar therapies that could be developed to address Duchenne muscular dystrophy and Rett syndrome. Targeted gene therapy using programmable DNA nucleus to correct mutations or introduce functional gene copies is also being developed, which could help to correct the mutation that leads to sickle cell disease. Examples include a zinc-finger nuclease, which permits genetic editing, and CRISPR-Cas9 gene editing.

Dr. Kemper also noted that gene editing, which uses viral factors to introduce functional gene copies is another promising avenue; Phase 1 clinical trials are being conducted that focus on SMA and Duchenne muscular dystrophy.

A. Discussion

Dr. Baker suggested covering induced pluripotent stem cells as well. Dr. Kemper said that there would be ongoing opportunities to add new technologies to the document in the future. Dr. Greene asked whether the Workgroup had thought of adding diagnostic technology, such as positron emission tomography (PET) scanners to determine whether patients with ALD need treatment; Dr. Kemper agreed that this was worth looking into over time. Ms. Saarinen suggested focusing on follow-up diagnostics, such as ways to reduce the cost of and increase resource-poor places' access to echocardiograms, which was mentioned at the World Congress on Pediatric Cardiology in Barcelona.

Dr. Tarini said that if the Committee decides to push through an assessment of diagnostic algorithms, it would be appropriate to consider congenital hypothyroidism, one of the oldest disorders on the screening panel. There is a lack of clear standards across the United States about which children who initially screen positive have permanent congenital hypothyroidism. In addition to new technologies, there are core disorders for which it is not clear how many of those who screen positive have the disease and there are challenges in terms of the variation of diagnoses, she added.

Dr. Matern asked whether there is a risk that the evidence-review group, by mentioning some of these technologies, is endorsing products. Dr. Kemper assured him that the Workgroup is not urging anyone to adopt any technology but is presenting an overview strictly for information purposes. Dr. Riley confirmed that mentioning technologies in the context of the evidence review is acceptable, as long as the Workgroup does not instruct anyone to use a particular one.

Dr. Cuthbert said that the CDC is considering developing a comparable type of educational tool and that CDC should confer with the Workgroup to make sure that new developments the two parallel efforts complement each other and new technologies are comprehensively represented. Dr. Kemper agreed while adding that this could help prevent duplication of efforts.

Dr. Greene pointed out that Dr. Kemper did not mention imaging and biochemical testing, such as enzyme assays and metabolomics, that is still the gold standard, whereas DNA is not. Dr. Kemper agreed, saying that he did not mean to leave those developments out but did not have time in his presentation to mention all of the developments the report could cover.

VIII. Education and Training Workgroup Update

***Cathy Wicklund**, M.S. C.G.C*
Chair, Education and Training Workgroup
Northwestern University Feinberg School of Medicine Center for Genetic Medicine

Ms. Wicklund explained that the Workgroup is working on a document that primary care providers can use to discuss initial out-of-range newborn screening results with parents, drawing on information gleaned from focus groups during which parents were asked what they felt was important for them to know. She stressed that this document would not replace the American College of Medical Genetics and Genomics' (ACMG) ACT sheets, which discuss disorders specifically and is geared toward physicians. A subgroup of the Workgroup reviewed and revised the resulting draft, which the Workgroup reviewed and suggested edits to be incorporated before reviewing the document again. Then primary care providers will review it and provide feedback on the document, which is intended to be about one page long and

provide helpful tips. Once the guidance is complete, the Workgroup will work with the ACMG to elicit its approval and link it to ACT sheets but it will be disseminated in other ways as well, such as through medical organizations.

The Workgroup's other project is a matrix or curriculum map to help those who wish to create an educational brochure for a specific stakeholder group such as parents, midwives, nurses or physicians. The matrix helps people to decide what content to include in an educational brochure, which could be called the Newborn Screening Educational Planning Guide. Ms. Wicklund explained that various stakeholder groups have reviewed the content. It was presented at the Beyond the Bloodspot Summit and four attendees provided feedback along with three parent Workgroups who were involved in Baby's First Test. The Workgroup will continue to work on it and all stakeholders will be asked to comment on it after which, the guide will be presented to the Committee for review. Then a list of partners who can disseminate it will be drawn up.

Ms. Wicklund also mentioned several future studies. One involves studying how an optional screening for Krabbe disease could be introduced, which is something Ohio and Georgia have done, and whether this could extend to other conditions and what role the Committee could play. The Workgroup will examine this topic in November. The Workgroup may also discuss how to educate physicians and the public on what an out-of-range screening result means and the need for appropriate workups if children are symptomatic.

A. Discussion

Dr. Parisi suggested reaching out to the Intersociety Coordinating Committee [for Practitioner Education in Genomics] (ISCC), which is convened by the National Human Genome Research Institute and other groups and could be a good venue for provider-focused educational efforts surrounding newborn screening. That committee has an interactive website with training modules and these materials could perhaps be posted there. Dr. Ostrander said that he is the American Academy of Family Practitioners' representative to the ISCC and could serve as a bridge to that organization, which is involved in genetics and genomics [education].

Dr. Brosco asked whether the Workgroup includes communications science experts who understand how to word concepts and messages, such as psychologists. Ms. Wicklund said that she hoped to have an expert in health communications review the document and that genetic counselors are doing so but she is considering also involving someone with the type of background Dr. Brosco mentioned.

Dr. Greene pointed out that she and Natasha Bonhomme learned from a focus group they held that parents want to know when they'll receive results, how worried they should be and what type or level of care they should give to or seek for their child when they hear the initial results. Parents may want to be given a choice of finding out immediately about the disease for which the child is being tested or just about the confirmatory testing process. Dr. Brosco agreed, saying that it is important to let parents decide what they want to know at this point.

IX. Follow-Up and Treatment Workgroup Update

***Jeffrey Brosco**, M.D., Ph.D.*
Chair, Follow-Up and Treatment Workgroup
Professor of Clinical Pediatrics, University of Miami School of Medicine

Dr. Brosco explained that the Workgroup is focusing on finishing two projects. It is editing the "Medical Foods for Inborn Errors of Metabolism" report, which the Committee accepted during the May meeting and should be finished by the November meeting after which the Workgroup will consider where to publish it. A draft of the quality measures for long-term follow-up that Dr. Zuckerman spearheaded should also be complete by November. Dr. Brosco explained that Dr. Kemper and Dr. Lam will do a scan of current, long-term follow-up activities across the United States and will present an interim report of their work during the November meeting to provide an overview of what has been done and how the Committee can help. He explained that, in thinking about this, it could prove helpful to fit children with newborn screening conditions into four groups, each of which offers the opportunity to measure and improve outcomes while ensuring that the child and family perspectives are included. The four populations he listed are children with newborn screening conditions (e.g., cystic fibrosis or sickle cell disease). These children are also included among the larger group of those who have been identified in other ways as having these conditions. They also fit in the larger category of children with special health care needs and, finally, they fit into the group of all children.

Dr. Brosco explained that there are quality improvement and long-term follow-up monitoring activities for each level. For children with specific conditions, formal quality measures regarding treatment and monitoring can be developed with quality improvement measures built around them, fostered by research networks. All of these activities can be nudged forwards, such as by improving the electronic medical record and these improvements can be driven by family/patient advocacy groups.
He pointed out that monitoring and quality improvement activities surrounding the group of children who have any condition identified by newborn screening typically occur at the state level, whether through the laboratories or Title V, but it's important to know how those systems are working. NewSTEPs can help with the early portion of that but it is not clear what comes afterward. Fortunately, many states have become involved in NewSTEPs, the Longitudinal Pediatric Data Resource and the National Coordinating Center and the Committee can help to move this forward.

With regard to children with special health care needs, HRSA focuses on this group through its National Survey of Children's Health. The question is whether there is a way to identify which children at this broad level may have a newborn screening condition. In the last group of all children, much of the focus is on value-based reimbursement, not at special needs or newborn screening conditions, so promoting the use of outcomes that are relevant to children with special health care needs at this level — the 15 million or so among the 80 million children in the United States — may be something the Committee can address. He noted that fewer than 1 million children probably have newborn screening conditions. He noted that children with special health care needs and newborn screening conditions can be most vulnerable to the factors that affect the everyday health of all children: poverty, immediate environment, school and family issues. So, policies that help the largest group of children can help these groups as well.

A. Discussion

Dr. Parisi concurred that there are quality measures that could apply to one of the subgroups Dr. Brosco mentioned but some could apply to and improve health care quality for all. Dr. Kus pointed out that although during yesterday's meeting the Maternal and Child Health Program and the Children with Special Healthcare Needs Program were discussed as separate but the latter program is supposed to receive 30 percent of Title V funding.

X. Laboratory Standards and Procedures Workgroup Update

***Kellie Kelm**, Ph.D.*
Chair, Laboratory Standards and Procedures Workgroup
Food and Drug Administration

Dr. Kelm explained that the Committee asked the Workgroup to consider the draft produced by APHL's QA/QC, subcommittee that Dr. Joseph Orsini and Patricia Hunt presented to the Workgroup on Aug. 3, which will serve as a guideline for determining cutoffs. The document provides an overview of some, but not all approaches newborn screening programs may take in determining a cutoff between abnormal and normal, but not positive, results for laboratories that have resources available.

The draft explains that a cutoff can be at the low or high end of the marker(s) reference range, depending on what the test method is intended to identify. A cutoff can be determined through a small population study, evaluation of demographic factors that can affect reference range or a creation of a frequency histogram or probability density function to determine the normal or reference range; then you determine this range statistically. The next step would be to conduct a literature search to identify disorder prevalence and incidence and any published ranges or cutoffs, followed by a request for cutoffs from other states for comparison and ending with evaluation results for the population study compared to true positives.

Dr. Kelm noted that there are cutoffs for specific newborn screening disorder categories and considerations for AA/AC, endocrine, LSDs, etc. The next step would be to challenge the preliminary cutoff by running known positives from other states for positive controls, use PT [proficiency testing] specimens in comparison to other programs and then take into account special considerations, such as age and birthweight dependencies although this will be difficult for the first laboratory that sets up the screening. Finally, the draft provides guidelines for monitoring and evaluating the cutoff and offers references.

The authors said that analytical tools such as R4S and CLIR will be included in the guideline. They were advised to tell programs that they should use the document to write their own standard operating procedures. After several stages of review, the draft document will be submitted to APHL's Newborn Screening and Genetics in Public Health Committee in October 2017. The document will be reviewed and updated over time.

The Workgroup would like to explore several topics in the future. One involves examining hearing loss detection that is not detected by a hearing screen — usually between birth and school age — using a

molecular first-line screening test. It was not clear whether this should be considered an extension of the current condition on the RUSP or a different one.

The second possible project was an update on NIH-funded Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) projects, especially one comparing next-generation sequencing to traditional newborn screening.

Other future topics included the potential for national data aggregation of newborn screening data outside R4S, CLIR and NBSTRN, second tier testing for conditions recently added to the RUSP, information sharing through a NewSTEPs peer network and a presentation on the Eunice Kennedy Shriver National Institute of Child Health and Development-funded pilot studies for LSDs.

A. Discussion

Dr. Parisi said that the University of California at San Francisco's NSIGHT study comparing next-generation sequencing to conventional newborn screening, showed that the next-generation [whole-exome-sequencing approach] was only picking up about 75 percent [of newborns with a condition identified by conventional, metabolite-based screening]. She also agreed on the need for pilot studies for LSDs and believed that in a year or so, data might be available from both [NIH-funded] studies.

XI. Clinical and Public Health Implications of Critical Congenital Heart Defects in Newborn Screening

***Scott Grosse**, Ph.D.*
Research Economist, Office of the Director
Defects and Developmental Disabilities, Centers for Disease Control and Prevention

***Matt Oster**, M.D., M.P.H.*
Director, Children's Cardiac Outcomes Research Program at Sibley Heart Center
Emory University School of Medicine

Dr. Bocchini introduced Dr. Grosse who serves as the federal advisor to the Evidence-based Review Group. Dr. Grosse defined CCHD as a specific set of heart defects that are associated with impaired oxygen circulation and screening is done through a pulse oximetry test. About 2,000 babies are born with the condition each year, up to 400 whom die in infancy. State testing policies vary and a difference-in-difference analysis was used to determine the effect of state policies that require hospitals to conduct infant screening for CCHD, not on the effects of hospital screening. The approach is similar to pre/post evaluation design in which data are collected before and after a policy or intervention has been implemented and comparing those two sets of data. Time series statistical methods are used to look, not at a single group, but at many points in time to conduct a multiple regression analysis to control for other factors that could account for variations. He pointed out that this method is often used to evaluate economic policies. The method assumes that the pre-policy trend is similar in areas where the policy was adopted and in those that did not and drew on birth-linked-to-death data collected by the National Center for Health Statistics covering 2007 through 2013 for infants from 24 hours after birth through 6 months of age. The data were grouped by state of birth and month/year.

The researchers also classified state mandatory and non-mandatory screening policies, including states in which mandatory policies had been adopted but not implemented and voluntary screenings. They then used the Poisson regression model of the numbers of deaths in a given cohort, took the natural logarithm of that number and adjusted it for state factors and regression analysis. A cost effectiveness analysis the CDC did (published in 2013) to determine the implications of CCHD being added to the RUSP in 2011, revealed that screening 4 million infants per year would prevent 20 deaths at a cost savings of $40,000 per life-year saved. Universal screening would prevent more than 120 deaths from recognized CCHD per year and 117 deaths from other CHD. States that implemented mandated screenings reported one-third fewer CCHD deaths than states that had not and other CHD deaths dropped by a fifth (21 percent). Non-mandatory screening had no statistically significant effect [association with CCHD deaths]. Dr. Gross noted there are more deaths from CHD than from CCHD. Dr. Grosse noted two limitations to the study: the small amount of time during which mandates were in effect and the lack of access to information on actual screening practices. Because data were not collected from hospitals that were screening in states that didn't mandate it, this was a conservative analysis.

Dr. Oster, who, in addition to his position at Emory University, is a medical officer in the CDC's National Center on Birth Defects and Developmental Disabilities, provided a clinical perspective of the concerns, challenges and opportunities CCHD screening poses. He explained that clinicians have questioned the need for the screening, pointing out that many cases were already being identified prenatally and just after birth through the newborn physical exam and hospitals were concerned about how to pay for it. He worked with Elizabeth Ailes and others at the CDC to explore these issues, starting with a literature review, which revealed that about a third of CCHD cases are identified without screening but this represents a range of from 5 percent to 56 percent. After birth, 40 percent are detected in a timely fashion but 30 percent risk late detection. He and the CDC researchers he worked with determined that pulse oximetry would identify half of infants who would otherwise be missed — about 900 cases — but an additional 800 to 900 might be missed through false negative results. Most of these cases would involve anomalous pulmonary veins, which are difficult to detect prenatally and during the first 24 hours after birth. Other factors include malfunctioning or improper use of equipment, algorithm misinterpretation, and the lack of availability or ability to correctly perform an echocardiography. The need to adapt to special settings — high-altitude environments, for example, which decrease oxygen saturation levels or out-of-hospital births — is challenging as well. He noted that a group in Pennsylvania refers to the screen as hypoxemia screening rather than CCHD when talking to midwives, which improves acceptance because this indicates that it picks up other conditions as well. Some states are looking into how to incorporate the screen in the neonatal intensive care unit.

Dr. Oster also collected data that identified 1,800 algorithms that incorporate various results but he and other CDC researchers found that doing one saturation of 94 percent or 95 percent in the foot yields a similar sensitivity across all algorithms, but it will increase the false positive rate as well. He also noted that the screen's sensitivity is relatively low at 50 percent to 75 percent but adding other testing tools brings the rate to 85 percent. He pointed out that sensitivity is affected by the timing of the test, differences in the flow across the patent ductus arteriosus, how it changes and disease severity.

The question also arose of how necessary it is to perform two repeat screens of children with low or indeterminate saturation rates rather than ruling poor results a fail after the first repeat screens are performed. It was determined that it would decrease the false positive rate and remaining fail results could indicate another cause of hypoxia, such as pneumonia, hypertension, pneumothorax, sepsis or other complication. This led the group to issue new guidance to clinicians instructing them to prioritize

additional evaluation and testing in accordance with the conditions that are most relevant to the case; such evaluation should not be delayed until after an echocardiogram has been done. The child should not be discharged until the cause of desaturation is identified or at least until potentially life-threatening conditions have been excluded. He also noted that an echocardiogram may not be necessary if a cause other than CCHD is identified so that there is no delay in treatment until after the echo is performed.

As Dr. Grosse noted in his presentation, the screen has proved to be cost effective and this triggered the question, if the state does not pay for it who would? But Dr. Oster found that hospitals that are doing the screen are including it as one component of standard newborn care — it is not being charged separately, although additional testing is charged separately. Concern was also expressed that adding the screen would burden the medical system, in part by delaying discharges and trigger concern from families but, through talks with nurses and pediatricians, Dr. Oster learned that parents are amenable to the test and his team worked with doctors to come up with a protocol that if the child doesn't appear symptomatic, follow-up tests do not have to be done immediately — in the middle of the night, for example — but can wait until the next day. He also reported that the test has not been burdensome to hospitals.

He also expressed concern that physicians might rely on screening to replace the current standard of care rather than viewing it as an additional step and referred to a letter to the editor in a journal that called for the American Academy of Pediatrics to require nurseries to document on each discharge summary cardiac conditions that were ruled out through a negative screen. He and several CDC clinicians wrote a response indicating that until a screening test for CCHD has close to 100 percent sensitivity, pulse oximetry should not preclude or replace routine clinical exams to detect the condition.

A. Discussion

Ms. Scott asked whether there is anything the Committee can do to help improve hospitals' collection of this type of newborn screening data. Dr. Oster said that a number of states are documenting when screening is done and some record pass or fail results but these can be misinterpreted. Those that collect number values do improve quality and can provide hospitals with feedback regarding interpretation and to help improve existing algorithms. Hospitals that have added pulse oximetry screening with values and outcomes on birth certificates have been the leaders in data collection. Dr. Grosse noted that the CDC held a "Beyond the Blood Spot" Public Health Grand Rounds about point-of-care newborns screening for hearing and CCHD; those presentations are archived on the CDC's website. It was noted that, unlike CCHD, there are many resources to support public health department surveillance of early hearing detection and intervention.

Ms. Wicklund asked what state-specific factors were integrated into the regression and how they were determined. Dr. Grosse said that the effects consisted of any factor that remained constant over time and controlled by a state-fixed dummy variable. Time-variable factors were included as well such as unemployment rate and demographic birth composition although those factors did not explain much.

Dr. Parisi asked whether clinicians' increased awareness of CHD in newborns may have contributed to earlier detection and Dr. Grosse confirmed that he believed this was a relevant factor and said that there has been a sharp decline in CHD-related infant deaths in recent years. Ms. Saarinen reported that the CDC estimated 4.2 percent of all neonatal deaths are attributed to CHD.

Dr. Watson noted that work is underway to identify genes associated with CHD and deletion 22 [DiGeorge syndrome or 22q11 deletion] has been mentioned as a possible candidate and wondered whether there are others. Dr. Oster said that that one is among the most common; others include trisomy 21 with AV canal for CCHD and it is one researchers look for, but others are more multifactorial or rare.

Ms. Saarinen asked whether the Committee can examine and recommend possible process improvements such as modifying a cutoff or a protocol for point-of-care screening. Dr. Bocchini confirmed that the Committee or a working group could evaluate the current status quo to see what is needed. Dr. Kelm said that such efforts in the past lead to the formation of other work groups that enlisted outside expertise (one example were States that used tyrosine instead of succinylacetone as a marker for tyrosinemia type 1). However, those workgroups have been relatively rare. Dr. Brosco mentioned that the Follow-up and Treatment Workgroup is also looking for projects. .

XII. New Business

In response to Dr. Bocchini's request for any new agenda items to bring up or cover during future meetings, Dr. Baker said that APHL is hosting an in-person meeting on SCID next week. This meeting will discuss the long-term follow up of SCID cases with immunologists that transplant those kids and the people that screen and diagnose those kids. She suggested that at the November meeting the Committee could hear a report of the APHL meeting. Dr. Bocchini concluded by reminding Committee members that they will soon receive ACHDNC's annual report to Congress for review and comment.

XIII. Adjournment

Dr. Bocchini thanked all of the participants for their involvement and adjourned the meeting.

The next meeting will be held on November 8-9, 2017, at HRSA headquarters in Rockville, Md.