Advisory Committee on Heritable Disorders in Newborns and Children

Summary of Eighth Meeting
February 9, 2017
The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) meeting was convened on Thursday, February 9, 2017, and adjourned on that day. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

COMMITTEE MEMBERS

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

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

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

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

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

**Stephen McDonough, M.D.**  
Retired Pediatrician

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

**Annamarie Saarinen**  
Co-founder, CEO  
Newborn Foundation

**Beth Tarini, M.D., M.S., 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 and Quality**  
Kamila B. Mistry, Ph.D., M.P.H.  
Senior Advisor  
Child Health and Quality Improvement

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

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

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

**Food and Drug Administration**  
Kellie B. Kelm, Ph.D.  
Chief, Cardio-Renal Diagnostic Devices Branch, Division of Chemistry and Toxicology Devices, Office of In Vitro Diagnostic Devices Evaluation & Safety
DESIGNATED FEDERAL OFFICIAL
Debi Sarkar, M.P.H.
Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau

ORGANIZATIONAL REPRESENTATIVES –

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

American Academy of Pediatrics
Robert A. Saul, M.D.
Medical Director, General Pediatrics
Children’s Hospital, Greenville Health System

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

American College of Obstetricians & Gynecologists
Joseph R. Biggio Jr., M.D.
Professor and Vice-Chair
Director, Division of Maternal Fetal Medicine
University of Alabama at Birmingham

Association of Maternal & Child Health Programs
Kate Tullis, Ph.D.
Family Health and Systems Management
Delaware Division of Public Health

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

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

Department of Defense
Adam Kanis, M.D.
Department of Pediatrics
MCHK-PE Tripler Army Medical Center
Honolulu, HI

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

March of Dimes
Edward R.B. McCabe, M.D., Ph.D.
Senior Vice President & Medical Director
March of Dimes

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

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

I. Administrative Business — February 9, 2017 ................................................................. 3  
   A. Welcome and Roll Call.................................................................................................. 3  
   B. Opening Remarks ..................................................................................................... 4  

II. U.S. Government Accountability Office Report — Newborn Screening Timeliness .... 4  
   A. Discussion .................................................................................................................. 6  

III. Public Comment .......................................................................................................... 6  
   A. Noreen Murphy, Batten Disease Support & Research Association: Needs for families in  
      rare disease and the NCLs ....................................................................................... 6  
   B. Amy Medina, SMA (spinal muscular atrophy) Community and Cure SMA: Recent  
      developments with respect to SMA and the importance of adding it to the Recommended  
      Uniform Screening Panel (RUSP) ............................................................................. 7  
   C. Kristin Stephenson: Muscular Dystrophy Association, Recent developments in the  
      therapeutic space for SMA and impact on the need for newborn screening .............. 7  
   D. Annie Kennedy: The Parent Project Muscular Dystrophy (PPMD), Duchenne Muscular  
      Dystrophy therapeutic approvals update and the Newborn Screening Infrastructure update . 8  
   E. Jessica Wade: Lack of uniformity of U.S. newborn screening programs .................... 8  
   F. Kim Tuminello, Heidi Wallis, Jerry Robinson, Beth Robinson, Jenny Wolf, Association  
      for Creatine Deficiencies (ACD) and newborn screening for guanidinoacetate  
      methyltransferase (GAMT) ....................................................................................... 9  
   G. Dr. Thomas Crawford, co-director of the MDA Clinic for Neuromuscular Disorders at  
      Johns Hopkins Medicine: Potential for substantial clinical benefit from early presymptomatic  
      identification of newborns and children with SMA .................................................. 9  

IV. Newborn Screening Cutoffs and Algorithms —Panel Presentation ............................ 10  
   A. Discussion ................................................................................................................ 15  

V. National Contingency Plan for Newborn Screening ...................................................... 16  
   A. Discussion ................................................................................................................ 18  

VI. Medical Foods for Inborn Errors and Metabolism: Issues in Patient Access and  
    Recommendations for Improvement ............................................................................ 18  
   A. Discussion ................................................................................................................ 20  

VII. Education and Training Workgroup Update .............................................................. 21
VIII. Laboratory Standards and Procedures Workgroup Update .................................................. 22
    A. Discussion ....................................................................................................................... 23
IX. Follow-Up and Treatment Workgroup Update ................................................................. 23
X. Future Topics..................................................................................................................... 24
XI. Adjournment ................................................................................................................... 25
I Administrative Business — February 9, 2017

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

A. Welcome and Roll Call

Dr. Joseph Bocchini welcomed participants to the February 2017 meeting of the Advisory Committee on Heritable Disorders in Newborns and Children (Committee) and took roll. The Committee members and ex-officio members who were present were:

- Dr. Don Bailey
- Dr. Mei Baker
- Dr. Colleen Boyle (ex-officio member, Centers for Disease Control and Prevention—CDC)
- Dr. Jeffrey Brosco
- Dr. Kellie Kelm (ex-officio member, Food and Drug Administration—FDA)
- Dr. Fred Lorey
- Dr. Michael Lu (ex-officio member, Health Resources and Services Administration—HRSA)
- Dr. Dietrich Matern
- Dr. Stephen McDonough
- 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
- Catherine Wicklund
- Debi Sarkar (Designated Federal Official)

*Dr. Beth Tarini was not present.

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. Joseph Biggio (morning only)
- Association of Maternal & Child Health Programs, Kate Tullis (morning only)
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Christopher Kus (afternoon only)
- Genetic Alliance, Jackie Seisman (attending for Natasha Bonhomme) (morning only)
- March of Dimes, Dr. Siobhan Dolan (attending for Dr. Edward McCabe)
- National Society of Genetic Counselors, Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Carole Greene

*Dr. Robert Saul from the American Academy of Pediatrics and Dr. Adam Kanis from the Department of Defense were not present.
B. Opening Remarks

Dr. Bocchini welcomed new work group members who were selected for, accepted assignments to and are now participating in the following three work groups: Education and Training, Follow-Up and Treatment, and Laboratory Standards and Procedures.

Two separate sets of votes were taken on whether to accept meeting minutes for the November 2016 and August 2016 meeting minutes (the minutes from the August meeting had not been available previously due to a technical glitch). No Committee members had additional changes to make to the minutes. By roll call vote, the August 2016 minutes, as corrected ahead of time, were approved unanimously. By roll call vote, the November 2016 minutes, as corrected ahead of time, were approved unanimously.

The Committee will hold three additional meetings in 2017:

- May 11-12
- August 3-4
- November 8-9

Meeting dates have been set through 2020 and are available on the Committee’s website: https://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/upcomingmeetings.html.

Dr. Bocchini listed the topics that would be covered during the webinar, one of which is a presentation by a panel covering newborn screening cutoffs and algorithms. This presentation is designed to provide the Committee with an initial overview of how laboratories set cutoffs and establish reference ranges, how newborn screening lab results are interpreted and how screening results are conveyed to providers. The discussion, which is designed to help the Committee to begin examining issues that are not related to cutoffs and algorithms, will be continued during the May 2016 meeting.

Ms. Sarkar provided a standard reminder on the Committee’s advisory role and related ethics issues. She asked that Committee members check with her or Dr. Bocchini before agreeing to media interviews. She also 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. U.S. Government Accountability Office Report — Newborn Screening Timeliness

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

Dr. Bocchini reviewed the report, a copy of which was included in the Committee’s briefing book. He explained that the Newborn Screening Saves Lives Reauthorization Act of 2014 stipulates that timeliness is an explicit goal for Health Resources and Services Administration
(HRSA)-supported newborn screening programs and that the law calls on Government Accountability Office (GAO) to review the timeliness of such screenings. The report examines what is known about the timeliness of newborn screenings and reviews the barriers that contribute to screening delays and strategies to address those barriers. The resources GAO used to develop its report are the Committee’s time frame goals, an August 2016 report by HRSA’s Newborn Screening Technical Assistance Evaluation Program (NewSTEPs), which contains data from 38 states collected from 2012 through 2015, and the results of a 2014 survey the Committee conducted. GAO also conducted interviews with Committee members, NewSTEPs leadership and sources from several states and used other relevant documents.

GAO’s review was based on and contains recommendations the Committee sent to then-U.S. Department of Health and Human Services (HHS) Secretary Sylvia Burwell on April 16, 2015, which called for newborn screening systems to complete all newborn screening tests within seven days of life and report to the newborn’s health care provider:

- presumptive positive results for time-critical conditions immediately but no later than five days of life;
- presumptive positive for all other conditions as soon as possible but no later than seven days of life; and
- all newborn screening test results as soon as possible.

To achieve these goals, the specimen should be collected within 48 hours after birth and received by the laboratory as soon as possible, ideally within 24 hours of collection. The Committee also encouraged states to monitor their progress in meeting these goals and to make results available to providers and the public.

GAO found that most states reporting 2015 timeliness data to NewSTEPs failed to meet the Committee’s 95 percent benchmark for reporting presumptive positive results for time-critical conditions within five days and for reporting these results for all conditions within seven days. However, most states showed improvement in completing the screening process over the three-year period.

The GAO report noted three significant barriers to compliance that were identified in reports submitted to NewSTEPs and in response to the Committee’s survey: (1) lack of awareness of the importance of timely screening on the part of those who collect and submit specimens; (2) limited access to couriers to transport specimens; and (3) insufficient laboratory hours.

The report also describes reporting and performance limitations. Only 38 states submitted data. This is concerning because missing data and variations in data collection could prevent a full analysis of timeliness trends. It was noted that states had only nine months after the Committee developed its recommendations to make the changes necessary for states to meet the guidelines.

The NewSTEPs 360 project (the result of a competitive funding opportunity to support state newborn screening programs to improve timeliness) will help states improve reporting timeliness
by standardizing data definitions and continuing and improving data collections, in part by involving all
states, if possible, and presenting an update during the Committee’s August 2017 meeting.

A Discussion

Dr. Tanksley said that the recommendation that labs receive specimens within 24 hours of
collection can be logistically impossible, even when the lab is open seven days a week because
the timing of multiple steps — the birth and the collection, courier pickup and delivery of the
specimen — must line up perfectly to achieve this desired result. Dr. Bocchini acknowledged
these challenges and said that the Laboratory Standards and Procedures Workgroup can
consider as it reviews the data how these obstacles could be minimized and whether the issue
needs to be addressed specifically in the Committee’s recommendations.

III. Public Comment

A. Noreen Murphy, Batten Disease Support & Research Association: Needs for
families in rare disease and the Neuronal Ceroid Lipofuscinoses (NCLs)

Ms. Murphy discussed the Batten Disease Support & Research Association’s perspective on the
need for early and rapid tests for newborn children. She explained that Batten disease is a rare
childhood lysosomal storage disorder that can trigger seizures an impairment in basic motor
skills including eating and swallowing, cognitive decline, and is the primary cause of dementia in
children. In some of the 14 forms of the disease, children progress normally until the age of 3
when they develop unprovoked seizures and language development delay after which they
decline for the next two years. The condition causes loss of independent function, resulting in
the need for gastrostomy (G) tubes, suctioning, and the development of sleep disturbance,
dysautonomia and other difficulties.

As is true of many children with rare diseases, efforts to diagnose the cause of the declines
associated with this condition are lengthy, expensive and often lead to multiple misdiagnoses
— as many as 32 have been reported. This lack of understanding about the disease can cause
parents to wonder what types of decline their children may manifest from one day to the next.
The association has learned through experience and patient surveys that earlier, correct
diagnoses through newborn screening and the appearance of new, effective treatments for
Batten and other rare diseases can reduce the trauma and treatment expense and early loss of
life while helping parents to adjust to the “new normal.” Newborn screening and even
pregestational testing, which is not yet available, would also allow parents to plan their families
with more safety. Some have lost up to four children to the disease because it was not
diagnosed in the first child until their siblings were born. However, human clinical trials of
treatments for Batten are available, and those who are diagnosed and then enrolled early in life
are most likely to have few symptoms. Those who have developed neurological damage are
least likely to recover fully. Correct diagnoses also allow parents to attend conferences and join
a community of those who are dealing with the disease, which can help combat isolation,
depression and the feeling of disconnectedness that those affected feel when surrounded by families who don’t face this challenge. These effects contribute to physical and mental illness that can affect all family members, especially siblings of Batten sufferers who don’t have the disease.

Dr. Bocchini thanked Ms. Murphy for her observations and asked that she provide the parent survey to the Committee so that it could use the information it has been used to collect; she agreed to do so.

A. Amy Medina, SMA (spinal muscular atrophy) Community and Cure SMA: Recent developments with respect to SMA and the importance of adding it to the Recommended Uniform Screening Panel (RUSP)

Ms. Medina began by explaining that her sons, age 1 and 5, have SMA, which is the leading genetic cause of infant death. She called for newborn screening to detect the disease and said that there have been significant advances in drug development to treat it, culminating in the Dec. 26, 2016, U.S. Food and Drug Administration (FDA) approval of Spinraza to treat motor weakness. She noted that early drug intervention improves the drug’s efficacy and said that studies of infants who received this treatment reached more motor milestones than did those who had already developed SMA symptoms. She noted that her first son, Mateo, showed signs of SMA at birth, such as lack of crying and rapid breathing but was not diagnosed until he was one month old and was expected to die before the age of two. Thanks to the support of a physician who was willing to help the family deal with the disease, including tracheal surgery and many hospital stays within the first seven months of his life. Mateo has reached the age of 5, but his mobility is slight, consisting of minor foot movement and an upturning of one side of his mouth to indicate a smile.

Ms. Medina reported that her second son, Javier, began receiving Spinraza 12 days after birth and can sit up, move by rolling over, stand with assistance, eat food by mouth and vocalize. He does not require breathing support, has been able to withstand a cold without hospitalization and can sleep on his stomach, which is rare for children with SMA. On behalf of the SMA community, Ms. Medina urged the Committee to consider a forthcoming SMA screening nomination with an emphasis on the availability of an SMA treatment, noting the success of the technology to screen for the disease and the demonstrated benefits of early screening. Dr. Bocchini thanked Ms. Medina for her presentation and said the Committee looks forward to receiving the SMA nomination packet.

B. Kristin Stephenson: Muscular Dystrophy Association, Recent developments in the therapeutic space for SMA and impact on the need for newborn screening

Ms. Stephenson is vice president of policy and advocacy for the Muscular Dystrophy Association. She said that, in addition to FDA approval of Spinraza, multiple therapies and clinical trials exist to treat SMA, and others are being developed. She noted that SMA screening pilot programs have been conducted in Taiwan and New York, each of which involved
treatment of at least one SMA-positive, asymptomatic infant. Both pilots were successful, and it is possible to predict who will develop SMA through a DNA test, which detects babies who lack both copies of SMN1 and are, therefore, highly likely to develop the most severe, infantile onset form of the disease, which can also surface in adults born without SMN1. She asked that SMA be added to the RUSP.

C. Annie Kennedy: The Parent Project Muscular Dystrophy (PPMD), Duchenne Muscular Dystrophy therapeutic approvals update and the Newborn Screening Infrastructure update

Ms. Kennedy said she is representing PPMD and Dr. Michele Puryear and Dr. Jerry Mendell, who have been helping to lead the National Duchenne Muscular Dystrophy newborn screening efforts. She reported that Exondys 51, a disease-modifying therapy that targets the underlying cause of Duchenne. Exondys 51 works by triggering a skipping of the targeted DNA section Exon 51 and is estimated to benefit about 13 percent of the Duchenne population. The product sponsor is working to conduct trials involving patients under the age of four and another Duchenne-specific product is under review. She also pointed out that steroids are an off-label treatment for the disease for patients as young as three years old and in some cases, even younger. Currently, U.S. patients typically are prescribed prednisone, while non-U.S. patients have access to deflazacort. Ms. Kennedy said that because the two drugs have different safety profiles, U.S. providers and patients are seeking the option to use deflazacort, which, marketed as Emflaza, is not mutation-specific and could be a treatment option for all Duchenne patients.

Meanwhile, commercial efforts are underway to develop a refined screening test for Duchenne in partnership with the California Department of Health Newborn Screening Program, using newborn screening residual blood spot specimens from the California Biobank. PPMD is conducting a study of female carriers, by, for example, teaming up with Nationwide Children’s in Ohio to study 500 women across a range of ages, demographics and phenotypes. PPMD also is working with a variety of registries and through a memorandum of understanding is exploring data integration and applicable resources that are available through the Newborn Screening Translational Research Network.

D. Jessica Wade: Lack of uniformity of U.S. newborn screening programs

Ms. Wade, who is from Michigan, has two sons with congenital hypothyroidism: Micah, age 8 and Eli, age 4. Micah, whose development is at about a 5-year-old’s level, does not speak, cannot go to the bathroom unattended and requires 24-hour supervision, while Eli is meeting all of his development milestones. Ms. Wade explained that states’ cutoffs for this condition vary. Michigan’s lab cutoff for the disease is a thyroid stimulating hormone (TSH) value of 33, which is considered borderline, but because Micah’s was 30, he was not rescreened and his pediatrician did not receive his lab results. Eli’s TSH value was 35, leading to rescreening and early diagnosis and treatment. Ms. Wade believes that the trigger for conducting uniform newborn screening for congenital hypothyroidism should be consistent nationwide.
Dr. Bocchini thanked Ms. Wade for her comments and pointed out that the Committee planned to discuss current lab practices for cutoffs later that day.

**E. Kim Tuminello, Heidi Wallis, Jerry Robinson, Beth Robinson, Jenny Wolf, Association for Creatine Deficiencies (ACD) and newborn screening for guanidinoacetate methyltransferase (GAMT)**

Ms. Tuminello explained that ACD represents families that are coping with GAMT, including those who will need patient support group assistance for children who were diagnosed too late to receive timely diagnosis and treatment. ACD was shocked that because of newly added criteria, GAMT was not moved to the Evidence Review Workgroup in November. Ms. Wallis said that families in support groups describe seeing their children miss milestones and are incorrectly diagnosed with autism. She stressed that GAMT is quite treatable and, if addressed early, can allow children to live normal lives.

Mr. Robinson has three children, two of whom were diagnosed with GAMT: Ben at age 6 and Celia at age 1. Ben underwent many procedures, tests and hospital stays in attempts to diagnose the cause of his seizures. He has low muscle tone, is nonverbal and chokes on his food, which can require CPR. He must also be put under general anesthesia to receive dental care and, at age 13, is still learning toileting skills; he will require life-long care. Celia, who was diagnosed early is now at a developmental level commensurate with her peers although she receives medication through a G tube.

Jenny Wolf has twin sons who were not diagnosed with GAMT until age 6, despite developmental delays that were incorrectly diagnosed as autism by physicians, including specialists, at multiple medical centers. She and her husband paid for full genome testing to arrive at the proper diagnosis.

**F. Dean Suhr: MLD Foundation RUSP Roundtable update**

Mr. Suhr reported that the MLD Foundation, which represents families throughout the world dealing with metachromatic leukodystrophy (MLD), held the third day-long meeting it sponsors for the MLD community in Rockville, MD, in August 2016; an informal gathering of representatives from several dozen newborn screening working groups and forums. He asked permission to provide summaries of the deliberations and the work these groups are doing at a later date. Dr. Bocchini said the Committee will figure out the best way for this information to be conveyed.

**G. Dr. Thomas Crawford, co-director of the MDA Clinic for Neuromuscular Disorders at Johns Hopkins Medicine: Potential for substantial clinical benefit from early presymptomatic identification of newborns and children with SMA**

Dr. Crawford pointed out that the drug FDA has approved for treatment of SMA is indicated for patients of all ages and with all types of the disease and stressed the need for early diagnosis. He said that 25 children are being treated presymptomatically for SMA using a protocol called
Nurture, which singles out children whose siblings died of the disease. All who have been treated are responding well to it, Crawford reported. They are able to stand and walk, and the magnitude of delay in symptoms also has increased. He said the protocol can identify people with a high level of specificity and sensitivity. Dr. Crawford said SMA is a high priority project for the RUSP.

IV. Newborn Screening Cutoffs and Algorithms —Panel Presentation

*Michele Caggana,* Sc.D., F.A.C.M.G.
*Director, Newborn Screening Program*
*New York State Department of Health*

*John Thompson,* Ph.D., M.P.H., M.P.A.
*Director, Newborn Screening Program*
*Washington State Newborn Screening Program*

*Carol Johnson*
*Iowa Newborn Screening Program*
*University of Iowa*
*Department of Pediatrics*

Dr. Caggana outlined the laboratories’ perspectives on newborn screening and cutoff determinations. She explained that, as clinical laboratories, newborn screening programs are subject to the Clinical Laboratory Improvement Amendments (CLIA) of 1998, which are federal regulatory standards that apply to all clinical laboratory testing that is conducted in the United States except for clinical trials and basic research. The Centers for Medicare and Medicaid Services (CMS) promulgates these standards and issues laboratory certificates, conducts inspections and enforces regulatory compliance. The Centers for Disease Control and Prevention (CDC) supports clinical laboratory testing by providing analysis research and technical assistance, developing technical standards and lab practice guidelines, conducting lab quality improvement studies and monitoring proficiency testing practices. CDC also manages CLIA’s advisory committee, CLIAC. FDA categorizes tests based on their complexity, reviews requests for waivers and develops rules and guidance for categorizing CLIA-regulated tests.

Dr. Caggana explained that New York laboratories are CLIA-exempt but they, and other labs that accept samples collected in New York, must hold a New York permit and must meet standards that are as or more stringent than CLIA rules.

New York’s newborn screening programs also can seek various types of accreditation, which involve meeting the standards set by the accrediting organization, which conducts site visits to ensure lab quality. Labs also must adhere to good laboratory practices, the best known of which are set by the College of American Pathologists (CAP). Other organizations publish guidance on how to practice good laboratory science, such as the Clinical Laboratory Standards Institute and the American College for Medical Genetics and Genomics.
Dr. Caggana listed several well-known definitions. Fixed cutoff refers to a fixed number and a predetermined point at which an analytical result is deemed to be a positive or negative screen. The number can be revised and can incorporate baby-specific factors. A floating cutoff is applied to an analytical result that can be affected by environmental factors such as season or temperature. In such cases, because the population mean isn’t stable over time due to seasonal variation, tests that fall within a certain range would be sent off for more testing; one example would be measurement of immunoreactive trypsinogen (IRT) to test for cystic fibrosis. Specimens with IRT results in the top 5 percent of the population would be sent for molecular testing. An algorithm is a type of flow chart that outlines the various decision points for determining whether to recommend for or against a diagnostic evaluation and follow-up, which takes into account a baby’s health and laboratory components.

Retests of specimens are conducted when an infant has an out-of-range result to see if there are any errors or specimen-specific variation that warrant concern. Borderline results are slightly out of range, which generally leads to a request for collection of a second specimen. This specimen usually is collected by the physician or the hospital of birth and does not require specialist notification. However, two borderline results can lead to a referral. Repeat testing involves collection of a second specimen after a borderline result, rather than the retesting of the first specimen and may involve either testing for only the analyte that was out of range or of the entire panel.

A second-tier or reflex test refers to a test different from the first that is conducted on the initial specimen in-house before results are reported to reduce the number of referrals; the results are not reported to the medical community unless an analyte is found to be extremely out of range or due to other extenuating circumstances.

Confirmatory testing is outside the purview of newborn screening. It is conducted after a positive result to such a screening occurs, during the follow-up, clinical and diagnostic evaluation period and could consist, for example, of a molecular analysis of a freshly collected sample that is sent to a diagnostic laboratory or an enzyme analysis using a different specimen type, such as skin.

Dr. Caggana stressed that newborn screening is not diagnostic; it is a risk assessment of specimens collected from asymptomatic infants who usually do not have family histories of genetic disease. Screening is done to spot, among an entire population, infants who are at highest risk for certain conditions; it focuses on the entire population and takes all comers. Diagnostic testing focuses on the individual infant or family that that may be sick.

She also pointed out that newborn screening is a high throughput program in which the entire spectrum of disease is identified, which yields results that range from classic to so mild that an abnormal biochemical result may not equate to a recognizable clinical phenotype. She cautioned that screening tests should never be used as the basis for a clinical diagnosis; infants that are found to be at risk must undergo confirmatory testing. The values used are set to allow follow-up as a way of minimizing the number of false negative results and many infants are culled for extra evaluation. Unlike diagnostic tests, screening programs expect and accept some false positives; efforts are made to minimize them; however, that is impossible if the number of missed infants increases.

Newborn screening programs also rely on the medical community to inform them about an infant with a diagnosis that the lab did not report to the provider. Conversely, the screening lab should instruct the
physician to conduct confirmatory testing on any infant with symptoms that could involve that condition.

Dr. Caggana pointed out that variations in follow-up tests can muddy the waters when it comes to obtaining results and that the provider's clinical experience often determines whether abnormal results are followed up. She mentioned other variables that could affect test results. A repeat test may not be conducted by the same lab that conducted the initial one, which can be problematic because follow-up tests can differ from one lab to the other; and different labs may use different cutoffs for a single analyte. Other factors that can affect results are the types of instruments used and when the test was conducted. The equipment and the algorithms used must be tested to provide the same result over time. Finally, clinicians can manage results based on other factors, such as a patient’s medical condition or their complaints. In short, screening is simple on one level but complex on others.

When conducting population-based screening and establishing cutoffs, test validation must take into account differences in infants caused by gestational age, birthweight, feeding — the timing and amount of which can be influenced by physician-ordered tests — and transfusion status. Other factors that must be considered include treatment for underlying medical conditions and maternal health, as well as the infant's race and ethnicity. Obtaining accurate information from the birthing hospital can be a challenge, which can affect the lab’s turnaround time for information gathering after the specimen is received.

Statistical analysis of the population also is conducted to determine what the cutoff values should be, followed by continuous quality improvement to assess new technologies, newly available analytes and feedback from the community.

Dr. Caggana pointed out that the Clinical Laboratory Standards Institute, or CLSI, has published guidance on regulatory requirements for test validation and CAP has a similar list for laboratories to follow.

She advises labs to set conservative cutoffs and to conduct tests in a high throughput way to search for rare conditions among what could be 99-plus-percent negative result. Redundant equipment must be in place, high-quality reagents must be available consistently and when considering the validation of a new test, factors that should be accounted for include the composition of a state’s population and temperature fluctuations, which extends to the time of year the test is being conducted.

Due to privacy concerns, parents must authorize the use of specimens from infants with conditions for test development and validation. Positive controls also are needed, but those for rare conditions are often hard to obtain, especially in states with low birth rates or have rules about specimen storage and destruction. In New York, gaining parental consent involves institutional review board submission and approval. Dr. Caggana stressed that this is important because, although adult samples are easier to obtain, they are not the same as newborn screening samples; it is necessary to get specimens from known newborn carriers and factor the results into the cutoff establishment process.

Both CDC’s Newborn Screening Quality Assurance Program and NewSTEPs help to achieve quality improvement and timeliness, and NewSTEPs acts as a portal for community members to share lessons learned.

Dr. Caggana concluded by saying that physicians need to be educated about what newborn screening can and cannot do and be reminded to assess a sick child as though it had never been screened and to provide as much information as possible in medical records, which can include analyte values. Labs also can work together to standardize how new tests are validated to devise a schema that is acceptable to
all states and create a forum to share continuous quality improvement efforts. Labs also should be informed when a newborn screening does not detect a positive case; reliable data collection from the medical community is very important to capture this information. Finally, all cases must be defined in the same way.

Dr. Thompson discussed the interpretation of newborn screening results. He said that clear and consistent communication among laboratories, follow-up programs and clinical consultants is critical. He stressed that both false-negative and false-positive tests can have a severe effect on families and the medical system.

He defined several terms. A test’s sensitivity is its ability to detect a condition; a test’s specificity is the test’s ability to determine whether a baby does not have the condition. A test’s positive predictive value refers to the percentage of babies who are referred for diagnostic testing because they have a positive screen and are then diagnosed with the screened condition. Most screenings involve measuring the extent to which a biochemical marker is elevated or low in affected babies to determine the natural distribution of these analytes. He pointed out that, ideally, a comparison of the distribution of the markers between patients with the biochemical disorders and unaffected babies would completely separate the two groups but some degree of overlap usually occurs. As a result, establishing a cutoff to rule out any false positive results for a condition would lead to a certain percentage of undetected cases while a cutoff designed to catch every baby with the condition would yield a percentage of false positive results. Lab and follow-up work are needed to devise cutoff algorithms, which are schemes to stratify results, based on their predictive value. Dr. Thompson also pointed out that follow-up in anticipation of a potentially urgent positive result does not have to be delayed until all test results are available. He said that his staff may contact a pediatrician about such a result while a retest on the original sample is being conducted to permit the initiation of clinical care if the baby is symptomatic.

Dr. Thompson noted that no standard set of terminology exists to describe newborn screening results. Normal results can be described as “normal,” “within normal range,” “within normal limits,” “negative” or “passing.” Results that are not normal may be referred to as “abnormal,” “out of range,” “equivocal,” “indeterminate” or “positive.” Abnormal results are stratified into presumptive positives, which require diagnostic testing, and borderline results, which require a follow-up newborn screen. Some conditions are stratified into even more precise categories.

The establishment of a new test may have a conservative cutoff — for example, the cutoff value for normal in screening biotinidase deficiency in 2004 was evidence of more than 30 percent enzyme activity. Due to a high false-positive rate over the first five years of testing, the cutoff to indicate normal was changed to 20 percent enzyme activity. Data are conducted longitudinally to determine how the test is performing and guidance from clinical experts and data analysis are used to improve cutoff schemes.

He noted that various factors can affect test results. For example, the results of some tests can be affected by therapies that may be administered to premature or sick infants. In addition, research has shown that age of the baby when blood is collected as well as the infant status and specimen handling factors that Dr. Caggana described in her presentation can affect results.

Several resources are available to assist in interpreting newborn screening results. Funding from HRSA and CDC and other organizations such as the Association of Public Health Laboratories (APHL), the National Newborn Screening and Global Resource Center (NNSGRC), among others, have supported
learning in this area. Two collaborative newborn screening information databases also exist. The Mayo Clinic has developed Region 4 Stork (R4S) database, which is mentioned in the Milwaukee Journal Sentinel newspaper articles in the Committee’s briefing book, the APHL-administered Newborn Screening Data Repository and NewSTEPs. Many states also maintain databases or spreadsheets to monitor trends in newborn screening results. Clinical specialists publish case studies in medical literature and newborn screening programs reach out to experts for help.

Dr. Thompson thanked the federal government, nonprofit organizations and parent advocacy groups for providing support to improve newborn screening. He added, however, that many newborn screening programs continue to face challenges in interpreting newborn screening results and establishing and refining cutoffs. These include the lack of technical expertise to perform complex data analysis, lack of manpower to record confirmed cases in databases, technical challenges and disagreement between clinical specialists.

Ms. Johnson discussed how newborn screening results are communicated to primary care providers (PCP). Providers may also receive recommendations to obtain a repeat screen due to poor sample quality, to get a post-transfusion sample or to follow up on a borderline, indeterminate or presumptive positive result. False positive results are also reported to PCPs and, in some states, carrier or trait status is conveyed as well. If a baby with a presumptive positive result needs to see a specialist, the PCP will participate in the discussion.

Newborn screening programs communicate with PCPs by mail, fax, email, orally and/or through web portals, and the method can be based on the program’s infrastructure constraints. The mode of communication used often is based on the urgency of findings. Follow-up staff will call the PCP to report a time-critical disorder and possibly for a borderline result. Newborn screening staff will typically not contact the PCP when a screening test is normal.

Ms. Johnson noted various reasons for miscommunication about screening results. The variety of communication methods — and ways in which information may be conveyed to the provider — can cause confusion. Errors or incomplete information can filter through if it is conveyed to a provider’s staff member because the physician is unavailable or when the result is entered into a medical record. The variety of terms that can be used to describe a result — ranging from a number or reference ranges to words or phrases, such as “within normal limits” or “borderline indeterminate” also can cause confusion. Providers may need to be reminded that the screening is not a diagnostic test and advised when follow-up testing is needed. Because most of the disorders newborns are screened for are rare, providers’ understanding of them may vary. In the hospital setting, a hospitalist or attending physician may order or receive screening results back before they have even met that patient, which can cause confusion as well.

Communication between newborn screening program staff and the PCP will often take the form of discussions and can be supported with written recommendations and educational materials that explain results and provide more information about the disorder. In some cases, the discussion may involve a laboratory representative, specialist or medical director.

Ms. Johnson went on to discuss the challenges of explaining newborn screening results to parents, which is typically conducted by the PCP but may be done by potentially less-knowledgeable clinic staff. Failure to use consistent terminology, fully explain a disease to parents or give them specific instructions on what to do next can confuse and worry them. Educational materials should be made available to parents. The PCP should encourage parents to read them.
A Discussion

Dr. Matern asked why Dr. Caggana did not mention the R4S database — as Dr. Thompson had in passing — and the Collaborative Laboratory Integrated Reports (CLIR), used by the Mayo Clinic. Dr. Caggana said that her program uploads normal data into the R4S system and uses it to compare cutoffs and reference ranges between programs. She stressed that there needs to be uniformity in the data that are entered, along with cases and case definitions between databases. Dr. Matern said the briefing book contains a paper that addresses this issue.

Ms. Seisman asked Dr. Caggana what mechanisms could be developed for educating physicians about the benefits and limitations of newborn screening. Dr. Caggana said that many states have written materials on newborn screening and specific conditions for parents. The New York Department of Health has posted information for providers on its website but it can be challenging to get people to read it and determine what additional information is needed. She reiterated that using proper terminology to differentiate between a newborn screening test as opposed to a diagnostic test is key. She suggested using social media and working with marketing professionals to craft effective messages.

Dr. Boyle asked how cutoffs are established from state to state — whether the examples Dr. Caggana provided from New York and Dr. Thompson from Washington are representative of what other states are doing. Dr. Thompson said he believes the approach varies from one state to another. Some states expend considerable resources to establish cutoffs and make state- or region-specific modifications and some use FDA-developed kits and follow the manufacturer’s recommendations closely.

Dr. Caggana agreed and said that it would be advantageous to examine different algorithms and their performance in different states, possibly through a committee. She noted that her state has made changes to several algorithms over time.

Dr. Greene said that using anecdotal examples to illustrate why accurate, consistent terminology helps to prevent confusion and allay unnecessary concern is the best way to encourage its adoption among clinical staff. Families can contribute stories and the American College of Medical Genetics and Genomics is developing a tool that may include communication recommendations. She also asked why states need to use state-specific cutoffs.

Dr. Caggana explained that race, ethnicity and other factors in people’s backgrounds can be predictors for some conditions; cutoffs need to work for the entire state.

Dr. Kelm mentioned that she learned through reviewing work done on many newborn screening assays reviewed by FDA that many do not specify cutoffs. FDA acknowledges that most states determine and validate their own cutoffs.

Dr. Matern pointed out that ethnicity is often not tied to a particular region; people move across state lines, which makes a disease range cutoff more useful than having a cutoff that
applies to a presumed ethnic background for a population in a single state. He also said that the metabolite profile for a disease should be examined rather than single analytes.

Dr. Caggana said that, when validating a new test, up to 20,000 or more specimens are tested before a cutoff value is established. Factors considered include people who are already affected, along with prematurity, birthweight and reported false-positive rates. She noted that it can be difficult to adjust a cutoff for very rare diseases. Retrospective and prospective data need to be considered as well. New York does not have race- or ethnic-specific cutoff, although some states probably do, but New York does adjust for migration.

Dr. Thompson noted that introducing new standards and controls, equipment and testing kits, along with changes in analyte trends can make it difficult to establishing one cutoff for all states.

Dr. Bocchini suggested that because states approach these issues in various ways, the Committee might play a role in proposing best practices. He noted that existing repositories or other tools could be used more effectively to examine data and improve performance. He noted that the Education and Training Committee Workgroup could examine ways to improve communication and education of clinicians about the differences between screening and diagnostic tests. He proposed that attendees consider what was discussed to devise what the Laboratory Standards and Procedures Workgroup or another group could contribute.

Dr. Parisi suggested considering examples of states’ use of R4S or CLIR tools to improve their disease ranges. Dr. Bocchini said that this could be a topic for the May meeting.

V National Contingency Plan for Newborn Screening

Kate Taft, M.P.H.
Associate Director for Child and Adolescent Health, Association of Maternal and Child Health Programs

Ms. Taft explained that emergency contingency planning helps to ensure the availability of critical resources, continuity of operations and in setting standards for organizations that help to activate the plan. Adhering to established standards and maintain continuity of testing and follow-up procedures are essential in screening, diagnosing, referring patients and treating diseases identified through newborn screening, especially during public health emergencies.

She pointed out that APHL established a subcommittee of its Newborn Screening and Genetics in Public Health Committee in 2004 to develop a framework to help public health laboratories prepare for and respond to natural and manmade disasters and shortages of testing materials and supplies. In 2005, Hurricanes Katrina and Rita destroyed the Louisiana State Public Health Laboratory and prevented the state from performing newborn bloodspot screening, which highlighted the need for a national contingency plan. With the help of the Emergency
Management Assistance Compact, the Iowa Public Health Newborn Screening Laboratory was able to take over screening Louisiana’s newborns.

The Newborn Screening Saves Lives Act of 2008, directed by CDC, HRSA and state agencies, helped to develop the National Newborn Screening Contingency Plan (CONPLAN). Published in 2010, the plan can be used to by one or more states or a region during a public health emergency or interruption in services. The plan contributed to preparedness for and recovery from the effects of Hurricane Sandy in New Jersey and New York in 2012. The 2014 reauthorization of the Newborn Screening Saves Lives Act called for the plan to be updated at least every five years and that effort is underway.

HRSA and the HRSA-funded Regional Genetic and Newborn Screening Service Collaboratives, their national screening center and APHL also launched a process to create regional newborn screening emergency preparedness plans. They have also provided a mandate for emergency preparedness for all state newborn screening programs.

In 2015, the Association of Maternal and Child Health Programs (AMCHP) partnered with CDC, HRSA, APHL and expert stakeholders to provide updates to the CONPLAN, with funding from the March of Dimes and CDC. Updates to the plan include a focus on addressing gaps in laboratory, clinical and long-term follow-up, addressing point-of-care screenings and incorporating an emphasis on family engagement. In both this and the earlier version of the plan, variations in the availability of state resources were considered. The above-mentioned agencies worked closely with an expert advisory committee that included a broad range of public health department representatives, health care specialists, families and consumer representatives and national organizations and partners

CONPLAN revisions and recommendations were developed through June of 2016 and included calls and an in-person meeting with the expert advisory committee to solicit feedback and a public comment survey. The expert advisory committee approved the final set of document revisions and submitted to it CDC and HRSA in June and it is undergoing federal internal review for potential release by March 2017.

Ms. Taft provided a high-level overview of the recommended revisions. Among the proposed changes to the plan’s strategic objectives are new communications objectives and the movement of these and family education objectives to the top of the document to reflect that these should be the first steps to consider in contingency planning for newborn screening programs. The document’s responsibilities matrix was updated; it outlines strategic objectives, supporting activities and lists which state or federal organizations would be responsible for the objectives. Appendices also were added, including a contingency planning checklist and a resource list of articles and state examples of tools and templates states have used in their contingency planning or emergency response to ensure comprehensive, uninterrupted newborn screening. Ms. Taft pointed out that states can use the material in the appendices in their work and can also update them independently and as needed rather than going through a formal plan revision.
Ms. Taft mentioned several efforts to educate stakeholders about the CONPLAN revisions. AMCHP plans to host a workshop during its annual conference in March 6 in Kansas City, Mo., to provide an update on the plan, potentially release it in draft form to members and discuss how Title V agency families can work with their newborn screening partners to ensure comprehensive newborn screening planning in states and communities. An APHL symposium, which will be held in September 2017, will hold focus sessions on emergency preparedness for newborn screening laboratories and a dissemination plan has been developed to publicize the plan when it is released.

A. Discussion

Dr. Bocchini thanked Ms. Taft for her presentation and said that the Committee would be happy to help disseminate the plan and help expedite its incorporation into state newborn screening programs.

Mr. Watson pointed out that, outside the state screening component, the issue of preparedness was not addressed in the current version of the CONPLAN, which makes it difficult to do contingency planning. He asked whether such gaps still exist. Ms. Taft said that this is an area that she hopes will be strengthened in the revised plan by incorporation of the Emergency Management Assistance Compact into the document and she hopes that newborn screening will routinely be included in state emergency preparedness planning; she noted that this will be focused on during some sessions at the APHL symposium.

Dr. Greene asked, in the event of a disaster, how children with conditions that need treatment such as phenylketonuria (PKU) and methylmalonic acidemia will continue to receive it; in other words, how records, medication and access will be provided where they are needed. Ms. Taft explained that the language the Committee members strengthened in the document ensures that the planning elements include follow-up care and services, including receipt of multi-disciplinary care through an established medical home and establishing a mechanism to track displaced populations.

VI. Medical Foods for Inborn Errors and Metabolism: Issues in Patient Access and Recommendations for Improvement

*Sue Berry, M.D.*, Member, Follow-Up and Treatment Workgroup, Medical Foods Subgroup

Dr. Bocchini explained that the Committee tasked the Follow-Up and Treatment Workgroup to develop a white paper to indicate issues that need to be addressed in connection with providing medical foods to infants whose inborn errors of metabolism (IEM) are detectable through newborn screening.
Dr. Berry explained that the workgroup has held two meetings on this subject and that the medical foods subgroup has met monthly. The in-progress draft the workgroup is preparing on medical foods was included in the briefing book to invite Committee feedback. The workgroup also has prepared a two-pager that briefly describes this issue. She noted that the Orphan Drug Amendments of 1998 defines medical foods as foods that are specially modified or processed for consumption or enteral administration under a physician’s supervision for specific dietary management of a disease or condition for which distinct nutritional requirements, based on scientific principles, are established by medical evaluation and that they are not classified as drugs. Drugs are used to diagnose, cure, mitigate, treat or prevent disease. By contrast, medical foods are designed for patients who have limited capacity to ingest, absorb, digest or metabolize ordinary food or nutrients and do not involve modification of the normal diet alone. The definition also indicates that they are agents or dietary elements that cannot be obtained by conventional means (e.g., purchased at a grocery store). Dr. Berry pointed out that FDA issued final language in 2016 that clarified draft guidance to indicate that medical foods are specially formulated and processed—not naturally occurring—and are designed for partial or exclusive feeding, orally or by tube.

Dr. Berry explained that the workgroup was asked to provide a policy analysis brief that summarizes the state of current coverage for medical foods and previous work on this done by the Committee as well as non-Committee efforts to improve this coverage. The document will be a preliminary report; the workgroup hopes to present an action statement during a future Committee meeting.

Dr. Berry noted that inherited metabolic diseases are included on the RUSP because effective interventions are available, including medical foods. She explained that the issue of varying levels of health care coverage needed to access these foods was raised in May 2008 when the Committee sent a letter to the secretary of HHS that recommended ways to address coverage gaps and offer reimbursement to families purchasing medical food. The Committee recommended that the Medicaid program be amended to ensure that state programs provide uniform coverage. The Secretary responded by saying that the agency was unable to pursue the matter because it does not have the power to enact legislation. Dr. Berry pointed out that the Committee was not necessarily requesting legislative action; in any case, no action was taken. A year later, the Committee suggested during a discussion of health care reform in connection with the Affordable Care Act that such reform should ensure that access to medical foods and foods modified to reduce the amount of protein they contain is provided to those who need it, regardless of the source of health care coverage. The Secretary declined the request, until more information about this topic, which is being studied, is available. Seeing no further action on this issue, the Committee decided to move forward and has several reports and presentations on this topic.

She noted that laws or programs can cause access to foods to vary from one state to another. For example, coverage may vary by age—the cost of medical foods may be covered for babies and children with newborn screened conditions but not for adults. Health insurance laws, which also vary by state, may provide this support for some conditions but not for others.
Dr. Berry reported that the American Medical Association, the American College of Medical Genetics and Genomics, the Society for Inherited Metabolic Diseases and the American Academy of Family Physicians and Genetic Metabolic Dieticians International are among the organizations that have called for coverage of medical foods but, although supporting legislation has been introduced, it has yet to pass. A lack of clarity over what aspects of the issue should be addressed by federal or state regulations and ambiguities over the status of medical foods and their regulation has resulted in inaction, she explained.

The workgroup has drafted a policy recommendation for the Committee to consider endorsing that would stipulate that “Medical foods, which require ongoing medical supervision whereby dietary intervention cannot be achieved by modification of a normal diet alone, and that are authorized by a medical provider for management of an IEM, should be considered medical benefits and be included in coverage as essential health care services. Affected persons should have access to these essential interventions irrespective of the source of their health coverage. The Department of Health and Human Services (HHS) regulations should ensure that individuals of all ages who are diagnosed with an IEM, either specified on the RUSP or identified clinically, should be able to access comprehensive coverage for care of their disorder. Medical foods must be considered to be a covered medical benefit as part of essential health services for patients with inherited metabolic disease. HHS regulations should ensure that this coverage would apply irrespective of the beneficiary’s age, source of health care coverage or whether the condition is specified on the RUSP or identified clinically.”

Dr. Berry said that one option could be to ask the HHS Secretary to include coverage for medical foods in the programs it oversees, such as Medicare, Medicaid, the Children’s Health Insurance Program (CHIP) and the Indian Health Service, which, by setting an example, could encourage change in other programs. The workgroup recommends convening a meeting of stakeholders to achieve expeditious achievement of this goal, starting with suggestions during this meeting of who should convene the meeting.

A. Discussion

Dr. Bocchini asked for discussion of the current draft of the white paper, suggestions on how to complete it and whether, efforts to move the issue further should involve a third recommendation to the HHS Secretary or another approach entirely.

Ms. Wicklund suggested that including major third-party payers and representatives from CMS in the type of meeting Dr. Berry proposed could be useful.

Dr. Greene pointed out that CMS has said that medical foods falls under FDA’s purview while the FDA has said it falls under CMS’s, which is another reason to bring representatives from both agencies together to discuss it; however, this does not address the issue of coverage.

Dr. Kus pointed out that, Medicaid coverage is decided on a state-by-state basis; therefore, HHS would not be able to influence coverage at this level. Dr. Berry suggested that CMS could make recommendations to states on how to handle coverage for medical foods. She also noted that
many Medicaid programs are outsourcing CHIP and pediatric coverage to the private sector, which could encourage private payer participation.

Dr. Boyle said that reaching out to the Association of State Medicaid Directors could be a means of establishing best practices in this area.

Dr. Bocchini encouraged the Committee, as it reviews the white paper draft, to provide feedback to Dr. Berry and the subgroup or through Ms. Sarkar.

VII. Education and Training Workgroup Update

_Catherine Wicklund, M.S. CGC, Chair_

Ms. Wicklund began by discussing the workgroup’s current projects, the first of which is the creation of a tool that PCPs could use to discuss out-of-range and positive newborn screening results with parents. The group decided to draw on findings from a study conducted to determine what types of information parents of infants with positive screens would find useful and asked Genetic Alliance to work with ACMG to incorporate this information into ACMG ACTion (ACT) sheets or as a separate but linked document. Because the group subsequently learned that many steps would be involved in this approach, the workgroup decided to pursue a parallel path by developing its own provider-to-parent communication tool. A small group of Workgroup members is working on this project and will seek input from PCPs.

Ms. Wicklund went on to discuss the workgroup’s educational outreach projects, the first of which involves developing a matrix of relevant stakeholders and topics that stakeholders need to understand about newborn screening. The resulting matrix covers a broad range of topics and indicates which of seven sets of potential stakeholders might find each topic relevant. Examples of topics/stakeholders range from benefits of screening and what screenings should be done, when and how, both of which could be shared among all stakeholders, to the importance of newborn screening for public and state health, which might be of most use to pediatricians and well-baby care providers.

In the course of this work, a question arose: Should the discussion focus only on current newborn screening activities or on the potential movement into the age of molecular medicine, such as return-of-carrier results in genomic sequencing be discussed as well? The workgroup decided that both topics might merit a broader discussion with the Committee. The next step will be to determine how to use this outreach approach. It was suggested that it could be used to apply it to existing educational resources to fill gaps, which might inform future work and education; the question of how to disseminate this information arose as well.

The workgroup’s next project focused on how to use workgroup members’ organizational relationships to encourage submission of educational materials to the newborn screening clearinghouse. Natasha Bonhomme of Genetic Alliance is putting together a summary of the project for committee members to disseminate to their relevant professional organizations,
and Cate Walsh Vockley will work with Genetic Alliance and the National Society of Genetic Counselors to find the best way to reach genetic counselors in this organization and both will connect with dieticians to figure out how to reach this group.

Ms. Wicklund also stressed the need, especially in the absence of the former Timeliness Workgroup, to continue to monitor timeliness education and it was suggested that phlebotomists might benefit from additional education in this area although it has been difficult to find a specific professional group to target.

The workgroup also plans to check with Committee members who attended the NewSTEPs 360 meeting in November to identify educational or training opportunities this in which it could participate.

**VIII. Laboratory Standards and Procedures Workgroup Update**

_**Kellie Kelm, Ph.D. Chair**  
**Susan Tanksley, Ph.D., Co-Chair**_

Dr. Kelm explained that, during a call the workgroup held a week before this meeting, most of the time was spent listening to an oral presentation on implementing screening for lysosomal storage disorders and x-linked adrenoleukodystrophy (X-ALD) and some of the difficulties involved in implementing screening and meeting timeliness goals. The group also discussed California’s experience using the R4S tool.

Dr. Kelm reiterated the timeframes for communicating newborn screening results to providers that Dr. Bocchini outlined in his presentation on GAO’s report on newborn screening timeliness earlier in the meeting. She also noted that using couriers has helped states improve specimen transit time, although, for many, this is still a challenge and improvement is still needed in the timeliness of hospital submissions. She said that a major logistical challenge to timeliness that was described earlier — the difficulty in aligning the timing of collection, pickup and delivery — can be compounded by the fact that it takes two to four hours for the specimen to dry before it can be shipped. Holidays can delay shipping by courier as well. She also noted that that some testing methods take longer than others, which affects timeliness as well.

With this in mind, it was suggested that the workgroup could examine recent timeliness data and use them as a basis for asking the Committee to consider alternate timeliness goals. Examples could include developing a measure that takes into account the age of the baby when a specimen is received, rather than the current timeliness goal. It was also suggested that different timeliness goals be set for different conditions that account for those that are more or less time critical. Finally, establishing a network of state labs to conduct second-tier tests for regional screening labs, which would allow states to work together to get these tests done.

Next, Dr. Kelm discussed a study California and representatives from the Mayo Clinic conducted involving a retrospective analysis of samples and screening results produced through use of the
R4S tool. The results showed a decrease in the false positive rate from .5 percent to .02 percent with no false negatives.

Dr. Kelm mentioned several other topics the workgroup may wish to explore. One involves an examination of the infrastructure and services state labs use to conduct safe newborn screening by talking to them to see, for example, which are implementing X-ALD screening and how that is progressing and other timeliness issues.

The workgroup also may wish to review more recent data NewSTEPs has received and examine efforts that data states submit are more uniform, along with new screens that are being performed to see whether these developments might inform recommendations the Committee has already made.

Finally, the workgroup also could consider efforts to ensure that the various databases such as NewSTEPs and R4S are using the same case definitions to improve data analysis.

A. Discussion

Dr. Matern suggested that, given the previous discussions about cutoffs and Dr. Parisi’s suggestion that a study of how states use R4S and CLIR tools to improve their disease ranges might be useful, an examination of Pompe versus X-ALD screening could also be a future topic of discussion. With this in mind, he suggested that new workgroup member, Dr. Tricia Hall from Emory University, provide an update on a pilot study she is conducting using Pompe and MPS1 in Georgia. Dr. Bocchini said the Committee should consider that suggestion and, if there is consensus, ask the workgroup to pursue it.

IX. Follow-Up and Treatment Workgroup Update

Stephen McDonough, M.D., Chair
Alan Zuckerman, M.D., Member, Quality Measures Subgroup

Dr. McDonough listed new workgroup members and the members of the Medical Foods subgroup, whose work Dr. Berry reported on earlier, and members of the Quality Measures subgroup.

Dr. Zuckerman’s presentation explains why the workgroup is examining quality measures, which he described as standardized assessment tools that are an essential first step in conducting quality assessment activities or designing decision tools. They typically consist of ratios, such as the percentage of children with sickle cell disease who are prescribed penicillin. Each measure expresses a specific definition of quality or a goal for care. Some quality measures are subsets of comprehensive research databases, such as the Newborn Screening Translational Research Network’s Longitudinal Pediatric Data Resource. They are used to add to existing knowledge and their collection requires informed consent and often duplicate entry.
He explained that quality assessment improvement is part of routine care, can be embedded in electronic medical records and eliminates the need for separate data entry or chart review. New standards permit the development of electronic definitions and measurement reporting of quality measures that can be shared across states. Of major interest is the fact that quality measures must be used and reported to maintain certification for participation in incentive programs, which creates an opportunity to apply them to long-term follow-up newborn screening.

Dr. Zuckerman pointed out that the Committee has been working on long-term follow-up, which emphasizes the need for quality chronic disease management, condition-specific treatment and age-appropriate preventive care. It also contributes to continuous quality improvement through the medical home and evaluation of data related to care and outcomes.

During its initial six months of work, the subgroup learned that three types of quality measures can be applied to long-term follow-up of newborn screening. The most familiar one is disease-specific measures, which involve tracking process and physiologic outcomes. There are also post-screening public health services to connect children with conditions to necessary care, including those that may be provided outside the newborn screening program. Finally, there are child-specific measures of wellbeing, including access to medical homes and services. Dr. Zuckerman explained that these three sets of quality measures often overlap. For example, consumer advocacy groups often go to consumers to collect disease-specific measures.

The subgroup has also been collecting case studies to illustrate the value and feasibility of using quality measures for follow-up of newborn screening and to reveal barriers that need to be overcome. For example, the subgroup learned a lot from the work the National Quality Forum did to certify early hearing detection and intervention measures. The development of sickle cell measures has uncovered barriers to initiating preventive care. Comparing best practices in centers of excellence has dramatically improved care of patients with cystic fibrosis and an electronic health record-embedded checklist for medium-chain acyl-CoA dehydrogenase deficiency (MCAD) in mountain states has helped to identify gaps in care and alert providers to emergencies involving children with special needs. Finally, the National Survey of Children with Special Health Care Needs reveals gaps in access to medical homes and state health departments are applying some of the questions in this survey to their populations.

The subgroup hopes to deliver a final report on its work in August and hopes to enlist the Committee’s help in promoting quality measures to ensure long-term follow-up of newborn screening.

X. Future Topics

Dr. Bocchini pointed out that several potential future topics the Committee could discuss during the next meeting already had been identified. The first was Dr. Matern’s suggestion and that an examination of Pompe and X-ALD screening could also be a future topic of discussion and Dr. Parisi’s suggestion that examples of states’ use of R4S or CLIR tools to improve their disease
ranges could be considered by the Committee as well. The Committee also may take up the question the Education and Training Workgroup raised regarding whether educational outreach efforts should focus only on current newborn screening activities or also on potential breakthroughs in molecular medicine, such as return-of-carrier results in genomic sequencing.

Dr. Brosco asked whether there is a mechanism for removing conditions from the RUSP. Dr. Bocchini said that this has been filed as a future topic for the Committee to discuss or a workgroup may be asked to examine how to do this most efficiently and effectively.

**XI. Adjournment**

Dr. Bocchini thanked all of the participants for their involvement and said a number of important topics were discussed that have the potential to move forward in an effective way. He then adjourned the meeting.

The next meeting will be an in-person, two-day meeting and will be held May 11-12, 2017, at HRSA headquarters in Rockville, Md.