

**Advisory Committee on Heritable Disorders in  
Newborns and Children**

**Summary of Ninth Meeting  
May 11-12, 2017**

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) meeting was convened on Thursday, May 11 and Friday, May 12, 2017, and adjourned on May 12. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

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## I. Administrative Business — May 11-12, 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 ninth 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. Baker was not present at roll call but joined the meeting soon thereafter)
- Dr. Diana Bianchi (ex-officio member, National Institutes of Health—NIH )
- Dr. Bocchini
- Dr. Jeffrey Brosco
- Dr. Carla Cuthbert (attending for ex-officio member Dr. Coleen Boyle, Centers for Disease Control and Prevention —CDC)
- 
- Dr. Kelly 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)
- Annamarie Saarinen
- Dr. Beth Tarini
- Catharine Wicklund
- Dr. Catharine Riley (Acting Designated Federal Official, attending for Debi Sarkar, Designated Federal Official)

Organizational Representatives present were:

- American Academy of Family Physicians, Dr. Robert Ostrander
- American Academy of Pediatrics, Dr. Robert Saul
- American College of Medical Genetics, Dr. Michael Watson
- Association of Maternal and Child Health Programs, Dr. Kate Tullis
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State and Territorial Health Officials, Dr. Christopher 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

\*American College of Obstetricians & Gynecologists—Dr. Britton Rink, attended day 2 of the meeting.

## **B. Opening Remarks**

Dr. Bocchini introduced and described the professional background of two new organizational representatives. Dr. Siobhan Dolan is professor and vice chair for research in the Department of Obstetrics and Gynecology and Women’s Health at Albert Einstein College of Medicine at Montefiore Medical Center in the Bronx and medical advisor to March of Dimes. Her research interests focus on the integration of genetics into maternal/child health. Dr. Britton Rink is director of Perinatal Genetics at the Mount Carmel Health System in Columbus, Ohio, is dual board certified, and maintains a practice in both maternal-fetal medicine and genetics. She served on the ACHDNC for several years, most recently as vice chair and has a particular focus on prenatal diagnosis, advanced fetal imaging, fetal therapy and recurrent pregnancy loss. Dr. Bocchini thanked both of them for participating in the meeting.

## **C. Vote on February 2017 Meeting Minutes**

A vote was taken on whether to accept meeting minutes for the February 2017 minutes, which, Dr. Bocchini noted, now include some typographical changes and clarifications to address Committee members’ questions. By roll call vote, the minutes were approved by all Committee members except for Dr. Baker who had not yet joined the meeting.

The Committee will hold two additional meetings in 2017

- August 3-4
- November 8-9

## **D. Additional Remarks**

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 first day of the meeting.

Dr. Riley, standing in for Ms. Sarkar who is on maternity leave, 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. 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.

## I. R4S and CLIR —Interactive Web Tools

**Piero Rinaldo, M.D., Ph.D.**

*Professor of Laboratory Medicine, Director, Biochemical Genetics Laboratory  
Mayo Clinic*

Dr. Rinaldo explained that the Region 4 Stork (R4S) laboratory performance database is a post-analytical tool that was initiated as a publicly funded laboratory quality improvement project that is intended to expand newborn screening through the use of tandem mass spectrometry (MS/MS). It was initially introduced in seven states' newborn screening programs. R4S was selected in 2004 as one of three priority projects of the Regional Genetics Collaborative Program funded by the Health Resources and Services Administration (HRSA). In May 2012, the R4S database became part of the Newborn Screening Translational Research Network (NBSTRN), which is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

R4S is used exclusively to conduct newborn screening through MS/MS and is limited to the first specimen. The system is being used by 258 sites in 68 countries, 1,227 users have an active password. In 2016, an average of 72 people logged in per day, 335 per month (27 percent). Those who logged in that year used it extensively — 88 million times for 17 million newborns. However, efforts to expand R4S's use for other applications, such as severe combined immunodeficiency (SCID), biotinidase deficiency and MS/MS have not been overwhelmingly successful because a limited number of people asked to serve as curators and few content experts opted to participate. For this and other reasons, R4S is not conducive to use in pilot studies of new conditions.

Collaborative Laboratory Integrated Reports (CLIR) is second-generation multivariate data recognition software developed by the Mayo Clinic with the collaboration of Oslo University Hospital in Norway and the California Department of Health. The software was released in 2005 and has been modified several times; the most current version was released in April 2017. Dr. Rinaldo noted that use of R4S is based on outdated (2013) code, which Microsoft may ultimately stop supporting, whereas CLIR is using 2017 code.

Like R4S, CLIR is used for newborn screening through MS/MS for any specimen up to 1 year of age; as a result, repeat specimens can be used as well. But CLIR differs from R4S in that it replaces traditional cutoff values with continuously adjusted data to account for age, and other multivariate reference ranges displayed in percentile charts. The ranges are derived through retrospective analysis of up to hundreds of thousands of data points collected from a growing, global community of collaborators. It enhances the clinical usefulness of individual markers by factoring in all possible ratio permutations and replaces sequential algorithms ("AND") with tool-based parallel algorithms ("OR"). And, unlike R4S, which uses cumulative percentiles — processed, manipulated but uncurated data, which are cumbersome to collect — CLIR uses raw data, which is easy to upload and are verified by a curator. Another advantage of CLIR is that it can be used to create site-specific panels and, therefore, an application can be customized to meet a state's needs, in part because IT professionals manage and supervise its testing.

CLIR is being used at 57 sites in 34 countries, including 13 U.S. states. To date there are 275 users with an active password. Of the more than 100 other applications—newborn screening in diagnostic laboratories and biochemical genetic research—enough data have been collected to make 39 of these

applications clinically relevant. Dr. Rinaldo stressed that CLIR is ideal for use in pilot studies involving new conditions that are being considered for addition to the Recommended Uniform Screening Panel (RUSP).

Dr. Rinaldo noted that anyone who is in any way affiliated with a newborn screening program (e.g., medical residents/fellows, advocates) can request free access to both R4S and CLIR although CLIR users are expected to contribute data to the system.

He provided a performance comparison of R4S and CLIR, noting that last year in Minnesota, R4S yielded a false positive rate of 0.024 percent, whereas the first 14 months using CLIR for three lysosomal disorders yielded a 0.0015 percent false positive rate. CLIR has not yielded any false positives for the small number of babies within the Mayo Clinic system that were tested for the three conditions that were recently added to the RUSP: mucopolysaccharidosis, adrenoleukodystrophy (ALD) and Pompe disease. Dr. Rinaldo said he believes a false-positive rate of near zero can be achieved using CLIR.

## **A. Discussion**

Dr. Baker asked whether a threshold was built into CLIR. Dr. Rinaldo explained that it depends on what CLIR is being used for. For lysosomal disorders, results that fall just above or below normal move to the next step: use of the dual scatter plot. Anything higher than zero is moved to the next level of evaluation, which eliminates up to 99 percent of false positives and the remainder are evaluated through second tier tests. He noted that results reflect a highly conservative definition of the term “false positive.” He also explained that there is a three-level evaluation process: an initial, single-condition tool that answers the question “yes” or “no.” A possible yes is assigned to a result with even one marker that falls slightly out of the covariate-adjusted reference range. The second tool makes a differential diagnosis between true and false positive and the third level is the second tier test, which the CLIR development team is trying to develop for every condition for which a test is available.

Dr. Greene asked whether R4S and CLIR uses case definitions to determine whether a result has accurately been identified as false positive or false negative. Dr. Rinaldo said that the approach depends on the type of condition. A true positive for lysosomal disorders must involve a known and verified pathogenic genotype, for example. But this underscores the need for curators. If a biochemical phenotype is not consistent with the current definition and verifying information is not provided by the submitter, those cases are removed.

## **II. CDC’s Newborn Screening QA/QC Program**

***Carla Cuthbert, Ph.D., FACMG, FCCMG***

*Chief, Newborn Screening and Molecular Biology (NSMBB) Branch, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC)*

Dr. Cuthbert provided an overview of how the NSMBB branch works with state programs to ensure the analytic validity and usefulness of screening tests and provide quality control and test materials to evaluate the performance of new screening tools. The CDC is authorized to fill these roles through the

Newborn Screening Saves Lives Reauthorization Act of 2014. The specific goal is to ensure early and accurate detection of newborn conditions through blood spot testing; this is carried out by five teams of up to 50 scientists and other technical experts.

The CDC's Newborn Screening Quality Assurance Program (NSQAP) has been in existence for about 35 years and is intended to sustain and strengthen existing quality assurance programs and services for newborn screening laboratories. It helps to implement such programs, provides technical assistance for recent and anticipated additions to the RUSP and works to improve public health laboratories' ability to detect inherited newborn disorders through molecular screening methods. The program also supports newborn screening initiatives by working with federal, state and other interested partners.

The program provides comprehensive quality assurance materials world-wide, which cover proficiency testing, method development, training and consultation and performs data review for a program's current screening and for screens a program is introducing. NSQAP also does filter paper evaluation to monitor performance of new commercial lots. Vendors voluntarily send their materials to NSQAP, which evaluates them and sends each vendor a report.

Dr. Cuthbert explained that NSQAP's role is educational, not regulatory; no penalties are assigned to false negative or false positive results. The goal is to work with state programs to reduce patient testing errors by monitoring test method performance with an emphasis on conducting a set amount of quality control testing with each test run and providing supplementary materials. It also provides some funding for state programs to implement newborn screening.

Proficiency testing, which all screening and diagnostic laboratories must undergo, involves monitoring laboratory performance using simulated patient samples. NSQAP has quality assurance material programs for every condition on the RUSP and is close to seeing 1 million dried blood spots produced and certified annually, all in-house. The testing consists of three challenges of five-blind-coded specimens per year and, as a rule, 80 percent consensus must be achieved for a specimen to be graded. NSQAP maintains an online reporting system. Unexpected results, which could be caused by transcription errors or techniques will trigger a visit by a subject matter expert or scientist to the state program to improve methods. The branch works closely with the Association for Public Health Laboratories (APHL) on many of its projects. More than 650 laboratories participated in 2016 and 78 countries have been represented from 2006 to 2016; other countries are being encouraged to develop quality assurance programs and materials of their own.

Dr. Cuthbert encouraged anyone who is considering nominating a condition to the RUSP to contact the CDC to ensure that methods and quality assurance materials are developed to cover that condition. NSQAP has methods for lysosomal disorders, X-ALD, guanidinoacetate methyltransferase deficiency and spinal muscular atrophy. A biochemical assay for Duchenne Muscular Dystrophy is ready and work is being done on molecular testing.

Dr. Cuthbert mentioned that a mass spectrometry course NSQAP offered attracted 30 applicants and, to make this course more available, her program has contracted with the Society for Inherited Metabolic Diseases to create 10 online training modules for newborn screening professionals. NSQAP offers a training course in various types of molecular assays and other activities and has developed a molecular assessment program, which consists of a group of expert peers who visit laboratories to assess their activities and issue a report. NSQAP is considering applications to support sequencing implementation

as well. She urged attendees to visit the molecular resource page on APHL's website, which provides various resources for state programs.

In terms of new initiatives, NSQAP has three molecular repository programs to obtain unique patient specimens and is collaborating with universities on this effort. The program is also studying ways to develop and validate DNA sequencing and large deletion reference methods and has a cooperative agreement with the state of New York to develop sequencing technologies for genes associated with SCID.

## **A. Discussion**

Dr. Watson pointed out that, traditionally, molecular testing involving variant interpretation associated with clinical phenotypes has been done by diagnostic laboratories, which have training and licensing requirements for their directors. However, of late newborn screening laboratories are starting to move into a pseudo-diagnostic role with sequencing, leading to a lack of uniformity in what testing is being performed in what setting. Dr. Cuthbert said this issue had been raised at a meeting on newborn screening sequencing NSQAP held with APHL, led by the Newborn Screening Molecular Subcommittee and it was noted that not every newborn screening laboratory has access to molecular geneticists to assist with interpretation. She noted that this topic would be discussed at a breakout session later in the day.

## **III. Identifying and Following up on Out of Range and Borderline Results—State Perspectives – Panel Presentations**

***Michele Caggana, Sc.D., FACMG***

*Director, Newborn Screening Program*

*New York State Department of Health*

***Scott Shone, Ph.D.***

*Research Scientist/Program Manager*

*New Jersey Department of Health Newborn Screening*

***Amy Gaviglio, M.S., CGC***

*Follow-Up Supervisor/Genetic Counselor*

*Minnesota Department of Health Newborn Screening Program*

Dr. Caggana began by discussing her laboratory's approach to screening, validation and cutoffs for SCID. She pointed out that there are multiple case definitions for SCID, ranging from three types of severe combined immunodeficiency disorder, various types of T-cell lymphopenia and syndromes with an immunodeficiency component. Her department used about 6,400 specimens and worked over nine months to develop an assay and, over seven years of development, the algorithm used has changed several times. She stressed that this DNA test is used, not to diagnose but to assess risk without considering clinical information about the subjects.

Initially, all babies with fewer than 200 T-cell receptor excision circles (TREC) were referred, leading to two referrals per day statewide. Subsequent examination of the data led to the laboratory's reducing the cutoff to 125 TRECs, partly in response to adjustments such as ruling out cases involving failed

amplification, reducing extraction time and performing primer redesign when necessary. As a result, the number of referrals dropped by 90 percent, the positive predictive value for SCID exclusively rose by 5 percent and a policy was instituted that infants with no TRECs in triplicate on the assay are referred, regardless of gestational age.

Dr. Caggana went on to discuss Krabbe disease, a deficiency in the lysosomal enzyme that causes demyelination and damage to the central and peripheral nervous system. The infantile form has quick onset and leads to death by two years of age. The state screened 157,000 samples over about three-quarters of a year before the screen went live in August 2006 and after examining various cutoffs is using a floating cutoff that does not take into account strict enzyme activity alone because there is seasonal fluctuation in activity. Testing to rule out the presence of non-disease-causing polymorphisms was instituted as well to reduce the referral rate and as well as resequencing of the entire gene. Dr. Caggana's team settled on a cutoff of 10 percent of the daily mean, which was later raised to 12 percent; any result below that goes for DNA testing; results with one or more mutations are referred. A proof of principle study has shown that elevated psychosine levels are a good indicator for Krabbe disease, and could be used as a biomarker after an enzyme test has been conducted. Since then, the algorithm used to detect Krabbe has been used with changes to test for Pompe disease.

Dr. Caggana pointed out that the laboratory has been sending Krabbe and Pompe screening data to CLIR, which runs it through a three-plex, single condition tool that produces a score, which assesses whether the patient has a positive or negative screen and can retest for six enzymes. The data is then again analyzed by CLIR using a seven-plex tool that takes into account birthweight and gestational age. This in turn produces a score that is used in the assessment. Any results that are indeterminate are sent for second-tier testing.

She provided an example of results of analysis using CLIR. Among four months' worth of population data her team uploaded there were 33 babies who required second-tier DNA analysis. Twenty of those were for Krabbe, and 15 were for Pompe. Twenty-one infants were referred for follow-up diagnostic testing. Eight were for Krabbe and 13 for Pompe. All of the eight infants that were referred for Krabbe were negative, and nine of the 13 cases were false positive. Using the CLIR tools, 10 of those would have required DNA rather than the original 21 and the CLIR tool was able to detect all the possible Pompe cases that were put in retrospectively.

Dr. Caggana pointed out that any changes made to kits, reagents and assays or to post-analytical tools can affect results and must trigger revalidation of cutoffs and laboratory procedures and this should be explored in prospective and retrospective studies. She also noted that the training set for positive controls must be sustainable, which is difficult when dealing with blood spots.

Dr. Shone began his presentation by explaining that the terms cutoffs are not the same as reference ranges and reference intervals, which refer to the range within which results would be considered normal, whereas a cutoff is the point above or below which a value would be considered abnormal. Reference ranges and intervals must be established for all types of screening, not just newborn screening. Various factors influence the establishment of reference ranges, including those that cannot be controlled, such as birthweight and those that can, such as elapsed time between feeding and sample collection, when the sample was collected and how long it took to reach the laboratory. He also stressed the importance of ensuring that the population being studied is as varied and in other ways, representative of the population the laboratory serves.

Dr. Shone also stressed that establishing solid cutoffs and reference ranges can be challenging, especially when collaboration is occurring between state laboratories, each of which may be using a different set of instrumentation or kit. The extent to which a metabolic geneticist is being consulted can be an important factor and case definition can vary from one state to another. In addition, in areas with small populations, obtaining enough confirmed positive or negative specimens to establish cutoffs or ranges can be difficult. It can also be challenging to identify and find examples of all possible biological variants within a disorder, especially those that are rare.

Dr. Shone went on to discuss continuous quality monitoring, which requires a routine review of assay performance and the process used to conduct it. As the number of specimens tested increases, so will variation in the population, which will lead to specimens that are at the edges of the limits — borderline results, which need to be identified in case they turn out to be positive. CLIA requires as a corrective action that reference ranges be adjusted if the laboratory finds that the interval is inappropriate. If a screen does not spot a newborn but should have, the cutoff must be adjusted and the reason the case was not identified, along with any corrective action needed, must be identified.

He also pointed out that there are times when a tool, such as R4S and the laboratory algorithm findings agree but the results turn out to be a false positive. False results can also occur when the two approaches are contradictory, which indicates that no one tool can be counted on. Any tool should be treated as part of a system in which follow-up-based discussions of cases are conducted, both with colleagues and with subspecialists. Therefore, no one tool or methodology meets all regulatory requirements, addresses all good laboratory practices or addresses challenges for establishing reference ranges and cutoffs. A multi-disciplinary and collaborative approach is needed to identify at-risk newborns, he concluded.

Ms. Gaviglio discussed cutoffs within the context of the post-analytical or follow-up phase. She explained that follow up involves staff contacting the appropriate primary care provider or subspecialist to ensure that the family of a newborn with an out-of-range screening result is connected with the health care system. She stressed the importance of continuing communication between the laboratory and follow-up staff and with primary care providers to ensure review of cutoffs and testing algorithms. She also noted that lowering a cutoff too conservatively can bog down an already burdened subspecialty system by triggering false results, which can negatively affect families and providers.

To illustrate her point, she described how her state's laboratory handles a relatively common condition, congenital hypothyroidism (CH), the only blood spot condition that is not typically inherited. Screening for it usually involves examining thyroid stimulating hormone (TSH) or thyroxin, which can also indicate secondary hypothyroidism. (She noted that term congenital hypothyroidism can be an umbrella term for several conditions or screening results.)

Various factors can influence interpretations of and cutoffs for CH, such as a temporary endocrine surge at birth, which elevates TSH and changes thyroxin, leading to a high number of false positives, especially when specimens are collected less than 24 hours after birth. Alternatively, delayed elevations can occur in premature infants, causing inaccurate findings if a subsequent screen is not conducted after the initial 24 to 48 hour period. Other factors that may affect screening results include mothers who are being treated with radioactive iodine for hypothyroidism or hyperthyroidism or are receiving cardiac medications, head cooling of infants in the natal intensive care unit or extracorporeal membrane oxygenation.

States have taken various approaches to addressing this issue. In Washington, cutoffs vary based on age at time of collection to factor in endocrine surge but accuracy is contingent on the integrity of data the program is collecting. Many states have implemented a policy of conducting multiple screenings of low birth weight or premature babies or a second screen that is conducted one to two weeks after the initial one to account for delayed elevations.

Ms. Gaviglio stressed that providers must communicate with newborn screening programs to ensure the collection of data about false negative screening results and noted that this is challenging because most CH infants have primary care providers. In addition, some forms of CH are transient — with findings reverting to normal after two to three years of age — which many new born screening programs are not equipped to track.

She also noted that even a post-analytical examination of data from the follow-up team can reveal broad variability in reference ranges, which forces program staff and subspecialists to either accept values within the context of a reported reference range or choose a value over or under which they will continue to recommend follow-up without factoring in the reference range. The latter approach will alter the reported incidence rate and outcomes, she warned. The varying views of subspecialists can influence decision making and outcomes as well. Pediatric endocrinologists, for example, often disagree on preferred screening strategies and on the definitions of various types of congenital hypothyroidism, which affects both screening and diagnostic results and treatment approaches.

In short, a newborn screening program's success is contingent on the amount and quality of communication among the laboratory, follow-up staff and providers, and the availability and expertise of subspecialists with which the newborn screening programs work.

## **A. Discussion**

Dr. Tarini asked how the rate of identification of false negative results could be improved. Ms. Gaviglio suggested that more fully educating primary care providers on the difference between a screen and a diagnostic test would be helpful. They and specialists might also benefit from education on the importance of reporting back to avoid missed cases. Dr. Shone noted that birth registries in some states inform follow-up programs of diagnosed cases and, in New Jersey, each subspecialty group meets with the state newborn screening program every six months and the specialists often share new findings with the program between those meetings.

Dr. Caggana mentioned that some states require the reporting of all false negative findings to the state newborn screening program and in New York, such findings must be reported by the time the patient is two years old. She also mentioned that her program works with the state birth defects registry to detect structural anomalies in children and, although the registry does not have much newborn screening data, this approach is worth pursuing more robustly. She also noted that there can be various reasons for a false negative, some of which have nothing to do with testing, such as failure to receive a sample. Ms. Gaviglio said that, like newborn screening programs, the way birth registries operate can differ from one state to another (e.g. active versus passive reporting) and in some states, newborn screening conditions are reportable only when they're associated with a structural defect.

Dr. Bocchini asked how Minnesota's program began evaluating patients whose results fell just above or below the cutoff once the decision was made to do so. Ms. Gaviglio said that the laboratory worked with

subspecialists to determine when more follow up was needed, followed by a note requesting that a repeat test be conducted within two to four weeks.

Dr. Bailey mentioned the need to gather massive amounts of data on hundreds of thousands of children to arrive at an understanding of when a genotype/phenotype correlation to the full range of expression of a biochemical or genetic marker as well as a clinical phenotype occurs. However, it is also necessary to get case-by-case information to understand how each child is affected. This calls for a marrying of the two systems—a large database repository but also case-by-case work, each of which can inform the other.

Dr. Saul, speaking as a provider, said that he and many colleagues do not feel they have close communication with the state's newborn screening programs, which could be due to staffing shortfalls.

Dr. Dolan and Dr. Bianchi suggested that some of the difficulty in obtaining follow-up information could be avoided by referring to prenatal diagnoses and that developments in prenatal carrier screening are occurring. This type of information and making medical record data from the mother's workup available in the context of newborn screening could be helpful. Dr. Bianchi also noted that some medical centers are offering non-invasive prenatal screening for single-gene disorders.

Dr. Bocchini suggested that the ACHDNC might have a role in helping to advise on how to reduce the rate of false negative screenings and asked whether the workgroups would consider this issue in their sessions later in the day. He noted that APHL survey results, which will be released in August, could be helpful as well.

## **IV. Public Comments**

### **A. Dr. Jill Jarecki, chief scientific officer, Cure SMA: Newborn screening for spinal muscular atrophy (SMA)**

Dr. Jarecki explained that she is testifying on behalf of the SMA community regarding its nomination of SMA to be added to the RUSP. She noted that recent advances toward developing a treatment for SMA culminated in the Food and Drug Administration's (FDA) approval on December 23, 2016, of Spinraza, the only therapy for the condition. She noted that clinical trials of the drug have shown efficacy across all SMA types, including statistically significant reduction in the risk of death or permanent ventilation as well as gains in motor milestones in infants with SMA, resulting in FDA's broad labeling for it. Dr. Jarecki also pointed out that data suggest early drug intervention is required for the drug to be most effective. Type 1 infants exhibit severe loss of motor neurons during the first three months of life and more than 90 percent loss by six months of age. Biogen's open-label study — NURTURE — of infants who received treatment pre-symptomatically obtained more motor milestones and better outcomes than those who received treatment after becoming symptomatic. She said these results, along with two ongoing SMA newborn screening pilots in New York and Taiwan and assays and diagnostic tests provide strong evidence for adding SMA to the RUSP.

### **B. Debra Schaefer, caregiver: Newborn screening for SMA**

Ms. Schaefer explained that two of her granddaughters were born with SMA, one of whom died in 2012 at seven months of age. Her second granddaughter, Bailey, born in 2014 was diagnosed with SMA in

utero and began receiving treatment with Spinraza when she was three months old; she is currently thriving. Ms. Schaefer credits Spinraza with improving Bailey’s respiratory function and with restoring a significant amount of lost mobility in her limbs and head. Ms. Schaefer said that most infants with SMA are not treated for the condition until 3.6 months of becoming symptomatic but, with newborn screening, would have the same access to Spinraza that Bailey had. She urged the Committee to move the RUSP nomination for SMA into evidence review with an emphasis on the possible benefits of early treatment and attention to the current ability to conduct early screening for SMA.

**C. Kristin Stephenson, vice president for policy and advocacy, Muscular Dystrophy Association: Newborn screening for SMA**

Ms. Stephenson said that SMA is an excellent, perhaps even ideal, candidate for newborn screening in view of the existence of a therapy that is available and showing efficacy and that an effective diagnostic test for the condition also exists.

**D. Dr. Michele Lloyd-Puryear, newborn screening consultant to the Parent Project Muscular Dystrophy (PPMD): Screening for Duchenne Muscular Dystrophy (DMD)**

Dr. Puryear said that she, Annie Kennedy and Jerry Mendell of Nationwide Children’s Hospital have been providing leadership for PPMD’s newborn screening project and, after addressing the Committee during its last meeting is here to provide an update on the therapeutic pipeline and their efforts to support newborn screening infrastructure. In February 2017, FDA approved the corticosteroid Emflaza (deflazacort) in both tablets and oral suspension for treatment only of patients five years old and older with DMD, but noted that this therapy is being studied for treatment of younger patients as well. The company that markets this drug has also released ataluren, which has been authorized for use by the European Commission and is under FDA review, which should be completed in October. These drugs, along with Sarepta’s drug, eteplirsen, provide treatment for a quarter of patients with different types of mutations for DMD. PPMD is still working with PerkinElmer to validate a newborn screening immunoassay for creatine kinase, which was developed by Stuart Moat, and is being developed into a kit by PKI. PPMD is working with the California Department of Health newborn screening program and biobank on a project that will begin by June to test the immunoassay by retrieving dried blood spots for DMD patients and, using as a control, children without DMD but who were screened at the same time. As Dr. Puryear’s team reported previously, six workgroups have been organized to study newborn screening issues, including evidence review for DMD and the examination of a follow-up system to support newborn screening and consideration of Ethical, Legal, and Social Implications (ELSI) for rare conditions on a population basis. Dr. Puryear said she would like to bring two recently written papers—one on DMD, the other on rare conditions in general—to the Committee to suggest ways of incorporating some ELSI questions into the Committee’s evidence review process once they’re ready for publication.

**E. Torrey Smith, adoptive mother of child with congenital heart defect**

Ms. Smith explained that she fostered five children, several of whom had different mothers and came from homes that suffered domestic violence and mental health issues or prenatal drug use. She said she did not know at the time the effects such circumstances could have on children nor what screening was available to identify health conditions or predict their consequences. Almost all of these children

displayed asthma-like conditions and were susceptible to many routine illnesses. Three of the boys Ms. Smith adopted were born prematurely and their mother was overweight, had hypertension, abused alcohol and drugs while pregnant and received no prenatal care. One of the boys unlike his brothers, spent no time in the neonatal intensive care unit (NICU), was sent home three days after he was born. One day, when he was 13 months old, he stopped breathing, received CPR on site, was taken to the hospital and three days later died in Ms. Smith's arms. She learned from the coroner eight months later that her son had multiple congenital heart defects that led to his death. She has heard similar stories from foster mothers who were not told about the possible health risks newborns can incur from unhealthy mothers or home environments or what screenings and other interventions may be available to diagnose, treat or prevent serious and life-threatening conditions in these children. She asked that foster parents be given this information so that they can better care and advocate for the children in their care.

## V. SMA Nomination — Summary

**Beth Tarini, M.D., M.S.** on behalf of the Nomination and Prioritization Workgroup  
Associate Professor and Division Director, General Pediatrics & Adolescent Medicine  
University of Iowa Hospitals & Clinics

Dr. Baker, Dr. Bailey, Dr. Cuthbert and Ms. Wicklund recused themselves from this discussion and vote.

Dr. Tarini explained that Cure SMA nominated SMA for addition to the RUSP; the nomination was co-sponsored by the Muscular Dystrophy Association and the SMA Newborn Screening Working Group.

SMA causes muscle weakness and atrophy caused by progressive degeneration and loss of the anterior horn cells in the spinal cord and brain stem, with onset occurring from birth to adolescence and potentially into young adulthood. Clinical features span a continuum with little or no clear delineation of subtypes. She said that, for this Committee, the focus is on types 1 (most severe) through 4; type 1 is known as Werdnig-Hoffman disease and is the severe infantile type, with onset occurring between birth and six months of age and has a median survival rate of 24 months. Seventy percent of patients with type 2 are typically alive at 25 years of age and lose the ability to sit independently by their mid-teens. Types 3 and 4 have later onset, more developed maximum motor activity and a normal life expectancy. SMA follows an autosomal recessive inheritance pattern and has a variable phenotype expression. The underlying genetics are an absence of the SMN1 exon 7 in most patients, independent of the severity of SMA; the SMN2 copy number modifies disease severity. Incidence is estimated at 1 in 10,000 live births with a carrier frequency of 1 in 40 to 1 in 60. In 2008, ACDHNC's Nomination and Prioritization Workgroup reviewed SMA and decided it was premature to have it considered for full evidence review and recommended prospective pilot studies of the screening method by one or more traditional public laboratories, after which the condition should be resubmitted.

The workgroup reviewed several key questions. *Question:* is the condition medically serious? *Response:* Yes, for the reasons described above. *Question:* is the disorder's case definition and spectrum of the disorder well described to help predict the phenotype of identified children based on a population-based screening and is there a continuum of clinical features? *Response:* The disorder has historically been diagnosed clinically, based on the highest-achieved functional milestone; therefore, characterizations are based largely on phenotype or clinical presentation, it correlates loosely with

genotype and there is a continuum of clinical features. *Question:* Are there prospective international or U.S. pilot data from population-based assessment for this disorder? *Response:* Pilot studies in Taiwan and New York detected an SMN1 deletion through screening. PerkinElmer is developing an assay that would permit real-time PCR assay that targets SMN1 and SMN2, SNPS and SNPs and exon 7. *Question:* Does the screening have established analytic validation? *Response:* Yes. The Taiwan pilot has been submitted for peer review publication and all positive cases have been validated by two other methods. *Question:* Are the characteristics of this screening test reasonable for the newborn screening system; for example, is there a low level of false negatives? *Response:* The data provided indicated the specificity of the screening test for SMN1 is 100 percent. Both pilots have a 5 percent false negative rate because neither detects a compound heterozygous case; however, the pilots have not reported any false negatives to date. *Question:* Are those most likely to benefit from treatment identifiable, especially if the treatment is onerous or risky? *Response:* Animal models of severe SMA show that induction of SMN expression in the early postnatal period substantially improved survival but later induction was less successful. These results have been borne out in early-stage trials. *Question:* Are there defined treatment protocols, FDA-approved drugs if applicable and treatment available? *Response:* Pulmonary, gastrointestinal, nutritional, orthopedic, rehabilitation and palliative care are available and drugs have been FDA approved and others are in the pipeline. Dr. Tarini also described the drug approval process and results for Spinraza, the clinical name for which is nusinersin. Two studies showed statistical and sustained improvement of motor skills and prolonged, event-free survival with no adverse effects or safety concerns. She noted, however, that there is no formal consensus on when to treat SMA patients who are diagnosed pre-symptomatically, but that is reportedly in process.

Dr. Tarini reported that the workgroup's recommendation is to move SMA forward to full evidence review while considering several issues: There are no recommendations or guidelines for specific SMA-type management strategies; there may be a burden associated with carrier identification and; the 5 percent heterozygous cases referred to above warrants consideration.

## **A. Discussion**

Dr. McDonough offered a motion to move SMA to evidence review as part of the process of adding it to the RUSP, citing the strong amount of evidence of its clinical benefit. Dr. Brosco seconded the motion.

Dr. Bianchi reported that the Eunice Kennedy Shriver National Institute of Child Health will award two contracts for state pilot screening projects that will each screen at least 50,000 infants for the condition.

Dr. Greene pointed out that the fact that a small number of heterozygous cases will be missed should not negatively affect SMA's nomination. She also agreed that the carrier issue will be a burden but not the most daunting the newborn screening community has faced and carrier testing will be conducted to an increasing extent even before a baby's 20-week gestation.

## **B. Vote**

A vote was then taken on whether to advance SMA to full evidence review. Voting in favor: Dr. Bianchi, Dr. Bocchini, Dr. Brosco, Dr. Kelm, Dr. Lorey, Dr. Lu, Dr. Matern, Dr. McDonough, Dr. Mistry, Ms. Saarinen and Dr. Tarini.

No one voted against the motion.

Recusals: Dr. Bailey, Dr. Baker, Dr. Cuthbert and Ms. Wicklund

Dr. Bocchini said that a nine-month analysis process will begin that the Committee hopes will yield results that will allow the Committee to decide whether to add SMA to the RUSP.

## **VI. Report on Medical Foods for Inborn Errors of Metabolism**

***Sue Berry, M.D.***

*Director, Division of Genetics and Metabolism, Department of Pediatrics  
University of Minneapolis*

Dr. Bocchini explained that Dr. Berry led an effort, on behalf of the Committee's Follow-Up and Treatment Workgroup, to write a white paper for the Committee's consideration, which discusses issues in connection with the proposal to provide medical foods to all patients with inherited disorders who need them. He invited her to discuss the paper, which has been distributed to the Committee.

Dr. Berry explained that medical foods are not those that can be purchased at a grocery store or drug store; they can be obtained and are to be consumed under medical supervision and are a primary intervention for specific conditions. They are not drugs, which are used to diagnose, treat or prevent disease. She explained that the paper is intended to serve as a policy analysis and to provide recommendations about actions to increase this food's availability for those who need them. She noted that access is highly variable because some conditions are covered by insurance but others are not and adults rarely receive it. Since the Committee's webinar-based meeting in February, the workgroup added sections to the paper that describe the use of medical foods by people with conditions on the RUSP and explain specifically how medical foods differ from regular food and why medical supervision is necessary. The workgroup also reviewed some consequences of not using medical foods and provided a low estimate of how many people are affected by the lack of access, along with details about coverage variations from state to state and the financial and other costs to families who cannot access the foods.

Dr. Berry suggested that the Committee not use the paper to deliver a suggestion for action to the Secretary of Health and Human Services because the Secretary cannot prepare legislation or provide funding that fulfills the Committee's recommendations. Instead, the paper's content reflects a set of principles that the workgroup is asking the Committee to affirm by accepting the document. Medical foods should be covered as medical benefits, not one that is provided for some conditions but not for others. All people who have an inherited metabolic disease, regardless of age should have access to these benefits, regardless of the source of their health coverage. She noted that the paper suggests the convening of a stakeholder's meeting to determine what conditions could be covered.

### **A. Discussion**

Dr. McDonough expressed disappointment that the previous HHS Secretary did not instruct Medicaid to cover medical foods and expressed no optimism that the current Secretary would do so. Ms. Saarinen asked whether, if the Committee takes a policy position on medical foods, it should adopt a position on reimbursement for virtually every condition that falls under the RUSP. Dr. Berry said she anticipates that this issue is likely to be an issue for all disorders, not merely newborn or rare conditions. Dr. Greene said that one way to express a medical foods recommendation is that they should be paid for just as drugs are. Dr. Ostrander and Dr. Greene suggested that the Committee advise the Secretary to convene the

stakeholder's meeting Dr. Berry mentioned. Dr. Bocchini said that a goal previously discussed was to give the paper broad exposure rather than making specific recommendations to the Secretary so that the Centers for Medicare & Medicaid Services (CMS) would be aware of the problem. His goal is to attach the paper to a letter to the Secretary, indicating that this is an unsolved problem that needs to be addressed with the option of asking for a stakeholder's meeting as well. Ms. Bonhomme suggested that payers should be included in any broad discussion of medical food coverage. Dr. Ostrander expressed concern that the letter might be overlooked as some on the Committee felt its recommendations had been and suggested proposing a specific action — a call for hearings on the topic, for example. Dr. Tarini mentioned this is a timely issue because many professional medical organizations, such as the American Medical Association and the American Academy of Family Physicians recently endorsed broad access to medical foods. Dr. Greene said that some insurance companies have expressed willingness to cover medical foods because they are not as widely used as drugs and cost less but would cover these items only if all or most other insurance companies provide this coverage as well to prevent everyone who needs medical food from seeking coverage only from companies that will cover this expense.

A vote was taken on whether to accept the white paper on medical foods for inborn errors and adjust the principles stated in the paper as follows: Medical foods, which require ongoing medical supervision, whereby dietary intervention cannot be achieved by modification of a normal diet alone, that are authorized by a medical provider for management of an inborn errors of metabolism must be covered as required medical benefits across the lifespan.

Dr. Bailey moved to accept the report and the modifications to the principles, Dr. Brosco seconded the motion.

### **B. Vote on whether to accept report**

Voting in favor: Dr. Bailey, Dr. Baker, Dr. Bianchi, Dr. Bocchini, Dr. Brosco, Dr. Lorey, Dr. Matern, Dr. McDonough, Ms. Saarinen, Dr. Tarini and Ms. Wicklund.

Abstaining: Dr. Cuthbert, Dr. Kelm, Dr. Lu, Dr. Mistry

No one voted against the motion.

Dr. Bocchini said that the statement will be posted on ACHDNC's website when it is finalized and the Committee will send a letter to the Secretary to indicate that access to medical foods is an important problem that needs to be addressed. He added that he is willing to discuss with any Committee member any suggestions for specific recommendations or a broader overview that states what the Committee wants to achieve rather than how to achieve it.

Christine Brown with the National PKU Alliance said a bill will be introduced soon in the Senate, the Medical Nutrition Equity Act for which congressional sponsors are being sought.

Workgroup Meetings were held for the remainder of the day.

## **VII. Administrative Business — May 12, 2017**

*Joseph A. Bocchini, Jr., MD  
Committee Chair  
Professor and Chairman*

## **A. Welcome and Roll Call**

Dr. Bocchini welcomed the participants to the meeting, and conducted the roll call.

Committee Members in Attendance:

- Dr. Don Bailey
- Dr. Mei Baker
- Dr. Joseph Bocchini
- Dr. Jeffrey Brosco
- Dr. Carla Cuthbert (attending for ex-officio member, Dr. Coleen Boyle, Centers for Disease Control and Prevention—CDC)
- Dr. Kelly Kelm (ex-officio member, Food and Drug Administration—FDA)
- Joan Scott (HRSA) (attending for ex-officio member, Dr. Michael Lu, 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
- Dr. Beth Tarini
- Catharine Wicklund
- Dr. Catharine Riley (Acting Designated Federal Official, attending for Debi Sarkar, Designated Federal Official)

Organizational Representatives present were:

- American Academy of Family Physicians, Dr. Robert Ostrander
- American Academy of Pediatrics, Dr. Robert Saul
- American College of Obstetricians and Gynecologists, Dr. Britton Rink
- American College of Medical Genetics, Dr. Michael Watson
- Association of Maternal and Child Health Programs, Dr. Kate Tullis
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State and Territorial Health Officials, Dr. Christopher 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. Recognition of Service**

Dr. Bocchini announced that three members of the Committee will be rotating off after the meeting and said he wanted to recognize them for their many contributions while serving beyond their regular terms because appointments had been frozen. They will receive certificates from HRSA to mark their service.

Dr. Bocchini thanked Dr. Bailey for ensuring that the Committee kept its focus on children and their families. He thanked Dr. Lorey for ensuring the Committee knew about the challenges newborn screening laboratories face and his various leadership roles. He thanked Dr. McDonough for his advocacy on behalf of children with special needs and his leadership during his years on the Committee. Those recognized thanked the Committee for the opportunity to serve.

## **VIII. Implementation of Critical Congenital Heart Defects (CCHD) Newborn Screening**

### ***Annamarie Saarinen***

*Co-founder, CEO*

*Newborn Foundation*

### ***Amy Gaviglio, M.S., CGC***

*Follow-Up Supervisor/Genetic Counselor*

*Minnesota Department of Health Newborn Screening Program*

### ***Careema Yusuf, M.P.H.***

*Manager, NewSTEPS Newborn Screening and Genetics*

*Association of Public Health Laboratories (APHL)*

Ms. Yusuf explained that the Newborn Screening Technical Assistance and Evaluation program (NewSTEPS) is designed to provide data, technical assistance and training to newborn screening programs across the country and is implemented through a collaboration between APHL and the Colorado School of Public Health. Newborn screening programs share information about the screenings they perform with NewSTEPS, including the status of screening for conditions on the RUSP, which the program uses to support continuous quality improvement.

She reminded the Committee that CCHD was added to the RUSP in 2011 and at that time the Secretary called for activities the Committee recommended, including research on technologies for screening, diagnosing and surveilling CCHD, the development of screening standards and of the infrastructure needed to implement a public health approach to point-of-care testing as well as the development of educational and training materials for families and public health officials. She noted that only two states have not implemented universal screening for CCHD: Idaho, which is seeking legislative approval and Wyoming, which recently achieved legislative approval. NewSTEPS is collecting information about what types of data programs that are doing universal screening are collecting. The type of data can vary from aggregate, hospital-provided data listing whether children passed, failed or did not receive a screen to provision of oxygen saturation data and time. Fourteen programs are not submitting data to public health programs.

Ms. Gaviglio presented on CCHD screening from a state program perspective. She explained that CCHD screening uses pulse oximetry to detect low oxygen saturation in the blood — hypoxemia — which is

often associated with CCHD but can also indicate non-critical CHD and several pulmonary conditions and bacterial infections. The condition requires intervention, be it catheterization or surgery, in the first year of a newborn's life. When CCHD was recommended to add to the RUSP, there were seven targets (e.g. Hypoplastic Left Heart Syndrome, Pulmonary Atresia, Tetralogy of Fallot, etc.) of pulse oximetry; since then, the number has increased to 12, although the most recent five (e.g. Coarctation of the Aorta, Double-Outlet Right Ventricle, etc.) may not always be detected. Ms. Gaviglio described three algorithms that are used throughout the United States to detect CCHD: a saturation level above 95 percent in the right hand or foot, in both the right hand and foot or above 97 percent saturation level in the foot followed by a pre- and post-ductal. She noted that this screen is the only newborn screening method that is conducted after prenatal screening and a clinical exam, either of which may predict the condition, making it the third line of defense. Birth defect registries are also tracking for the condition and most states require reporting of primary targets. She also noted that whether the screen is considered necessary can depend on location; it may be viewed as less crucial in locations that have high levels of prenatal and clinical care.

Ms. Gaviglio noted several challenges: some programs are having trouble getting hospitals to report the data and in a timely fashion, quality issues and getting data on babies who are born in one state but are screened in another. Getting echocardiogram results after a failed screen and delineating all non-cardiac findings can be difficult as well. Case definitions are being developed to ensure that targets are being correctly identified but some, such as coarctations of the aorta, for example, are not being picked up by pulse oximeters, which were developed as monitoring devices, not for screening. As a result, neither best practices nor the best algorithm have been identified yet and it's not always clear when an algorithm has been followed correctly. There is also disagreement on how to do screening on infants in the neonatal intensive care unit (NICU) and out-of-hospital births. It's not clear whether the program should be constantly checking the algorithm is being interpreted correctly and conducting follow up on these patients. Support for data collection and analysis is needed to determine current performance and how to improve.

Ms. Saarinen began her presentation by describing how her third child went into heart failure shortly after birth, and almost went undetected because the only initial sign was a heart murmur. An easy opportunity to conduct an echocardiogram revealed an enlarged heart, supraventricular tachycardia and mitral valve disease. She noted that babies with this condition often present as mildly cyanotic. Once CCHD was added to the RUSP in 2011, pilot studies of pulse oximetry as a point-of-care screen for CCHD started to be conducted in the United States, in Europe and beyond, some involving large populations and studies were widely published, which is leading to implementation. By 2012, 15 countries had pilot projects, including the largest one involving 120,000 newborns in China. In the United Kingdom, the National Health Service is getting close to implementing the screening after conducting it on babies eight hours after birth, which is when new mothers are discharged. However, more information is needed on how many babies are diagnosed with CCHD and how many die from it. As better nutrition lowers the number of other types of birth defects, increasing attention is being devoted to CCHD in less developed countries. There are many diagnostic and screening opportunities in poor rural areas;; however, many may not have access to pulse oximeters or other equipment or resources to stabilize a baby if they have both hypoxemia and potential heart disease. The need to reduce false positive and false negative rates where it may be difficult to get referrals and treatment is an issue as well. The fact that this screen can help to detect other serious conditions, such as pneumonia, is a selling point for the global community as well. An increasing number of countries are mandating screening, which is happening at a more than 90 percent rate even in countries where no formal mandate exists. China is close to standardizing CCHD screening, using a model similar to the United States' .. Today, 90 percent

of newborns are being screened in 10 countries and 48 are conducting multi-hospital and government studies of pulse oximetry to detect CCHD.

## **A. Discussion**

Ms. Wicklund asked whether it is better to continue point-of-care screening or to involve a state health department in the push to expand CCHD screening. Ms. Gaviglio said it depends on the goals involved. Treating it as a standard of care issue, as some states have, has helped to lower mortality rates but if the objective is to get more data to improve the algorithm, a different approach might be needed. Ms. Saarinen said that getting endorsements from relevant health bodies or pursuing legislation would have slowed the rate of acceptance and adoption. Dr. Tarini asked how the Committee can help APHL and others to get data to improve data collection. Ms. Yusuf said that each state handles the issue differently and some mandate it but don't provide resources or guidance to support it. She pointed out that NewSTEPS has a data repository and the capacity to collect data and are working on case definitions but much of the work is being done at the state level. Ms. Gaviglio noted that Minnesota has a statute mandating CCHD screening data reporting by birthing facilities to the state public health department, and that it's taken two years to get the state's 91 birth hospitals connected so that data can be transmitted electronically directly from the screening devices to the health department, which also maintains a birth defects registry.

Dr. Terese Finitzo, representing OZ Systems, said that the stronger a state health department can be in promulgating rules and requirements for a screening program, the stronger that program will be and the health departments should have the capability, whether financial or through legislation, to stipulate how they want to receive the data.

## **IX. Consumer Friendly Summaries (MPS-1, ALD, Pompe); Developing Methods to Assess Costs of Expanding Newborn Screening; Evidence-Based Review Process**

*Alex R. Kemper, M.D., M.P.H, M.S.  
Professor of Pediatrics, Duke University  
Chair, Evidence-based Review Group*

Dr. Kemper explained that the consumer-friendly summaries will summarize — not update — existing reviews and will be tied to relevant recommendations from the ACHDNC. To be publicly accessible, they will be written at or under the eighth-grade reading level. Each will start with an executive summary and will summarize newborn screening and the specific condition, including how each condition affects the patient, organized according to the report outline. When the summaries are finished, they'll be sent to HRSA for posting on its website; neither they nor the reports from which they are derived will be updated but each will bear the date of publication.

The cost assessment is driven by the Newborn Screening Saves Lives Act, which calls for the ACHDNC to evaluate the public health impact of newborn screening, including the cost to the public health laboratories — not to the individual, the insurance provider or screening's long-term effectiveness — of adding a condition. Specifically, what is being considered is the short-term follow-up of the presumptive-positive screens; the first year of initiating screens and as far as five years of subsequent implementation. The goal is to determine the cost per specimen and the total cost per hundred thousand for the start-up year. The primary cost is for equipment, which can be a direct purchase, a

lease or a reagent rental agreement as well as expenses such as maintenance, repairs, adding components to the laboratory information management system and new hires. Indirect costs, such as space-building utilities must be factored in as well and these costs will vary based on the size of the state, its population and whether it's a one- or two-specimen state. Other issues also come into play, such as who pays for what, how newborn screening is set up in a particular laboratory and how algorithms for testing are put into place. Another complication is that some laboratories do not provide costs in a form we can use and state privacy issues may limit the types of information they can provide. Meanwhile, technology improvements and competition can cause price shifts. The cost assessment needs to be done within nine months, at which time the Committee will vote on whether to add the condition to the RUSP.

Dr. Kemper went on to discuss condition review, which involves a systematic evidence review and an estimate of the public health effect at the population level, which involves modeling and estimating the expected number of cases and the effects of a newborn screening for a condition being adopted nationally. A public impact assessment, wherein various newborn screening programs are surveyed to determine whether laboratories can implement the screening, must be done as well. He explained that past evidence reviews have often involved more work than a traditional evidence review usually entails. For example with adrenoleukodystrophy, his team had to obtain primary, unpublished data from several centers and analyze the data in order to have the information the Committee needed to move forward. The people/organizations that provided these data had not considered doing the type of analysis the Evidence Review team conducted to inform the Committee. The process was helpful, but data collection took a long time.. The team needs to determine how complex the decision analytic model needs to be, to be able to get population health-level estimates and obtain the cost data, which could be challenging. Dr. Kemper's team will then leverage preliminary data from the nomination package, which is used as a launching point to a full understanding of the condition, while taking care not to be biased by that information and continuing to consult other sources.

The Committee will factor the information Dr. Kemper's team provides into its decision making regarding the SMA nomination.

## **A. Discussion**

Dr. Tarini expressed concern that the cost analysis focuses exclusively on the laboratory activities because there are other costs involved, which results in a cost estimate of a test system, not a newborn screening system. Dr. Kemper said that it would be useful to understand the societal level costs — how many resources are needed to conduct the screen, conduct follow up, and the cost of providing life-long care for patients, but many of these data are not available, in part because they change over time. Ms. Saarinen expressed concern that data used to arrive at cost estimates could quickly become dated, as has occurred with CCHD and wondered whether this information could be updated. Dr. Kemper said that this is outside his purview but that educational material should indicate when the cost data were collected.

Joseph Schneider, who is on the Long-Term Follow Up and Treatment Workgroup, asked if reducing newborn screening costs nationwide was in the purview of the Committee, especially on achieving cost reductions for smaller states?? Dr. Bocchini said that because cost considerations have become part of the Committee's responsibility, if there is an opportunity to think through how to reduce cost it is something the Committee could consider pursuing. Mr. Schneider followed with a lesson learned from

businesses and other organizations is that cost savings can be achieved by centralizing or regionalizing the data collection the process.

## **X. Education and Training Workgroup Update**

*Cathy Wicklund, M.S., CGC, Co-Chair*

*Beth Tarini, M.D., M.S., FAAP, Co-Chair*

The workgroup discussed relevant updates for members and issues on the horizon. For example, Pam Clark discussed Georgia's legislation to add Krabbe disease as an optional newborn screen; one deciding factor was its \$10 cost. Discussions are underway on how the state newborn screening program would roll that out. How to collect data on who is opting in or out of that initiative was discussed as well. The workgroup also discussed how to get involved with newborn screening education activities the American Academy of Pediatrics and the National Society of Genetic Counselors are conducting.

Dr. Tarini said that the workgroup will create a guidance document to help providers discuss initial out-of-range newborn screening results with parents using existing resources based on focus group research and best communication practices, which, a member of the audience suggested, could be shared with adoptive and foster parents as well. This would be a cross-cutting document that could be used in discussing an out-of-range result for any disorder. Members decided on the best way to disseminate the document and to identify what information it should contain. It will then be submitted to the American College of Genetics and Genomics for its committee's review and to the ACTsheet Committee for review, for approval to link it to existing ACT sheets and find other ways to distribute this information, such as by including it in information packets that states fax to providers when an out-of-range result occurs.

Another, educational outreach project involved mapping of educational resources, using educational curriculum development principles, beginning with the crafting of a matrix that could be displayed on an X-axis and a Y-axis showing which newborn screening topics could be of most interest to stakeholders. The next step is to obtain feedback from stakeholders to determine what topics are most relevant to them. The workgroup also discussed what types of new or emerging information should be included — such as issues related to the age of molecular medicine or return of carrier results. These are topics that should be discussed with the Committee. The next step would be to decide how to use this matrix. It could, for example, be applied to existing educational resources and/or shared with other programs and educational organizations to help guide the development of future documents. Dr. Tarini suggested seeking feedback at the Beyond the Blood Spot Summit in early June, which stakeholders are likely to attend and using workgroup members' organizational relationships to encourage educational submission materials to the Newborn Screening Clearinghouse. It was also suggested that it might be useful to include opt-in information in educational materials for stakeholders.

## **XI. Laboratory Standards and Procedures Workgroup Update**

*Kellie Kelm, Ph.D., Chair*

The workgroup discussed next-generation sequencing in newborn screening and in a preliminary way about the data the Committee will hear about from NewSTEPS in August regarding laboratories' efforts to meet timeliness goals the Committee recommended in 2015.

Rachel Lee, head of APHL's Molecular Subcommittee, provided an update on APHL's February meeting in Atlanta, in collaboration with CDC and HRSA, which attracted participants from 40 states, to discuss the current status of gene sequencing and common barriers, such as knowledge gaps, costs, lack of resources, reporting issue, variants of unknown significance and reporting consistency and IT and bioinformatics barriers. Some laboratory and follow-up specific barriers were discussed as well. Potential solutions included the need to create regional laboratories for sequencing, peer-to-peer training, training videos, a call site laboratories could use as a resource and a clinical variant database with information specific to newborn screening.

Dr. Watson described ClinGen's project to prioritize the genes involved in newborn screening for variant curation before pilot studies are conducted and prioritizing which studies are pursued. Devising action plans for individual states, possibly involving the creation of a decision-making matrix for states to use when considering whether it is advisable for them to initiate gene sequencing was discussed as well.

Sika Singh and Sari Edelman from APHL and Careema Yusuf who represents both APHL and NewSTEPS provided the workgroup with an informal update on timeliness issues. APHL will present timeliness data collected from 39 states from 2012 to 2015 during the Committee's August meeting, which was given to the Government Accountability Office (GAO) for its report on the issue. APHL's interpretation of progress is likely to be different from GAO's and may contain more current data. States' timeliness performance is improving but falls short of meeting the recommendations that states meet the following goals 95 percent of the time by 2017: Report presumptive positive results for time-critical conditions to the newborn's health care provider and complete all newborn screening tests within the first seven days of life and specimen collection no later than 48 hours after birth and laboratory receipt of the specimens, ideally within 24 hours of collection. APHL is working on a policy statement on the timeliness goals, which it hopes to publish in a white paper in 2017.

The workgroup also heard about some of NewSTEPS' 360-funded projects 28 states are participating in and their many success stories but acknowledged that laboratories need to do a better job of sharing their success stories with the public. Dr. Kelm noted that the workgroup was excited to work with the March of Dimes, the Association of State and Territorial Health Officials and the Association of Maternal & Children Health Programs to develop a toolkit state programs could use to increase their program hours and courier service by, for example, helping them to advocate within the state to get those resources.

In connection with the workgroup's ongoing discussion of cutoffs, APHL is conducting an anonymous survey to capture state practices. Workgroup members wondered whether data could be obtained that compares screening with cutoffs alone versus cutoffs with covariates. Another suggestion was to determine how to normalize data between laboratories and, rather than using cutoffs in the traditional sense, developing a risk-assessment algorithm that uses analytes and other variables similar to that used in the maternal serum screening test. Workgroup members also agreed that existing resources and strategies could be used to improve screening algorithms and that states should share strategies to improve laboratories' false negative and false positive results. Dr. Kelm said she wondered what role if any the Committee might play in this area.

## **A. Discussion**

Dr. Greene pointed out that the CDC is trying to determine how to find resources such as molecular networks and experts and that finding curated information on a new, previously unidentified mutation is difficult, especially since it is not clear who will make sure that the expert who would need to be consulted is properly licensed. Providing compensation to obtain that expertise is an issue as well.

Ms. Bonhomme noted that, although cutoffs are being done in the laboratory setting, it is being discussed publicly and that needs to be discussed. She also suggested, with regard to the timeliness discussion, that this workgroup could work with the Education and Training Workgroup, especially in the context of sharing laboratories success stories in this area.

Dr. Matern suggested that information on timeliness, time-critical conditions, such as infantile Pompe disease and all of those on the RUSP be prominently displayed on HRSA's or the Committee's website. Dr. Bocchini agreed, saying that a specific timeliness page could be created, which would contain the recommendations as well as the conditions and that recently added conditions should be examined to see whether they meet the critical condition criteria.

Dr. Riley said that HRSA is updating the Committee's website and moving it to a new platform and that the way RUSP information is presented will be updated as well.

## **XII. Follow-up and Treatment Workgroup**

*Jeffrey P. Brosco, M.D., Ph.D, Acting Chair*

Dr. Brosco explained that the workgroup's primary focus is on medical foods and quality measures. He noted that, although the Committee accepted the white paper on medical foods, the workgroup would like to continue to meet on this critical topic and plans to write a publication based on the report.

In terms of quality measures, he explained that long-term follow up has three central components: care coordination, evidence-based treatment, and quality improvement; its features are quality chronic disease management, condition-specific treatment, and life-long care. He added that national, state, provider and family perspectives need to be taken into account. In 2016, an ACHDNC workgroup published a paper containing a framework for assessing outcomes; the paper included sickle cell disease and phenylketonuria as detailed examples of the types of quality measures that could be used to ensure appropriate care for children and families. The current sub-workgroup undertook the task of developing a background document to determine what's known about quality measures and newborn screening, examining case studies, and describing other key findings such as comparing quality measures to performance measures and comparing different approaches to disease-specific measures with public health services or with patient/child-specific measures. Dr. Brosco then turned the presentation over to Dr. Alan Zuckerman, attending pediatrician and clinical informatics specialist at Medstar Georgetown University Hospital, who has been working with the workgroup over the past year to discuss the workgroup's efforts to find a role for clinical quality measures to promote long-term follow-up in newborn screening.

Dr. Zuckerman said that the importance of quality measures has been demonstrated in several conditions such as cystic fibrosis and sickle cell disease but gaps and barriers need to be addressed. Case

studies reveal the value of quality measures and challenges. Quality measures limit data by asking specific questions but long-term follow up also entails not just data collection but improvement in the way care is delivered and finding useful measures against which to gauge performance.

One concern is gaps in evidence caused by conditions with different subtypes but there are measures that could be applied to any screening condition. He pointed out that developing measures is not easy especially for rare disorders and the National Quality Forum (NQF) Process is difficult and newborn screening validation is expensive. In addition, there is the challenge of getting people to use those measures and the cost of data collection, the small numbers of patients and single locations, drive the need to integrate quality measures into routine care.

Dr. Zuckerman also noted that some traditional approaches to quality measurement may fall short for newborn screening because it is important to examine the entire newborn screening system through public health measures, tracking available services and even extend this domain into adult care. Child-specific measures are needed that focus on family access to medical homes, available treatment, the child's wellbeing and the family's satisfaction with the care process.

Models of long-term follow up used in some health departments may be hard to replicate elsewhere but one way to do so is to leverage available resources. The Office of the National Coordinator for Health Information Technology, CMS and the Agency for Healthcare Research and Quality have a comprehensive clinical quality improvement resource center that has standards for defining and reporting measures, data models and access to quality measures and incentive programs.

All quality measures are essentially ratios and the NewSTEPS case definitions can help in preparing meaningful denominators and the NBSTRN Longitudinal Pediatric Data Resource database can help define and access data fields, including many core and public health variables. The workgroup hopes to finalize a report based on its tasks by August but needs more time to develop specific suggestions for next steps for the Committee.

## **A. Discussion**

Dr. Finitzo said that NQF-approved quality measures greatly increased the rate of hearing screening prior to hospital discharge of newborn infants and could do so for CCHD as well. Dr. Brosco said that quality measures are being implemented at the insurance plan level, in Medicaid, and at the hospital level.

## **XIII. New Business**

Dr. Bocchini asked whether the Committee or others wished to raise any other issues. Dr. Tullis, said that she believes return of results and carrier screening, which were discussed during the Education and Training Workgroup meeting should be discussed by the Committee.

Dr. Bailey said he hoped the Committee would continue to think broadly about the benefits and risks of newborn screening, especially in terms of families.

Dr. Greene said that she believes the Committee should also focus on heritable diseases that are not detected in newborn screening such as Down Syndrome, neurofibromatosis, Duchenne Muscular Dystrophy, and fragile X syndrome. Dr. Bocchini concurred.

Ms. Bonhomme said she believes it is important to have discussions about the “opt in” model in newborn screening, since this has been implemented in two states to date, and this type of model impacts the newborn screening system.

Dr. Margie Ream, a neurologist at Nationwide Children’s in Columbus said that she became involved in local screening after Krabbe disease was mandated to be added to Ohio’s state screening program. She believes states would benefit from guidance or clarification on what the informed consent process should look like in the case of an “opt out” option for diseases.

Dr. Bocchini concluded by reminding Committee members that they will soon receive ACHDNC’s Annual Report to Congress for review and comment and a draft of the medical foods white paper, which members should comment on. New members will be needed for the 2018 cycle as well.

#### **XIV. Adjournment**

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

The next meeting will be an in-person, two-day meeting and will be held Aug. 3-4, 2017, at HRSA headquarters in Rockville, Md.