Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Summary
November 8-9, 2017

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) meeting was convened on Wednesday, November 8 and adjourned on Thursday, November 9, 2017. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

COMMITTEE MEMBERS

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Designated Federal Official –

Catharine Riley, PhD, MPH
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Organizational Representatives –

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Robert Ostrander, M.D.
Valley View Family Practice

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Pending Assignment

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I. Administrative Business — November 8-9, 2017

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

A. Welcome and Roll Call

Dr. Bocchini welcomed participants to the fourth meeting of the Advisory Committee on Heritable Disorders in Newborns and Children (Committee) for 2017, highlighting this is the 47th meeting since the committee was formed in 2004.

He introduced three new Committee members. Dr. Susan Berry, Professor in the Department of Pediatrics at the University of Minnesota and Chair of the Newborn Screening Translational Research Network. Dr. Cynthia Powell, Professor of Pediatrics and Genetics at the University of North Carolina (UNC), Chapel Hill and Medical Director of the Cytogenetics Laboratory at UNC Hospitals and Director of the Medical Genetics Residency Program. Dr. Scott Shone, Senior Research Public Health Analyst at the Center for Newborn Screening, Ethics and Disability Studies at RTI International.

Dr. Bocchini also introduced Laura Kavanagh, a new ex-officio member representing the Health Resources and Service Administration. Ms. Kavanagh is currently the Acting Associate Administrator for the Maternal and Child Health Bureau. Dr. Bocchini thanked that the previous HRSA ex-officio member, Dr. Michael Lu, for his service on the Committee. Dr. Bocchini also thanked Dr. Fred Lorey who was asked to extend his tenure on the Committee until new members could be brought on board and thanked him for his service both to the Committee and the newborn screening community. Dr. Lorey thanked the Committee and everyone associated with its work for their contributions.

Dr. Bocchini introduced Dr. Catharine Riley as the Committee's new Designated Federal Official (DFO). Dr. Riley is the lead for newborn screening in HRSA's Genetic Services Branch. Dr. Bocchini thanked the previous DFO, Ms. Sarkar, for serving as the DFO since 2013, indicating she is now serving as Chief of the Genetic Services Branch.

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

- Dr. Mei Baker
- Dr. Susan Berry
- Dr. Joseph Bocchini (chair)
- Dr. Jeff Brosco
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention)
- Ms. Laura Kavanagh* (Health Resources & Service Administration)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Dieter Matern
- Dr. Kamila Mistry (Agency for Healthcare Research & Quality)
- Dr. Melissa Parisi (National Institutes of Health)

- Dr. Cynthia Powell
- Ms. Annamarie Saarinen**
- Dr. Scott Shone
- Dr. Beth Tarini
- Dr. Catharine Riley (Designated Federal Official)

*Ms. Kavanagh attended only the morning portion; Joan Scott (HRSA) attended the afternoon portion on her behalf.
**Ms. Saarinen attended only the afternoon portion.

Organizational Representatives in attendance were:

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

B. Vote on the August 2017 Meeting Minutes

Before calling for the Committee to vote on whether to approve the minutes from the August 2017 meeting, Dr. Bocchini asked whether any members had any changes they wished to offer, noting that a substantial number of minor edits had been submitted by November 7. Dr. Baker asked that the word "far" be added to at the end of a phrase she had written: "We are running a parallel study of using both the traditional cutoff method and Collaborative Laboratory Integrated Reports (CLIR) and so …" The change was accepted. By roll call vote, the minutes were approved by all Committee members who were present except for Dr. Berry, Ms. Kavanagh, Dr. Powell and Dr. Shone, who did not join the Committee until after the August meeting.

C. Opening Remarks

Dr. Bocchini announced this meeting is the Committee's fourth meeting for the year. The next meetings will be held on February 8-9 and May 10-11 of 2018. Meeting dates have been set through 2020; this information is available on the Committee's website. He also outlined the topics that would be covered during the meeting.

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

II. Working Toward Newborn Screening Timeliness Goals

Joshua Miller, M.P.H.
Research Instructor
Colorado School of Public Health
Project Manager, NewSTEPs 360

Dr. Bocchini introduced the speaker, Joshua Miller, and reminded the Committee of the newborn screening timeliness goals: presumptive positive results for a time-critical condition should be conveyed to the newborn's health care provider immediately and no later than at five days of life; presumptive positive results for all other conditions should be conveyed to the health care provider as soon as possible and no later than at 7 days of life and; all newborn screening tests should be completed within 7 days of life and conveyed to the health care provider as soon as possible. To achieve these goals, the initial specimen should be collected no later than 48 hours after birth and delivered to the laboratory, ideally, within 24 hours of collection. Dr. Bocchini explained that HRSA had funded an initiative, which led to the development of NewSTEPs 360, to improve timeliness of newborn screening diagnosis and treatment. He introduced Joshua Miller as the Project Manager of NewSTEPs 360.

Mr. Miller presented data from the NewSTEPs data repository, highlighting changes implemented by newborn screening programs to improve timeliness and work toward the Committee's timeliness goals. NewSTEPs is the Newborn Screening Technical Assistance and Evaluation program funded by HRSA; a collaboration between the Association of Public Health Laboratories (APHL) and the Colorado School of Public Health. NewSTEPs provides data services, which include the maintenance of a newborn screening data repository and technical assistance and training to newborn screening programs. The program also assists states that are conducting quality improvement initiatives. NewSTEPs collects data on eight quality indicators. This presentation focuses largely on quality indicator 5, which measures timeliness. Twenty Eight newborn screening programs participate in NewSTEPs 360, 22 of which have submitted data. Data submission is voluntary. The participating states may only contribute data on select quality indicators.

Timeliness recommendation 1, the median percentage of specimens with a presumptive positive result for time-critical disorders that were reported within five days of birth increased from 23 percent in 2012 to 24 percent in 2015.The NewSTEPs 360 cohort showed more recent improvement, from a median 40 percent in 2016 to 50 percent in 2017. He cautioned that the data he presented in his slides represent a subset of the data submitted for the GAO report but they show that states are increasing their adoption of timeliness measures.

Timeliness recommendation 2 calls for reporting presumptive positive results for non-time-critical disorders within 7 days of birth for 95 percent of initial specimens. Data that was submitted to the GAO for 2012 through 2015 shows that the median percent of specimens with a presumptive positive result for non-time-critical disorders reported within 7 days of birth increased from 52 percent in 2012 to 55 percent in 2015. In 2016, the NewSTEPs 360 cohort was reporting a median of 65 percent of non-time-critical results within 7 days, and that increased in 2017 to a median of 82 percent.

Timeliness recommendation 3, calls for reporting all results from all tests within 7 days of birth for 95 percent of initial specimens. For the data submitted to the GAO for this measure, the median percentage of specimens for all results reported within 7 days of birth increased from 45 percent in

2012 to a median of 59 percent in 2015. When NewSTEPs 360 data were added, 2016 data showed a median of 83 percent of all results reported within 7 days, rising to 89 percent in 2017.

Timeliness recommendation B.1 calls for 95 percent of all initial specimens to be collected within 48 hours of birth. The median in 2012 was 86 percent, and it rose to 93 percent in 2015. In NewSTEPs 360 cohort data, the median reached 95 percent in 2016 and rose to 96 percent in 2017 with narrow range distributions. In short, on average, more than 96 percent of specimens are being collected within 48 hours of birth. Eleven participating states achieved this goal in 2016 and 2017.

Timeliness recommendation B.2, laboratory receipt of 95 percent of initial specimens within 24 hours of collection, may not be realistic for many programs to achieve and offered a shift of the benchmark to 48 hours. Mr. Miller also noted that many programs have trouble recording this statistic in their LIMS systems in hour units leading to the decision to collect the data by day units and stipulated that laboratories should receive all specimens within 2 days of collection. For the 24-hour laboratory delivery goal, the median only increased by 4 percent to 7 percent from 2012 through 2015. However, for the 48-hour benchmark, the median increased from 36 percent in 2012 to 53 percent in 2015. And, the median percent of specimens received within 2 days of collection for the NewSTEPs 360 cohort was 75 percent in 2016 with an increase to 78 percent in 2017.

Mr. Miller presented examples from Newborn Screening Programs that are participating in NewSTEPs 360, and how the changes they made are affecting their timeliness measures.

Virginia conducted educational hospital site visits, covering issues such as specimen collection quality and drop-off locations. As a result, they saw a an increase in the number of specimens collected within 48 hours of birth and the number of specimens received within two days of collection. These educational activities improved report times. For example, the percentage of specimens with non-time-critical results reported within 7 days of birth increased by almost 63 percent and specimens with time-critical results reported within 5 days of birth increased by nearly 55 percent.

Montana focused on extending their courier services, which is challenging due to the long distances couriers travel to deliver specimens. In March 2016, they added a 6-day courier service for their larger facilities on the courier route and overnight UPS shipping for smaller facilities that were not on courier routes. These changes increased the number of specimens with all results reported within 7 days by 8 percent and the number of specimens received within 2 days of collection by 17 percent**.**

Indiana added a Sunday courier to all of its hospitals and simultaneously opened up for Saturday operating hours, which helped them to consistently report all results within 7 days of birth for more than 96 percent of specimens for the first time.

Texas shifted staffing hours from 7 a.m. to 4 p.m. to 8 a.m. to 5 p.m. daily, permitting specimens received at 2 p.m. to be accessioned and tested on the day they were received rather than the next day, increasing the specimens with time-critical results reported within 5 days by 126 percent, and those with non-time-critical results reported within 7 days by 56 percent.

Alaska has 20 birthing hospitals, 10 of which are only accessible only by aircraft. Of the 10 that are road-accessible, four of them are a 1 to 6 hour drive to an airport. The state's newborn screening program is in Anchorage but all specimens are transported from there to Oregon for testing. In September 2016, only 33 percent of their specimens were received within 2 days of collection. Following the education program, by April of 2017, about 48 percent of specimens were received within 2 days of collection. In

June 2017, they began using a courier that flew 7 days a week (adding weekends and holidays) and now the Oregon NBS laboratory receives almost 64 percent of specimens within 2 days of collection. The Oregon NBS laboratory has also made internal improvements. These efforts combined results in a 538 percent increase in the number of specimens reported within 7 days of birth for the state of Alaska.

Iowa found that a specimen collected on Friday may not be delivered to the laboratory until Monday and not tested until that day or Tuesday, resulting in a 6- to 7-day report time. Iowa also noticed 80 percent fewer births on weekends, due in part to Cesarean sections and induced births being scheduled during the week. Iowa NBS program now provides a same-day, 7-day courier service and their laboratory is open 20 hours per day, every day. They stress to couriers that they are carrying packages the delivery time for which, could affect a life. As a result, more than 96 percent of specimens are collected within 48 hours of birth and more than 96 percent of specimens are received within 1 day of collection, more than 90 percent of time-critical results are reported within 2 days of receipt and, more than 96 percent of non-time-critical results are reported within 4 days of specimen receipt. In addition, more than 99 percent of time-critical results are reported within 5 days of birth, and more than 96 percent of non-time-critical results are reported within 7 days of birth.

Mr. Miller summarized lessons learned. Improving timeliness requires educational activities, expansion of courier services and operating hours and improving lab processes. Even incremental improvements take a lot of time and effort and programs face geographical barriers. States also need to examine their data for challenges, such as Iowa's differences in their day-of-week births. He also pointed out that out-of-hospital births still pose timeliness challenges, including midwife birth sand babies in the NICU; anything that falls beyond a standard well-baby unit birth. One of the greatest outcomes from NewSTEPs 360 so far is the opportunity it gives newborn screening programs to collaborate to develop new ways to address timeliness obstacles and concluded that since activities began for NewSTEPs 360 in January 2016, in the participating states, more than 74,000 additional newborns have had specimens collected within 48 hours of birth that otherwise would not have, an additional 62,000 newborn specimens were received within 2 days of collection, an additional 378 newborns' time-critical results were reported within 5 days of birth, and 2,000 more non-time-critical results were reported within 7 days of birth. Finally, all results for an additional 117,000 newborns were reported within 7 days of birth.

A. Discussion

Dr. Powell noted that time-critical conditions are not uniformly defined by states. There are professional organizations that provide guidance on this. States do not all use the same metrics. Participating state programs submit differing data metrics and define these metrics differently. Is there something the Committee could do to help make data reporting more consistent across the states and encourage more states to participate? Mr. Miller welcomed Committee support, noting funding would be needed. Dr. Tarini indicated the Committee might be able to make written recommendations on data collection practices. Dr. Bocchini pointed out that part of the Committee's responsibility is timeliness in reporting and he suggested that the NewSTEPs stay in touch with the Laboratory Standards Workgroup, which is responsible for following efforts in this area to develop a better understanding of how the Committee can help; he agreed that written recommendations could help to have an impact. Dr. Shone said that the need for resources is not limited to timeliness, there are also issues implementing screening for new diseases and follow up efforts; for example, many states lack the time or staff to provide the data NewSTEPs is requesting. Dr. Matern suggested the Committee recommend Iowa's approach as a best practice. Mr. Miller said that some states may not have the resources to follow Iowa's example. Dr. Baker suggested that NewSTEPs provide an incentive for states to report data by

offering them reports, perhaps in the form of infographics, similar to those Mr. Miller displayed in his presentation, that they could use in their reports. Mr. Miller said NewSTEPs has about 15 interactive infographics online that update automatically based on data entered into the repository. Dr. Tarini suggested that states be asked how these resources can be made valuable to them. Dr. Kelm noted that some states are not collecting data on time-critical conditions and "transport to the lab" could mean different things to different states. Mr. Miller said that states have trouble using their LIMS to record these cases and that it requires working with a vendor or programmer to vary the system's data collection parameters; thus, an examination of internal as well as external processes and procedures is necessary to improve timeliness. Dr. Parisi asked when in the process is a result considered to have been reported. Mr. Miller said it varies based on whether the result is time critical; at that point, it occurs when the laboratory is phoning the result to the physician; for all other results, it is when the final report is sent, which may not take into account when the physician receives it.

III. Public Comment

A. Dr. Darryl Devivo, Sidney Carter Professor of Neurology and Pediatrics at the Neurological Institute at Columbia University

Dr. Devivo addressed the need for newborn screening for spinal muscular atrophy (SMA) in light of the availability of Spinraza (nusinersen) an FDA-approved, effective therapy for the condition. He noted that clinical trial results were published in the New England Journal of Medicine on November 2, 2017. Studies of mice and humans indicate that early intervention is most effective because the degenerative process is most aggressive within the first six months of life; he also noted that destroyed motor neurons cannot be replaced. He cited the ENDEAR study in which 75 percent of younger-than-12-week-old infants who received the drug gained motor skills but the average age of clinical diagnosis for babies with type 1 SMA is 4.9 months. He noted that a pilot study of SMA newborn screening in New York identified an infant with a homozygous SMN1 deletion and two copies of the SMN2 gene. After being enrolled in the NURTURE clinical trial and treated with Spinraza at 15 days old, she is, at 16 months of age, meeting all normal developmental milestones and is walking and running. By contrast, most type 1 infants fail to make motor gains after initial presentation. He concluded by asking the Committee to recommend that SMA be added to the Recommended Uniform Screening Panel (RUSP).

B. Maria Spencer, Vice President of Policy and Advocacy, Cure SMA

Ms. Spencer spoke regarding the nomination of SMA to the RUSP. She indicated that SMA meets the required criteria for addition to the panel which are that it: 1. be identifiable within two days after birth, 2. have a screening test available; 3. benefit from early detection and intervention; and 4. have an effective treatment.. She noted that many children are being treated for this condition, which she referred to as the leading cause of death due to a genetic condition for children younger than two years old. She stressed the importance of treating SMA pre-symptomatically and the importance of adding it to the RUSP to ensure that treatment leads to the best possible outcomes and saves lives.

C. Cheryl Yoder, parent of two children diagnosed with SMA type 1

Dr. Bocchini explained that Ms. Yoder's son was tested at birth and treated with Spinraza by his third week of life. Ms. Yoder explained that her daughter, Ariel, was not diagnosed with SMA until she was six

months of age, five months after she began showing motor impairment. She passed away at 16 months of age. Her brother, Jace, was diagnosed at eight days of life, and enrolled in the NURTURE study. He received Spinraza on the 25th day of life. At two years of age, he has achieved many motor milestones, including walking independently, talking, singing and climbing steps. She stressed that newborn screening for SMA is the key to helping children with this condition to thrive.

D. Kristin Stephenson, Senior Vice President and Chief Policy and Community Engagement Officer, Muscular Dystrophy Association (MDA)

Ms. Stephenson explained that MDA represents more than 40 different neuromuscular disorders, including Pompe disease, SMA and muscular dystrophy. She said that MDA supports more than 150 care centers nationwide that handle the above-mentioned and other neuromuscular disorders. Many clinical trials that are held to investigate potential therapies for these disorders are held at these centers. MDA also has a disease registry that collects provider-entered data on SMA at 26 of the care centers in 16 states and plans to share these data with the Committee. She requested that SMA be added to the RUSP.

E. Annie Kennedy, Senior Vice President of Legislation and Public Policy, Parent Project Muscular Dystrophy (PPMD)

Ms. Kennedy spoke on behalf of PPMD noting that 8,000 people in the United States have Duchenne muscular dystrophy, one of the most common and fatal genetic disorders that is diagnosed in childhood, affecting about one in every 5,000 live, male births. Although always fatal, early treatment can add up to decades to an affected person's lifespan. Two therapies have been approved in the United States to treat Duchenne and the Food and Drug Administration (FDA) is reviewing a third that has been approved abroad. Other investigational therapies are being explored and three gene therapy programs are moving into the clinic in coming weeks. For the past three years, the organization has convened experts in Duchenne and newborn screening to build an infrastructure to develop evidence to support Duchenne newborn screening. These efforts have led to the creation of information technology tools to support screening development and diagnosis technologies and to enable longitudinal studies to understand health outcomes of infants who are diagnosed and treated early. PPMD plans to make these tools available for population-based newborn screening and state program screening program implementation. PPMD has also been working to achieve reauthorization of the Newborn Screening Saves Lives Act and federal funding for U.S. newborn screening. PPMD believes that the use of an established, centralized infrastructure for newborn screening pilots will accelerate the production of evidence, submission of a RUSP nomination packet, review and recommendation for RUSP status and from there, nationwide newborn screening.

F. Ernest Shu, Cardiovascular Product Manager, Admera Health

Mr. Shu explained that Admera Health is a Clinical Laboratory Improvement Amendments- (CLIA) certified and College of American Pathologists' (CAP) -accredited laboratory based in New Jersey that uses next-generation sequencing technology to advance personalized medicine. Admera Health focuses on pharmacogenomics, non-invasive cancer screening and inherited cardiovascular diseases. Physicians and patients receive diagnostic test results in reports that are designed to help them make informed treatment decisions. They recently launched two direct-to-consumer tests: one detects inherited high

cholesterol (familial hypercholesterolemia); the other is for inherited diabetes (mature onset diabetes of the young).

IV. Implications of Detecting Carriers through Newborn Screening

Michael Watson, Ph.D. FACMG
Executive Director
American College of Medical Genetics

Aaron Goldenberg, Ph.D., M.P.H.
Associate Professor of Bioethics and director of Research, Department of Bioethics
Case Western Reserve University

Michele Caggana, Sc.D., FACMG
Director, Newborn Screening Program
New York State Department of Health

Dr. Watson began with a reminder that newborn screening programs do not conduct carrier screening; carriers can be detected in the course of newborn screening, but the goals of each type of screening differ. Deciphering between carriers and non-carriers can be more difficult than deciphering between those with and without a condition; however, second-tier testing could change this. Example, immunoreactive trypsinogen (IRT) is the primary marker for most states for cystic fibrosis screening, however there is now a second tier molecular test that could potentially detect carrier status. Another example offered is lysosomal storage disorders, most of which have a second tier molecular test.

At this time, no conditions involving autosomal dominant inheritance, such as Huntington Disease, are part of newborn screening programs. Conditions with an X-linked recessive inheritance pattern, such as X-ALD and Fabry, are being screened for in some states. Female carriers who have one copy are at risk for disease because of the effect of X chromosome inactivation. It is possible to imagine a bell curve of cells in a female in which half of the cells may have one active X chromosome and in the other half, the other X chromosome is active. X-linked disease is often milder in females than it is in males. This impacts the ability of a screening method to differentiate carriers.

Among non-traditional inheritance patterns, conditions such as Fragile X are not covered by newborn screening but have been proposed as a candidate for the RUSP. People who have pre-mutations are at risk of instability, which means the triplicate repeat mutation can expand to a full mutation in offspring, leading to a child with fragile X syndrome. He predicted that consideration of each disorder will be necessary to determine the associated conditions manifested by carriers, their severity, and whether they should be detected in newborn screening because there are far more carriers than clinically affected individuals.

In newborn screening where the goal is to identify individuals with conditions in order to intervene to ameliorate the clinical phenotype, the focus is not on whether there are reproductive or familial implications of finding carrier status. . However, this information is valuable in a familial context when one wants to explain to a couple, both of whom are carriers, the potential risk of having an affected child. This also has implications for cascade testing, which refers to identification of an affected

individual in a family. Cascade testing can be effective among rare conditions because it is easier to detect when you know to look for it in relatives of someone who has, or is a carriers for, a condition. However, the question arises, if the person's status is not clinically relevant to that person, should the information be discussed? The decision to do so can have unforeseen consequences. For example the clinical genetic community is now following up on carriers of X-ALD that have been found related to infants detected by NBS; if this occurs with other conditions, it will further burden an already small workforce. In the case of carriers for autosomal recessive disorders, they rarely show a clinical phenotype related to the condition. There may be biochemical evidence, but rarely any clinical evidence.

In the end, it boils down to the clinical issues associated with those who are carriers: What proportion of them may develop the severe form that triggered screening in the first place versus those that may have one of these milder forms of disease, and then, whether whatever form they have is treatable? Whether the screening workforce can handle additional screening and follow up is also an issue in this time of limited capacity. Dr. Watson concluded by saying that the general recommendation has been not to test children unless the result will directly benefit the child, but decisions must also be made regarding whether carrier statuses will be reported; this too comes back to whether it holds any benefits for the child.

Dr. Goldenberg focused his presentation on the debate over whether, and when, to convey carrier status in newborn screening programs. He offered the example of sickle cell screening in the 1970s, when states started mandating screening but the laws were written without consideration of how much education and counseling would be needed, which led to confusion about the implications of being a carrier and the potential for stigmatization, including discrimination and the loss of self-esteem.

Dr. Goldenberg noted that the approach used to deliver this information can affect how it is received by patients and families, citing a UK study that revealed increased anxiety among parents who received carrier status results from screening for cystic fibrosis and sickle cell. He stressed the need to deliver such results in a way that makes recipients feel comfortable and called for more studies on the potential impact of imparting the carrier status results.

Despite these challenges, he argued for early detection of carrier status involving conditions that could cause health effects in early or later childhood but that the case is less clear for health benefits that emerge in adulthood. Although this knowledge could lead to more screening and intervention, it could also result in misunderstanding of the condition, potential discrimination, unnecessary screening and increased anxiety among children as well as their families. Dr. Goldenberg described the "child's right to an open future" as the concept that certain adults — including government officials and clinicians — should hold certain rights, including information, in trust for children until they are adults, a reflection of the fact that only adults have full autonomy. Many people are now electing to undergo carrier screening before having children for 100 or more conditions, many of which are on or could be added to the RUSP, such as cystic fibrosis, Pompe and SMA, which removes this whether-to-notify dilemma. On the other hand, some of the tests are expensive and not everyone has access to information they need to understand the test results or their implications. The argument has also been made that screening should be expanded beyond newborns to include those who might use it to make reproductive decisions. He posted the question as to whether this moves newborn screening away from focusing on potential benefits to individual newborn.

Another question ethicists are dealing with is whether programs can force parents to learn their carrier results; whether it is justified to violate the right not to know, especially if such information conveys no benefits to newborns. He asked whether there should be a consent process for carrier status and, if so, whether it would it resolve this debate. Some scholars have argued that only targeted groups should be screened. Some experts have called for recording carrier status in medical records to be revealed later. However, this could differ based on condition and when results would be clinically relevant, policies that are in place, and the potential impact of providing this information. The research he and Dr. Tarini conducted revealed some professional ethical conflicts. On the one hand, providing screening results does not mean that it will be clear how the results should be dealt with, which should perhaps lead to more debate on what type of and how much information to provide. On the other hand, many programs feel obliged to report what they find and withholding such information, even temporarily, could prevent a family from gaining a key piece of information.

He concluded by saying that deciding whether to provide carrier status should be accompanied by communication and education that helps parents feel comfortable about the information they are getting. This includes taking into account the traits and approach of the provider and the atmosphere and setting in which the information is delivered. It is also important to fully understand the potential impact of storing this information in a medical record for later transmission. Considering consent processes is important as well. More studies on these issues are also needed.

Dr. Caggana discussed lessons learned about the implications of detecting carriers through newborn screening. New York conducted an SMA pilot study, funded by BioGen, which began in January 2016 at three New York City hospitals. The results were recently published in the journal *Genetics in Medicine*. Project goals: 1) develop an SMN1 assay that can be used in newborn screening (which searches for homozygous deletion in the SMN1 gene); 2) demonstrate the feasibility of high throughput screening and; and 3) offer screening and assess uptake and outcomes, including how parents feel about receiving a carrier result. Recruitment was done using an opt-in model, which requires parental consent.

The team does not specifically sequence for carriers, however the screening methodology can identify carriers, in the process of screening for SMA. One deletion in exon 7 is reported as a carrier, a homozygous deletion is reported as affected.

As of about a month ago, 8,167 infants were screened; 93% of parents who were approached opted in for screening. In a birth population of 250,000, the team would expected to see between 24 and 40 cases per year. So far, one infant with SMA has been identified, among the 8,167 screened. The researchers believe this could reflect bias in terms of the location of the hospitals and the race and ethnicity of patients. That infant began treatment at 15 days after birth and remains asymptomatic at 21 months old.

Hospital-based coordinators describe the study to parents and a pamphlet and a You Tube video are also available; consent is conveyed through a tablet form. Genetic counseling was offered to the 113 parents of newborns with a carrier result; 16 agreed to a genetics referral, 11 made appointments, 8 kept the appointment. Although most parents initially expressed concern over the news, they understood the difference between being affected by a condition and carrier status. Almost 47 percent of parents who were counseled knew they had the potential to be carriers because they had been identified as such during prenatal screening and were less concerned at the beginning of these meetings. The report is available as part of the newborn screening test report and is posted on the website.

From the pilot, the researchers concluded that SMA testing is feasible at a cost of about 20 cents per infant but Dr. Caggana cautioned that this is because the team was able to multiplex it with SCID; thus, there was no need to set up a new assay or obtain equipment. The only cost was for probes and the cost does not factor in follow-up and education. Of the families who were approached about screening, 93 percent opted in. The overall carrier rate in New York is slightly lower at 1 in 72.

New York has three other conditions that are screened for that include carrier results: hemoglobinopathies, cystic fibrosis, and adrenoleukodystrophy. New York identifies approximately 7,300 carriers of a hemoglobinopathies. The information is included in the report no other follow-up or other action is taken. About 800 babies screened each year have a positive CF screening result. These infants are followed up, requiring a sweat test. Approximately 600 are found to be carriers. Overall carrier frequency is about 1 in 400, but the expected rate is about 1 in 35, so some carriers are not identified. Adrenoleukodystrophy carriers are recorded through reports and require follow up referrals. From data on almost 900,000 infants, 69 referrals were made, 25 female carriers were identified as well as one male carrier, a child affected with Klinefelter syndrome who was heterozygous for an adrenoleukodystrophy mutation. These cases are followed up and incidence rates are in line with what is published.

Dr. Caggana sent a note to genetic specialists, asking them whether SMA carriers should be reported. All of these specialists said they believed reporting would trigger a higher number of calls from pediatricians, primary care physicians and families. The specialists believe they do not have enough counselors to handle the volume and it would, therefore, be burdensome.

The counselor the team spoke to said that a number of people do not come in for a follow-up to prenatal screening because they are already aware of their carrier status. Many parents do not realize that they should not expect to spot symptoms and few parents request follow-up sequencing. The counselor also said it can be difficult to gain a parent's full attention during phone consults, that it is impossible to read body language and that each consult can take 15 minutes, which can be difficult to fit in if one has to conduct 13 or 14 per day.

Issues that need to be resolved include the fact that current regulations must be changed if carrier screening for SMA is taken to full scale, and the New York Department of Health is still in the process of forming a care center network of neuromuscular specialists to see the infants. Funding is provided for laboratory equipment but not for education and follow-up and the question of reporting carrier status must be resolved. Other considerations include how to conduct and manage late-onset detection, false negatives, the cost of treatment, when to initiate treatments, and how to decide treatment protocols.

A. Discussion

Dr. Berry asked what the Committee could do to help address the need for labor and other resources to improve reporting of carrier status and provide the counseling this would entail. Dr. Watson said it would be necessary to examine the capacity of the public health care system. Dr. Goldenberg said that the ability to do extensive counseling is lacking and more research is needed to determine how to alleviate anxiety over carrier status reporting in a time-effective manner. Dr. Caggana said that well-produced infographics could be a good way of relaying carrier information to providers who can share it with parents rather than sending parents to specialists who send them to counselors, but the message must be tested among various types of people to ensure the messaging is clear. Dr. Tarini warned that providing counseling about SMA carriers has to open the door for counseling for other conditions such

as hemoglobinopathies and that all conditions must be handled the same way. Dr. Caggana indicated that New York sends letters to families with hemoglobin carriers and encourages them to talk to their pediatricians about this information. Dr. Berry suggested that professional organizations might be able to do more to educate the general public about carrier status and its significance. Dr. Watson said this issue warrants more discussion, such as when it is clinically appropriate to refer carriers identified through newborn screening program to follow up services. Dr. Goldenberg said that discussion should focus more broadly on what condition-specific policies or educational materials and how many counselors are needed, especially as universal and expanded carrier screening becomes more common. Sharing lessons across the pre- and post-natal world could be helpful. Dr. Shone warned that increasing testing for carrier status will require a broad spectrum of adjustments over the screening/testing spheres, including more second-tier or diagnostic testing, which could be hard to sustain. Dr. Brosco pointed out that when deciding whether to add SMA to the RUSP, it is important to note the carrier rate is between 1 in 40 and 1 in 70. Ms. Scott asked how many potential SMA patients might be missed or classified as carriers if additional sequencing isn't done to ensure there is no point mutation. Dr. Caggana said the residual risk of an infant having SMA is less than 1 in 1,000 with a deletion copy of SMN1 and 1 in 2,000,000 that they would have two point mutations in a screen.

V. SMA Evidence Review — Phase II

Alex R. Kemper, M.D. M.P.H., M.S.
Division Chief, Ambulatory Pediatrics
Nationwide Children's Hospital
Lead, Evidence-based Review Group

Dr. Bocchini explained that Dr. Kemper is delivering a presentation on the status of the systematic evidence review for SMA, a nine-month process, conducted by an Evidence-based Review Group (ERG). Dr. Kemper is presenting interim findings today. Dr. Kemper introduced Dr. K.K. Lam, project leader, with whom he has been working on this project. He said that a great deal of evolution is occurring in the SMA sphere. Two major articles related to SMA were recently published in the *New England Journal of Medicine*, one of which focuses on treatment with nusinersen; the other discusses a gene therapy approach.

The ERG held its second technical meeting and is working on issues related to follow up interviews. In terms of literature review, of 2,447 journal articles that were published between 2000 and June 2017, 221 were retained for review and extraction. Most of these do not focus on treatment outcome because those studies are only now emerging; many focus on screening. Many results come from New York and CDC. Dr. Kemper reported that screening research projects have been conducted in Utah and Colorado and legislation has been approved in Missouri and Minnesota. Several other states are considering screening as well. Dr. Matern said a Minnesota advisory committee that advises the Commissioner of Health recommended that SMA be included on the state panel but, to his knowledge, no legislative action was actually taken.

CDC has developed screening methods and makes proficiency testing available and its focus is on real-time qPCR for SMN1 exon 7 deletion, which uses specific probes to increase specificity in the presence of SMN2. It is highly accurate in identifying exon 7 deletions in both alleles and can be multiplexed with SCID at an estimated cost of less than 10 cents per sample; it does not identify carriers.

Dr. Kemper summarized the ENDEAR study, a phase 3, randomized trial of nusinersen used to treat infants with SMA, which could be most relevant to the Committee's decision-making process. The study focuses on infants with a genetic diagnosis of SMA who have two copies of the SMN2 gene, developed symptoms prior to 6 months of age, and were 7 months or younger at the time of study. Infants couldn't have hypoxemia, at the time of screening for study participation. These infants were not identified through newborn screening but were symptomatic and referred for the study at an early age. He said that those who were enrolled in the study at 12 weeks of age, rather than 12 weeks after becoming symptomatic, appeared to show better outcomes.

A kick off meeting was held on the public health system impact (PHSI) assessment, which included discussion of an SMA screening information fact sheet and the PHSI surveys. The initial survey closed on November 17. Follow-up interviews will be conducted with states that have mandates to screen to understand how they are implementing screening. States will be asked to estimate costs using a tool the ERG developed previously. Modeling will be done to quantify the impact of screening all 4 million newborns in the United States compared to reliance on clinical identification. More information on motor deficits is also becoming available. The main focus has been on type 1 SMA; it would be ideal to model other forms that could be clinically significant but that may not be feasible. He noted that CDC data indicate that the false negative rate is likely to be quite low; copy numbers can be incorporated in the model to modify results as needed. The next step is to develop estimates for modeling parameters, much of which will be derived from studies under review. The Technical Expert Panel will convene in December to examine the model and see whether the parameters make sense. Dr. Lam said that available evidence seems to say that treatment is indicated for symptomatic SMA patients with copy numbers up to three, based on the ENDEAR and the (as yet unpublished) CHERISH studies.

A. Discussion

Ms. Scott asked how clear the treatment protocols are, what the level of consensus is on regarding the protocols among clinicians who will treat identified children, and if there are any potential harms of treating too soon or too late? Dr. Lam said that a group of experts on treatment, led by Cure SMA, is examining these issues using a Delphi process. Dr. Matern asked whether data are emerging that reflect treatment outcomes among infants that were detected through newborn screening. Dr. Lam explained that the NURTURE study, an open-label trial focusing on pre-symptomatic infants, is at an earlier stage and results are being compared to historic norms but interim results appear to be promising. Dr. Berry asked whether the cost of treatment, based on how many affected infants would be born in any given state, would be included in the review. Dr. Kemper said the review will be limited to the costs a newborn screening program would incur. Dr. Lam indicated there is research on the costs of treatment. Dr. Matern said that BioGen has a program to provide treatment to anyone, regardless of ability to pay. Ms. Saarinen asked whether any advocates or parents of SMA infants are on the technical expert panel. Dr. Kemper explained that a parent advocate was able to attend the first meeting. Ms. Saarinen questioned whether the evidence review report should dictate follow-up. Dr. Kemper said that the goal is not to develop clinical guidelines but to see whether there is some consensus about what to do when a case is identified — whether the benefit that may be derived from studies can be translated to care — but it does not imply total consensus. He also pointed out that, although the focus is on nusinersen for treatment, which has changed care for SMA dramatically, it is one component of a therapy for SMA; others include pulmonary evaluation, physical therapy, occupational and physical therapy, etc. Ms. Saarinen also expressed the hope that, because the most severe cases of SMA are being targeted in the

evidence review, the needs of children who may not need early life-threatening intervention will not be overlooked, pointing out that this touches on the issue of equity. Dr. Kemper acknowledged this, saying that 40 percent of infants do not have type 1 SMA but noted that most of the collected data focuses on this population. Dr. Shone asked whether the information process that is presented to the Committee as it considers SMA as a candidate for the RUSP should include the challenges the public health systems may face and potential additional resources that could help move the ball forward. Dr. Kemper said that the Group has talked to NewSTEPs but pointed out that it is constrained with regard to the range of information it can obtain about the public health system impact due to the Office of Management and Budget process that must be conducted before sending surveys to states. Dr. Tarini agreed with Dr. Kemper's point about trying to achieve consensus on care policies and strategies but pointed out that these can vary from state to state, which is a challenge to ensuring equity of care.

VI. Administrative Business — November 9, 2017

A. Welcome and Roll Call

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

- Dr. Mei Baker
- Dr. Susan Berry
- Dr. Joseph Bocchini (chair)
- Dr. Jeff Brosco
- Dr. Scott Grosse (Centers for Disease Control and Prevention)
- Ms. Joan Scott (Health Resources & Service Administration)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Dieter Matern
- Dr. Kamila Mistry (Agency for Healthcare Research & Quality)
- Dr. Melissa Parisi (National Institutes of Health)
- Dr. Cynthia Powell
- Ms. Annamarie Saarinen
- Dr. Scott Shone
- Dr. Beth Tarini
- Dr. Catharine Riley (Designated Federal Official)

Organizational representatives in attendance were:

- American Academy of Family Physicians, Dr. Robert Ostrander
- American College of Medical Genetics, Dr. Michael Watson
- American College of Obstetricians & Gynecologists, Dr. Britton Rink
- Association of Maternal & Child Health Programs, Dr. Kate Tullis
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Chris Kus
- Department of Defense, COL Adam Kanis
- Genetic Alliance, Ms. Natasha Bonhomme

- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Cate Walsh Vockley
- Society for Inherited metabolic Disorders, Dr. Carol Greene

Dr. Bocchini introduced the Workgroup updates and explained that they were tasked with providing a timeline for current projects and prioritizing potential new projects and topics for the Committee's consideration.

VII. Education and Training Workgroup Update

Beth Tarini, M.D. M.S. FAAP
Committee Member
Co-chair, Education & Training Workgroup
Amy Gaviglio
Education & Training Workgroup Member

Dr. Tarini began by discussing the Workgroup's progress on Newborn Screening Education Planning Guide, a tool used in educational curriculum design, which was mailed in the form of an Excel spreadsheet to the Committee. Dr. Tarini credited Workgroup members, Ms. Walsh Vockley and Dr. Jeremy Penn, for spearheading this effort. The guide is intended to be used by newborn screening programs and other stakeholders to develop and improve newborn screening educational resources that are provided to stakeholders such as midwives, nurses, health care providers, etc. She stressed that the guide is not intended to help people create educational guides or adopt modes of teaching, but to focus on what topics should be covered and where there is a need to provide and tailor content to meet various stakeholders' needs. The Workgroup tried to examine newborn screening through stakeholders' eyes rather than dictating what they would say or present. Once finalized, it will be posted on HRSA's website and disseminated through the Newborn Screening Program Listserv and professional organizations and distributed at national conferences such as APHL Newborn Screening Symposium webinars. She asked Committee members to review the document and provide comments to the Workgroup with the goal of having the Committee approve it at its February or May meeting.

Ms. Gaviglio presented on the Newborn Screening Result Communication Guide. This work builds on work done by Ms. Bonhomme and Dr. Greene with parents and their impressions of the abnormal result notification process. So far the Guide has been reviewed by Workgroup members, Baby's First Test staff, physicians, and genetic counselors. The guide is intended to help primary care providers frame the initial discussion with parents about newborn screening results; not from a clinical perspective but to aid in delivering news that can cause anxiety. The guide draws on the SPIKES model, which is rooted in oncology and genetic counseling literature. The name of the approach was changed to SCREEN: SHARE the result with the family, assess the family's COMPREHENSION of the results, REITERATE what screening is and is not, ENGAGE the family with information, address the family's EMOTIONS toward the result and given the family NEXT STEPS and resources. The goal was to deliver this information in a one-page document that states could include in their abnormal result notification packages, disseminate to primary care providers and/or be included in ACMG's Act Sheet process as a type of pre-ACT sheet. It could also be used to develop an American Academy of Pediatrics (AAP) Maintenance of Certification course module or be endorsed by AAP.

A. Discussion

Dr. Mistry said that it is important to ensure that the information being provided is being interpreted correctly and review from various stakeholders would be useful. Dr. Shone suggested that, rather than just disseminating the guide, there should be efforts to gain commitments from professional organizations to find ways to ensure their members use them. Dr. Baker called on the workgroup to stress that newborn screening is a risk assessment, not a test, the results of which can be found to be varied; not to be right or wrong. She also stressed the need to ensure that consultants are aware of the guide, not just physicians, so that messages are not mixed. Dr. Berry suggested asking HRSA-funded genetics networks or collaboratives to vet the guide. Dr. Tarini pointed out that the Workgroup has limited time and resources and may find it is not feasible in terms of time and resources to do validity testing. Dr. Greene suggested providing a companion sheet with the guide with suggested language on how to explain what a screen is and describing the risk. She also suggested that the disease being discussed should appear at the top of the guide and that a list of valid websites should be listed further down because many families will want to learn first —or exclusively — what they are expected to do next, such as where they should go for a lab test.

Dr. Tarini offered several potential workgroup projects, but also asked the Committee to consider whether it might be advisable to instead move several current projects into phase 2. One proposed project involves designing intervention strategies for optional newborn screening to reduce the number of parents who decide to opt out. Dr. Goldenberg agreed, saying that he would like to know why parents decide opt out. Dr. Matern did not think that the Committee should spend time studying why families may opt-out of screening for conditions that are not on the RUSP. Ms. Bonhomme disagreed. She said it is important to know what the states hear from families, because that is where most people get their newborn screening information. She asked whether the Committee is focusing strictly on conditions on the RUSP or on newborn screening.

Another potential project would be to determine the educational needs of those dealing with newborn screening conditions that become symptomatic at adulthood, which has been raised by the Committee and during recent nomination discussions. A third potential project is improving educational outreach about carrier status, especially in connection with hemoglobinopathies. Dr. Tarini acknowledged that all of these are broad topics and requested Committee guidance on where the Workgroup's time and expertise would be most effective. The Committee decided, on a general consensus basis, that the Workgroup should continue to work on gaining additional feedback on the guides to ensure that they are as useful as possible.

VIII. Follow-Up and Treatment Workgroup Update

Jeffrey Brosco, M.D. Ph.D.
Committee Member
Chair, Follow-up and Treatment Workgroup

Dr. Brosco thanked Katherine Camp, Jana Monaco and Alan Zuckerman who are departing from their official roles on the workgroup; he invited them to continue to attend and participate as they finish up the projects they have been working on. He announced that the report on medical foods for inborn

errors of metabolism is almost finished and the Workgroup is looking into publication options, in addition to posting on HRSA's website; preferably in a peer reviewed journal. Dr. Berry is taking the lead.

The Workgroup has also been working on a quality measures report, which quite long with appendices. In addition to ensuring that it is complete, the group is writing an executive summary and doing some additional work on ideas for future work. The group hopes to complete the report by February. The Workgroup has learned that there is a lot of work being done at the state level on quality measures but efforts tend to be piecemeal.

Potential new projects include assisting Dr. Kemper and Dr. Lam, who are conducting an environmental scan of long-term follow-up in newborn screening, consisting of documentation of current activities in newborn screening and identifying gaps to provide information to stakeholders. They will to generate a report that should be finished by July 2018. He reminded the Committee that the goals for long-term follow-up are improved survival and well-being with specific associated measures. The Workgroup has concluded that no single organization is likely to take responsibility for quality measures across the board but a federated system could emerge involving such organizations as state newborn screening programs, NewSTEPs and patient registries all playing a part and communicating with each other and the workgroup could propose steps each organization could take; this could be reflected in a roadmap. At least some of this work could overlap with the environmental scan. He envisions a completion date for this project of December 2018.

A. Discussion

Dr. Powell pointed out that many programs lack staff, financing, and the systems in place for entering data on long-term follow-up. Dr. Brosco conceded that these are some of the gaps the Workgroup identified and will discuss in the quality measures report and possibly the roadmap. Dr. Grosse suggested that the best way to persuade people that something is worthwhile is to show its value; describe how long-term follow-up has improved outcomes or had other positive results. Dr. Tarini commented that the Committee tends to be reactive, focusing on challenges because their solutions are mandated or priorities are triggered by scrutiny by outside entities, such as the media or the public at large. She called on the Committee to identify a list of newborn screening priorities by order of importance to determine how to allocate scarce resources. She also questioned whether long-term follow-up is as critically important as other priorities, such as timeliness, which the Committee felt was important enough to address in a letter to the Secretary of Health and Human Services. Dr. Greene pointed out that long-term follow-up is not just about data collection. She also noted that the road map approach, which has come up before, could help the Committee to identify priorities. Dr. Matern suggested that, because everyone agrees that long term follow-up is important, during the Committee's first meeting in 2019 if not before, a vote should be taken on whether to recommend to the Secretary what long-term follow-up is and what it entails, which could include work being done by other organizations, and ask the Secretary to determine how to provide incentives to states to pursue it. Dr. Greene offered that the Committee has defined what long-term follow up is. Dr. Powell said we often do not have a strong consensus on standard of care for conditions that have been screened for over many years, which has the potential to do as much harm as good and that long-term follow-up could help to determine care outcomes. Dr. Berry suggested that the Committee draft a document that specifies what long-term follow up is, what the Committee's responsibilities are, and strategies for addressing them. Dr. Bocchini noted, based on the Committee's consensus, the Follow up and Treatment Workgroup should proceed with developing the roadmap concept.

IX. Laboratory Standards and Procedures Workgroup Update

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

Dr. Kelm welcomed Dr. Shone to the workgroup and noted that Harry Hannon, Joanne Bodurtha and Koon Lai are departing; more members will join in February. The workgroup heard an update from Joe Orsini on the Association of Public Health Laboratories (APHL) QA/QC Subcommittee's work on a guidance document for determining national cutoffs in newborn screening. The draft has been reviewed by APHL's Newborn Screening and Genetics in Public Health Committee, which provided feedback. The document was found to focus heavily on what has been done historically but needs to focus more on guideline information, such as methods that could be used to calculate cutoffs, including multiples of medians, the Collaborative Laboratory Integrated Reports (CLIR) tool, the pros and cons of historical methods and newer ones. Other suggestions included incorporating more information from the College of American Pathologists' (CAP) checklist on cutoff determinations [and monitoring] in the document and more discussion of using goals for sensitivity and specificity when selecting cutoffs as well as assessing the effects of false positives and negatives and factors that affect cutoffs, such as second-tier testing. The APHL QA/QC Subcommittee hopes to solicit feedback from the newborn screening community and present the guidelines draft to the Committee in February. The Workgroup also discussed timeliness, including how improvements in this area can be linked to improved outcomes and the Workgroup would like to continue focusing on timeliness issues, such as why there is slow uptake for some tests. A future project could focus on understanding how molecular testing is likely to be used in the future for first-line and second-tier testing.

A. Discussion

Dr. Matern mentioned that the Committee suggested to Dr. Orsini that the cutoff guidelines document should include generally understandable language defining terms that are used for public consumption and asked whether APHL will make a special announcement about the guideline's availability. He also mentioned that there is no option on HRSA's website to reclassify or delete a condition from the RUSP. Dr. Bocchini concurred and said that an ad hoc workgroup might be convened, with other participants, to address this. Dr. Shone said that the Workgroups seem to be in siloes and because many of the projects the Committee is working on are cross-cutting, such as timeliness, education, and follow-up, he asked how the Workgroups could be integrated. He noted that HRSA-supported regional collaboratives and networks are required to work on multidisciplinary projects. Dr. Tarini agreed, saying that projects are being put into individual buckets and that ad hoc groups tend to bring together different people in a cross-cutting multi-disciplinary team. Dr. Tanksley said that APHL put a one-page document on its website about cutoffs months ago, which the Workgroup could use and can work with the Genetic Alliance on additional ways to share the document. Dr. Matern said that the APHL document is an overview of what has been done, but is not intended to serve as a standard operating procedure (SOP) on how to establish cutoffs and reference ranges, which laboratories need. He indicated the document still needs work and asked if the Committee would want to take on developing a subsequent document that did have SOPs?

X. Clinical and Public Health Impact of SCID Screening

Sikha Singh, M.H.S., PMP
Manager, Newborn Screening and Genetics Operations, Association of Public Health Laboratories

Adrienne Manning
Division Director, Newborn Screening
Connecticut Department of Public Health

Lisa Kobrynski, M.D., M.P.H.
Clinical Immunologist, Director, Jeffrey Modell Center for Primary Immune Deficiencies

Dr. Bocchini introduce Ms. Singh and explained that the Secretary approved the Committee's recommendation to add screening for SCID to the RUSP in 2010 and, as of August 2017, 47 newborn screening programs have been offering universal newborn screening for this condition while others are working toward full implementation.

Ms. Singh focused on NewSTEPs data that demonstrates the effect of SCID to promote nationwide screening and summarized lessons learned. In 2014, about half of states were conducting SCID screening. Today, 94 percent of infants are being screened with 48 states offering universal screening for SCID (the total takes into account Puerto Rico, the District of Columbia and Guam). Last August, APHL hosted a national SCID meeting for newborn screening stakeholders to strengthen relationships between the SCID clinical network and the newborn screening community in each state. She noted that, unlike other conditions, SCID requires molecular testing and the national SCID meeting focused on the unique challenges and opportunities this presents. In 2014, APHL provided funding for 11 states to implement SCID screening to cover implementation, technical assistance, training, education and network building. One key challenge was the lack of funding to support laboratory requirements to introduce necessary molecular testing, including space and training limitations. Another is the variability in algorithms used by states and long-term follow up procedures. Three awardees (and about 30 percent of state programs) use an FDA-approved kit whereas 7 awardees (and 70 percent of programs) use a laboratory-developed test (LDT). Interpretation of results for follow-up programs proved to be challenging as did the relative scarcity of pediatric immunologists nationwide. Ms. Singh noted that the national SCID meeting helped to foster relationships between program staff and clinicians. APHL has also been working with ACMG's Newborn Screening Translational Research Network (NBSTRN) to consider common data elements that can bridge the gap between short and long-term follow-up and understand the various databases that exist for immune deficiencies and with clinical experts to establish public health surveillance case definitions to achieve consistent diagnoses classifications across newborn screening programs. The clinical community led discussions about harmonizing diagnostic terminology, such as idiopathic versus variant and classical vs. typical. In terms of education, discussion focused on developing educational and awareness-enhancing materials and campaigns for families, clinicians, patient advocacy and support groups. APHL has worked closely with the Immune Deficiency Foundation, the Genetic Alliance and Baby's First Test to ensure programs are aware of resources. NewSTEPs, in collaboration with NBSTRN, hosts bi-monthly SCID education webinars. More information is available at www.newsteps.org.

Ms. Manning discussed Connecticut's newborn screening for SCID, was mandated in 2011. On the laboratory side they test and report abnormal results to the Newborn Screening Tracking Group. The

short-term follow-up and tracking program ensures all infants are screened and that abnormal results trigger collection of a repeat specimen or referral to a regional diagnostic treatment center.

Challenges related to implementing a molecular screening test in a newborn screening program come down to funding and space. Connecticut's newborn screening program's staff was reduced from 12 to 8 staff members by 2007 and down to 6 by 2011 due to financial constraints. After SCID screening was mandated in 2011, the state program chose the CDC's in-situ method, which is relatively inexpensive — $80,000 in instrumentation costs and $10,000 in ancillary costs — and worked with the agency to prepare for implementation. All infants born since October 1, 2011 have been screened, but the official start date was January 2012. That same year, the state newborn screening program moved into new laboratory space and acquired additional instrumentation from labs that were no longer using it. Due to lack of space, a storage area in the Serology Laboratory was converted into a sample preparation. An intern from the University of Connecticut joined the team and provided needed support. Dr. Kobrynski connected he program to a clinical immunologist to discuss guidelines for follow up. The New England Newborn Screening Program in Massachusetts provided second analyses of potentially abnormal results and guidance was provided by this program and the Wisconsin program and CDC. A total of 4,457 samples were collected for validation. Initially, cutoffs were set for all gestational ages at 55 TREC copies per microliter to avoid missing any. Initial post-validation cutoffs were broken down into full-term infants — infants greater than or equal to 37 weeks gestation — for which the cutoff was 40 TREC copies per microliter, which was later dropped slightly; for premature and infants at less than 37 weeks gestation the cutoff was 25. Five full-term infant samples were sent to Massachusetts for analysis during the validation. Four came back normal and one of was a confirmed SCID case. The current testing algorithm sets a lower limit cutoff of less than 10 copies per microliter for TREC for premature and full-term infants. Those with less than 10 get referred to flow cytometry and the same applies if there is no amplification. Results between 2011 and 2017 show that, out of 221,554 infants, there were three confirmed SCID patients, all of whom received transplants and were thriving. There were also some DiGeorge syndrome cases and a lot of T-cell lymphopenia cases identified. Ms. Manning concluded by saying that the following helped Connecticut implement SCID: the availability of an inexpensive, relatively simple screening method; assistance from Massachusetts, Wisconsin and CDC; and flexible use of limited space.

Dr. Kobrynski addressed the clinical effects of SCID. She described the findings in a study published in 2014 that showed a 95 percent survival rate among 5-year-old children with SCID who had received transplants by 3.5 months of age. Ninety-one percent of asymptomatic infants who received transplants after 3.5 months of age survived as well. She noted that survival was tied to age, not type of transplant. A study of infants in 10 states and the Navajo Nation (which has a relatively high incidence of a type of SCID revealed 52 cases among more than 3 million infants, or a birth prevalence of 1 in 58,000, compared to previous estimates of 1 in 100,000 which were based on centers or hospitals (i.e., non-population-based) reporting. Ninety-two percent of those who received hematopoietic stem cell transplants survived. Another finding from the study was that low T cells (T-cell lymphopenia), a hallmark of SCID, can also be indicative of other conditions such as DiGeorge syndrome, Trisomy 21, Trisomy 18, and ataxia-telangiectasia Another syndrome not previously associated with significant T-cell lymphopenia from birth is Jacobsen syndrome.

A study of Wisconsin data from 2008 to 2011 revealed five SCID cases among almost 208,000 births or 1 in 41,000, along with DiGeorge syndrome patients and idiopathic T-cell lymphopenia in which the infant has T cell counts significantly lower than normal but without the complications usually associated with SCID. Four received transplants, one received a synthetic adenosine deaminase (ADA) enzyme

replacement and all were thriving. New York reported nine diagnosed cases among nearly 500,000 births, a birth prevalence of 1 in 54,000 patients. Most of 9 had idiopathic T-cell lymphopenia and other syndromes. Eight of nine received transplants and one received ADA and all were thriving. California reported 26 cases of SCID in-state and six from other states, including some from the Navajo Nation and 94 percent were alive at the publication of that study. Georgia, which began screening for SCID in June 2016, has identified 3 cases in a little over a year among 129,700 births, a birth prevalence of about 1 in 43,200 births. Thus far there are 14 different genetic causes for SCID, all of which cause an absence of T-cells and severe combined immune dysfunction requiring transplantation. California cases showed that X-linked SCID is presumed to represent half of SCID cases and an almost equal number of them are caused by the IL-2 receptor gamma chain as by ADA deficiency, which can be treated using a synthetic enzyme rather than transplantation. There is now also a third option: gene therapy for adenosine deaminase deficient SCID. In addition, some other disorders, such as Sinclair syndrome, which occurs frequently in the Navajo Nation, can make children susceptible to cancers with irradiation, such as x-rays, because they have problems in repairing DNA breaks.

Dr. Kobrynski worked on a paper with Yao Ding from APHL [as well as CDC and the Washington Department of Health] that examined the cost of newborn screening for SCID. Based on public health data sources and expert opinion, they calculated the cost for screening and diagnosis [for one year in Washington State] at $741,376. The treatment cost per surviving infant was estimated to be about $197,260, compared with about $460,000 for an infant who had been diagnosed late and was symptomatic but survived. The cost of an infant with undiagnosed SCID who dies prior to transplant is $84,000, taking into account treatment for complications, compared to $27,000 for an infant who was detected through screening. The cost per life year saved was estimated to be $35,000; many published estimates consider an intervention to be cost effective if the cost per life year saved is under $100,000 to $50,000.

Dr. Kobrynski concluded that the studies indicate SCID is more common than was previously thought, that early diagnosis improves outcomes, and there is a need to develop referral and care networks that have martialed resources from many centers to gather data on treatment outcomes and analyze results to improve treatment, which, when dealing with rare diseases, is impossible to do in a single center. Lack of access to specialists in many states is a major barrier as well. How to go about sharing data is an issue as well, especially since state newborn screening labs have not traditionally focused on long-term follow-up. The multi-center Primary Immune Deficiency Treatment Consortium, which does transplants for SCID and other immune deficiencies is a potential model but not all centers report to it. A group of clinical centers, the USID Net Registry, reports on its immune-deficient patients and has been collecting data on idiopathic T-cell lymphopenia cases but, like the consortium, reporting is voluntary and there is no incentive to do so.

A. Discussion

Dr. Grosse pointed out that the benefit-cost ratio is a function of the assumed willingness to pay to avert premature death. If the figure is $9 million, the benefit-cost ratio is 5.3. If assumed willingness to avert premature death is $4.5 million, it has a 2.3 benefit-cost ratio. The figure used by U.S regulatory agencies and in Washington is $9 million to $10 million. Dr. Shone asked Ms. Singh what barriers the states who aren't screening yet are facing? He also noted that CDC has issued awards for SCID next-generation sequencing and asked if this has helped states progress toward screening? Ms. Singh cited the need for labs to retrofit to accommodate screening, to increase fees and, in the case of APHL-funded labs, to conduct validation and pilot testing activities. Other barriers are tied to legislation or are

laboratory-specific. Dr. Kobrynski pointed out that a number of laboratories have received funding from foundations to get started. Dr. Tarini asked what proportion of states have received funding to start SCID screening because it could be useful to compare timelines of those that received funding to those that did not, especially because federal funding levels and priorities are uncertain. Mr. Jelilli Ojodu who is with APHL, said that about half of the states received some federal funding from CDC, HRSA and NIH. Dr. Shone said it would be useful to know when a state has decided not to mandate screening for a disorder because it is not on the RUSP.

Dr. Greene commented on the lack of specialists and treatment in underserved areas, the challenges of developing referral networks, and the need for more specialists. She argued that the key access issue is more about maintaining funding for specialists and efforts to develop referral networks. Forty states have members of the Society for Inherited Metabolic Disorders. Where the real challenge lies is in obtaining support for ongoing access to expertise and resources.

XI. New Business

Dr. Baker proposed a new workgroup to focus on carriers and adult onset conditions and noted that Dr. Goldenberg has done a lot of research on these issues. Dr. Shone pointed out that the carrier issue touches on areas that cut across the various workgroups because it involves education, laboratory, technology and follow-up. Looking at these challenges and opportunities from a system-wide approach may be something the Committee should consider doing in 2018. Dr. Bocchini acknowledged that ad hoc workgroups have been created in the past and that it may be suitable in this case. He also suggested standardizing calls involving the chairs of each workgroup between meetings. Ms. Saarinen asked whether the workgroups have defined charters and/or expiration dates and whether the chair or the Committee decides whether they should change. Dr. Bocchini indicated that the Workgroups have specific mission statements and priorities, which were examined several years ago.

Dr. Kelm asked where short-term follow-up falls or “lives.” Dr. Greene said that when the workgroups were first formed, short-term follow-up was conducted in the laboratory although it does not necessarily need to remain there. She also said that there are various ways to examine issues and that one person’s “cross-cutting” approach is another one’s silo.

XII. Adjournment

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

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