

Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Summary
February 8, 2018

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) meeting was convened on February 8, 2018 and adjourned on that day. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

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I. Administrative Business — February 8, 2018

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 first meeting of the Advisory Committee on Heritable Diseases in Newborns and Children for 2018 and thanked attendees for their patience in accommodating the Committee's need to change the meeting schedule to a one day rather than two day meeting.

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

- Dr. Mei Baker
- Dr. Susan Berry
- Dr. Bocchini
- Dr. Jeffrey Brosco
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Dietrich Matern
- Dr. Kamila Mistry (Agency for Healthcare Research and Quality)
- Dr. Melissa Parisi (National Institutes of Health)
- Dr. Cynthia Powell
- Ms. Annamarie Saarinen
- Ms. Joan Scott (Health Resources and Services Administration)
- Dr. Scott Shone
- Dr. Beth Tarini
- Ms. Catharine Wicklund
- Dr. Catharine Riley (Designated Federal Official)

Organizational representatives in attendance were:

- American Academy of Pediatrics, Dr. Debra Freedenberg
- 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
- 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
- American Academy of Family Physicians, Dr. Robert Ostrander
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Chris Kus

- Society for Inherited Metabolic Disorders, Dr. Carol Greene
- LT COL. Adam Kanis, representing the Department of Defense, did not attend the meeting.

B. Vote on November 2018 Meeting Minutes

Dr. Bocchini assessed that Committee members need more time to review the minutes and submit edits. Minutes incorporating edits will be sent prior to May meeting and will be voted on at the May meeting.

C. Opening Remarks

Dr. Bocchini highlighted the Committee's new website format, which he invited attendees to examine. All of the information on the previous site is available on the new website. Dr. Matern asked where the link to conditions that have previously been nominated is located and where information would go about how to nominate conditions to be added to the RUSP or those that might be removed from the RUSP. Dr. Riley indicated the link to nominated conditions is accessible by clicking on the RUSP tab in the menu. HRSA staff are working to make the website easier to navigate, noting there will be a tab added to the menu to direct users to the 'how to nominate a condition' page. She noted that there currently is no form to nominate a condition for removal from the RUSP. If the Committee opts to develop this process, that information could be added to the website.

Dr. Bocchini announced that HRSA will put out a call for new members in the *Federal Register* in the coming months.

He also noted that the next ACHDNC meeting will be an in-person meeting and will be held May 10 and 11. Meeting dates have been set through 2020.

II. An Overview of Cutoff Determinations and Risk Assessment Methods Used in Dried Blood Spot Newborn Screening

Joe Orsini, Ph.D.

Wadsworth Center, New York State Department of Health

Co-Chair, APHL Newborn Screening Quality Assurance Quality Control Subcommittee

Dr. Matern was required to be recused from the discussion because it included discussion of Collaborative Integrated Laboratory Reports (CLIR).

Dr. Orsini provided an overview of the resource document, how it was developed and the intended end users, primarily state newborn screening staff, who have a strong understanding of newborn screening laboratory methodologies and risk determination. The Association of Public Health Laboratories (APHL) considers this a living document that will be updated over time.

APHL's Newborn Screening Quality Assurance Quality Control Subcommittee surveyed states regarding the use of analytical tools to establish and revise cutoffs. The survey results were presented to the Subcommittee and used to develop the first draft of the *Overview of Cutoffs and Risk Assessment Methods Used in Dried Blood Spot Newborn Screening* resource document. The document does not

provide detailed instructions on how to perform newborn screening risk assessment but describes historical and current approaches that laboratories use to conduct risk assessment as well as factors to consider when establishing and evaluating risk. It provides instruction on how to monitor and evaluate risk assessment and on when to re-evaluate cutoffs.

Dr. Orsini provided an overview of cutoff determination, explaining the use of biomarkers and different screening methodologies. Preliminary cutoffs are initially determined based on available literature, comparisons with what other states are doing, diagnostic test results, and recommendations from the manufacturers that developed the assays. Dr. Orsini also described special considerations in newborn screening, such as when to use fixed versus floating cutoffs.

He presented tools that can be used to help determine risk, such as Collaborative Integrated Laboratory Reports (CLIR). CLIR uses diagnosed case data results to help determine the distribution of markers in the affected population. Challenges with CLIR include access, which is contingent on the laboratory's ability to contribute data.

APHL has incorporated feedback from the Laboratory Standards and Procedures Workgroup as well as the newborn screening community at large; however, the document is still in draft form as feedback continues to be considered.

III. Laboratory Standards and Procedures Workgroup: Review of the Overview of Cutoff Determinations Document

Kellie Kelm, Ph.D.

Chair, Laboratory Standards and Procedures Workgroup

Dr. Kelm reminded the Committee that the Workgroup discussed the concept and reviewed previous drafts of the, *Overview of Cutoff Determinations and Risk Assessment Methods Used in Dried Blood Spot Newborn Screening* document at the February, May and August 2017 ACHDNC meetings and the Workgroup has provided feedback. In January of 2018, a revised draft that included most of the Workgroup's feedback was distributed to the newborn screening community for review and input. The Workgroup provided additional feedback at this point as well. After discussion, the Workgroup concluded that the APHL document describes the scientific processes states use to determine which specimens test within normal versus out-of-normal range and is a valuable resource for state newborn screening programs. The Workgroup also found that the document does not include best practices for screening for all conditions, nor does it offer a guide for harmonization across states. The Workgroup acknowledged that this is intended to be a living document that will be revised over time.

A. Discussion

Dr. Tarini commented that some tests, such as a complete blood count, can be performed uniformly from one hospital to another, and asked why such uniformity cannot be achieved in newborn screening. Dr. Kelm replied that many types of tests have been subject to standardization and harmonization but newborn screening varies by method and analyte. Dr. Cuthbert concurred, saying that different methods are being used and that the CDC does not prescribe what approach any given state uses; the markers and methods are decided on by the state laboratory directors who work within their populations to

establish cutoffs. The CDC receives cutoffs from the states through proficiency testing, has quality control materials with different marker levels to create a curve and is working to normalize cutoffs according to specific methods and analytes. The agency would like to collect true positive samples but is focusing on borderline samples right now, which are the most challenging to interpret and follow up on and will provide an opportunity for states to access samples from borderline specimens that they can use to identify “tricky” cases.

Dr. Greene pointed out other reasons for lack of uniformity in newborn screening results: variability in disease frequency; variability in state’s criteria; variations in the types of laboratory equipment used and the way it is set up. Dr. Freedenberg indicated that cutoffs may differ based on varying ethnic populations between states. Dr. Watson pointed out that CLIR can take a whole state’s population into consideration and compare a state’s data to the data in CLIR, which can help with borderline cases. Sometimes a re-screen is necessary. Dr. Orsini said that the overview document says that “borderline” is best used when the disease is not time-critical. When an infant can develop a disease in five days, there may not be a borderline category.

Dr. Tarini called on states which do short-term follow-up on false positive results to try to learn why they occur. Dr. Berry pointed out that there is no formal mechanism to ensure collection of false positive results across states. Laboratories that contribute to CLIR can do this but many states are not able to access this tool. Dr. Shone said that the NewSTEPS repository collects this data. Ms. Bonhomme said that Baby’s First Test is putting together material to help the public understand more clearly why false negative and false positive screens occur. Dr. Baker noted that collection of false negative results is passive; if physicians don’t relay these to newborn screening programs, there’s no way for them to know. It was suggested that different laboratories’ approaches to using CLIR or another database should be included in the overview document and that there should be a way to describe how CLIR with other database programs, such as NewSTEPS, can be used.

Dr. Bocchini asked whether the Committee felt it could vote to endorse the document as a valuable tool for states and the newborn screening community at this stage of completion. Dr. Kelm pointed out that this is an APHL document and, as such, does not need formal Committee approval and could live on APHL’s site. The Committee decided a vote was not required, acknowledged the document’s value and recommended that APHL continue to refine and improve it. It was also agreed that the Laboratory Standards and Procedures Workgroup should focus on what could be done to address public access issues and better ways to collect and store data on false positive results. Dr. Shone said that the entire newborn screening system’s needs should be examined, not just those of laboratories.

IV. Public Comment

A. Dr. Jill Jarecki, Chief Scientific Officer, Cure SMA

Dr. Jarecki discussed the nomination of SMA to the RUSP. She thanked the Committee for its careful review of all of the evidence supporting SMA newborn screening over the past nine months. She said that, in addition to the compelling anecdotal evidence of the benefits of pre-symptomatic treatment families of children with SMA have provided to the Committee, significant scientific evidence exists for it as well. Dr. Jarecki pointed to the need for early intervention, noting that babies who received Spinraza (nusinersin) 12 weeks before disease onset gained more motor milestones compared to those who received it after 12 weeks. She also noted that the average age of clinical diagnosis for type 1 SMA is 4.9

months, according to the Cure SMA database. Dr. Jarecki noted that no pre-symptomatic infant who was treated with Spinraza has died or required permanent respiratory support compared to 39 percent of symptomatic infants in one of the trials. She ended by urging the Committee to recommend adding SMA to the RUSP.

B. Ms. Elizabeth Moore, parent of children with SMA

Ms. Moore addressed the Committee accompanied by Mary, her two-year-old daughter. Her first son, William, began exhibiting declines in motor skills 30 days after birth and eventually lost the ability to eat, talk and smile. Diagnosed with type 1 SMA, he is now bedridden, unable to swallow, uses only his eyes to communicate, and needs round-the-clock care. Mary was tested and was also found to have type 1 SMA but received treatment at 2 weeks of age and walks, talks, eats, breathes, cries and screams, exhibiting all of the behaviors William couldn't. Ms. Moore said that screening newborns for SMA cannot only make the difference between life and death, "it is the opportunity to give the simple blessings of life to a family who has never heard of such a horrible disease."

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

(Because Ms. Stephenson was unable to attend this portion of the meeting, Dr. Bocchini read her prepared remarks for the record.) The MDA represents more than 40 different disorders, and promotes early screening, diagnosis and treatment for many diseases, including SMA. Ms. Stephenson urged the Committee to keep in mind that a strong follow-up and long term care infrastructure is in place — consisting of more than 150 MDA-supported care centers and more than 20 of these have SMA-specific clinics — to support the SMA community. In addition, MDA supports a provider-entered disease registry for SMA that collects data at more than 25 care center locations across 16 states and more sites are being added. Adding SMA to the RUSP will allow for earlier diagnosis of SMA patients, making it possible to collect information on early stages of the disease. Ms. Stephenson said she hoped that, in addition to seeing SMA added to the RUSP, MDA hopes it can approach the Committee again to include additional neuromuscular diseases to the panel.

D. Dr. Travis Henry, Laboratory Scientist, State Hygienic Laboratory, University of Iowa

Dr. Henry indicated that his remarks reflect his views alone. He praised the Committee for using a decision-making process and decision matrix to assess which conditions should be added to the RUSP. He added that one of the Committee's most important functions is to reduce health care disparities by reviewing and adding conditions to the RUSP for implementation by states. He called on the Committee to consider and include the legal and ethical implications of a mandate in its decision-making process. He explained that mandates take away parents' right to choose screening and argued that the state must have unquestionable certainty of the screening's benefit to justify this restriction of individual freedom, which he believes applies only to be those conditions with a readiness score of A1. If a condition does not merit such a score, more data should be collected before it is added to the RUSP, noting that the Committee followed this approach in determining whether to add severe combined immunodeficiency (SCID) to the RUSP. He concluded by saying that consideration of the responsibility of a mandate and state's legal and ethical responsibilities of removing personal freedom by making decisions that mandate screening should be included in the Committee's decision-making process.

V. Newborn Screening for Spinal Muscular Atrophy (SMA): A Systematic Review of Evidence (Part 1)

Alex R. Kemper, M.D., M.P.H., M.S.

*Division Chief, Ambulatory Pediatrics
Nationwide Children's Hospital
Lead, Condition Review Workgroup*

Lisa A. Prosser, Ph.D.

*Professor, Department of Pediatrics and Communicable Diseases
University of Michigan School of Public Health
Member, Condition Review Workgroup*

Dr. Kemper, Mr. Ojodu and Dr. Prosser presented the results of the evidence review. Dr. Bocchini pointed out that the Evidence Review Group (ERG) is independent of the Committee and does not provide recommendations or participate in the Committee's process of deciding whether to add a condition to the RUSP. Dr. Kemper asked the Committee to consider four questions as he provided a summary of the systematic evidence review: 1. The prognostic implication of SMN2 copy numbers and how that information should be used; 2. The importance of detecting compound heterozygotes and carriers and; 3. What the appropriate comparator would be to understand the effect of newborn screening compared to usual case detection, given FDA approval of nusinersen as a targeted therapy for SMA. The comparison, therefore, is not between newborn screening for supportive care alone but for early implementation of nusinersen; 4. How convincing are research data that are not available in the peer-reviewed literature.

SMA is an autosomal recessive disease that affects the motor neurons in the spinal cord and brain stem, resulting in motor weakness and atrophy. It has a broad phenotypic spectrum, ranging from birth to adulthood with differences in severity and clinical course. There are different types of SMA, which is distinguished by the maximum motor milestones each patient achieves. The evidence review focuses on types 1, 2 and 3, as they are the most common forms of the condition and manifest in childhood. SMA type zero typically affects fetuses who usually do not survive until birth.

The ERG screened 182 articles dating back to 2007 and evaluated five treatment studies as well as the Taiwan and New York pilot screening studies. Conference presentations and posters were considered as well. The ERG found itself relying more on gray literature than it had in the past, an indication of how quickly this research is developing.

One study looked into correlation between SMN2 and survival. Having more copies of SMN2 is associated with a greater likelihood of surviving longer, but it is not entirely predictive. The time between onset of symptom to diagnosis was about four months on average, with longer intervals for types 2 and 3. The type of treatment outcome data that can be collected and analyzed are limited in that they are collected primarily in early childhood. Outcome measures include ventilator-free survival and results from two motor milestone assessment tools: the Hammersmith Infant Neurological Examination (HINE), for infants age 2 to 24 months and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) for children between four months and four years of age.

Ninety five percent of cases of SMA are caused by a homozygous deletion of SMN1 exon 7; the remaining 5 percent are compound heterozygotes. In general, there are two approaches to screening. One screening approach looks for SMN1 deletions on both alleles and was used in a pilot study in Taiwan. The Taiwan approach does not seek to detect carriers. Another screening approach was used in a three-hospital pilot project in New York. This approach is designed to detect if SMN1 is present, and if it is, how the quantity of SMN1 relates to the quantity of other genes present. This approach can identify one or two deletions, making it possible to identify heterozygotes and carriers. CDC developed an assay that targets SMN1 deletion that does not detect carriers and can be multiplexed with SCID screening.

The New York pilot project screened 10,362 newborns. According to unpublished data, one newborn was identified with SMA. This newborn had a homozygous deletion of the exon 7 and two copies of SMN2. The case was identified seven days after birth; treatment began with nusinersen at 15 days of age and one year later, the child did not require mechanical ventilation and has met developmental milestones. One hundred forty four carriers were detected (1 in 72 screened newborns).

The Taiwan project was conducted from November 2014 through September 2016, before nusinersen was widely available. Among about 120,000 study subjects, seven were found to have confirmed homozygous deletions; the median age of diagnosis was at 8 days of life. Initial positive results from eight other patients were found to be false positives. The study did not detect carriers.

In terms of treatment, nusinersen is the only FDA-approved treatment for SMA; it works by altering the splicing of SMN2 pre-RNA, which results in more functional SMN protein. The ERG focused primarily on two of five manufacturer-funded studies of the drug.

ENDEAR is a phase 3 trial of subjects with infantile onset SMA (before 6 months of age) and two copies of SMN2. The study was terminated early when a dramatic difference in survival rate was detected—62 percent event-free survival in the treated group compared to 32 percent in the control group. The difference in motor milestones was also dramatic—41 percent compared to no response in the control group.

NURTURE is an ongoing phase 2, open-label study of infants identified as having presymptomatic SMA. 20 subjects with SMA were followed (no control group), 15 of whom are siblings; nine were alive one year after birth. Six have two SMN2 gene copies. Three who have three copies have a higher number of advanced motor skills than the group with two SMN2 copies. Limitations of the study include a small number of subjects (impacts ability to conduct statistical analysis), a relative lack of data on presymptomatic identification of infants with SMA, and the fact that outcomes are generally limited to the first year of life. The ability to gauge the extent of developmental changes is limited as well. There are no peer-review-published reports to compare presymptomatic detection to usual clinical detection.

Dr. Kemper concluded that more study is needed of the role the SMN2 copy number plays in risk stratification or prognosis. He also noted that Dr. Jarecki has been working with experts in the SMA treatment community to develop guidelines that use the Delphi technique to recommend when treatment of asymptomatic patients should begin, based on copy number and type of follow-up needed.

Dr. Prosser began her presentation by explaining that her team is using decision analysis and decision modeling to quantify screening and health outcomes for newborn screening of SMA compared to clinical identification with the assumption all probable type 1 SMA cases will be treated. Simulation modeling

was used to estimate ranges for population-level health benefits for a U.S. birth cohort of 4 million American births per year. The primary health outcomes the team modeled for were mortality and ventilator dependence but not motor function. The focus was primarily on SMA type 1 and on projected health benefits over year one of life.

Under clinical identification and taking into account an estimated birth prevalence of 1 in 11,000, more than half of the cases of SMA (type 0 through type 4) would be type 0 and 1. The three outcomes that were modeled were alive and non-ventilator dependent at age 1, ventilator dependent at age 1 or death. The model assumes all infants with likely SMA type 1 would be treated with nusinersen as opposed to watchful waiting until symptoms emerge. An estimate of how likely infants with a set number of SMN 2 copy numbers are to have SMA type 1 was developed as well based on available data. For example, 91 percent of infants born with an exon 7 deletion and two copies of the SMN2 gene would be expected to have type 1 SMA. No trials have been conducted that compare treatment for a newborn screened population to an unscreened, untreated one. To estimate the potential efficacy of treatment, the group examined infants in the ENDEAR study versus those who were treated later. For asymptomatic infants, the study involved results from the NURTURE study, focusing on the nine study subjects who were alive after one year.

The model estimated that among the infants clinically identified with SMA type 1, 52 cases would be ventilator dependent at 1 year of age and 36 would have died. In contrast, the model estimated that under newborn screening, only 4 would be expected to be ventilator dependent at 1 year of age and 33 deaths would be averted through newborn screening that would not have been averted under clinical identification. Some factors that could cause unknown variation in results include what proportion of cases are likely to be symptomatic or asymptomatic at time of confirmed diagnosis and conditional probabilities of subtype given the SMN2 copy number.

A. Roll Call

All Committee members and organizational representatives were present during the afternoon roll call except for Dr. Baker and Dr. Cuthbert who recused themselves from the next presentation and COL. Kanis, who did not attend the meeting.

VI. Newborn Screening for Spinal Muscular Atrophy (SMA): A Systematic Review of Evidence (Part 2)

Jellili Ojodu, M.P.H.

Director, Newborn Screening and Genetics

Association of Public Health Laboratories &

Project Director, Newborn Screening Technical Assistance and Evaluation Programs (NewSTEPS)

Mr. Ojodu's presentation focused on the public system impact of adding SMA to the RUSP. This assessment focuses on the net benefit, feasibility of implementing the screening, and newborn screening programs' readiness to do so. Readiness is defined as a newborn screening program's ability to implement screening within one year; developmental readiness as the ability to implement within three years and; unprepared as needing more than three years to implement screening. Feasibility is

defined as ensuring the availability of an established population screening test, the existence of a clear approach to diagnostic confirmation and an acceptable treatment plan and an established approach to long-term follow-up.

The state health department in New York has been conducting pilot screening for SMA through three hospitals, which began in January 2016; this limits the amount of screening implementation data available. Two states, Massachusetts and Utah, started population screening in January of this year. Wisconsin plans to start screening in July.

A fact sheet and Webinars were used to inform states about the survey and the condition (screening algorithms and treatment). Fifty-three states or territories, including Washington, D.C., Guam and Puerto Rico, were surveyed. Forty one states responded (87% response rate). The survey was designed to determine the supports they have and challenges they confront in implementation. Follow up in-depth phone interviews with five states that are screening, conducting or planning pilot projects provided additional information about the challenges these programs face in working to introduce screening. The challenges they highlighted were: 1. Getting legislative buy-in and funding approval; 2. Developing a reporting algorithm and deciding whether to report carriers; 3. Securing genetic counseling resources, which would be particularly important if carrier status were reported; 4. Establishing relationships with new groups of specialists such as pediatric neurologists and; 5. Ensuring that patients have access to evaluation and treatment (including late onset cases).

In terms of readiness, most of the states said that it would take one to three years after SMA was added to the RUSP to gain authorization to screen for SMA and another one to three years to obtain funding to do so. Some states said they would need another one to three years to implement the screening, in part due to the need to buy equipment, and develop the ability to report results (related to LIMS capability).

The level of feasibility is affected by six factors: 1. The existence of a reliable test using real time PCR, which thus far has yielded no false positives (the true rate of false negatives will not be known until true population testing is conducted at multiple sites); 2. An approved treatment, even though its long-term effects are unknown; 3. The rate of missed cases is anticipated to be from 5 percent to 7 percent (based on the reported frequency of affected infants who are not homozygous for the SMN1 exon 7 deletion); 4. Potential treatment cost issues, including insurance and Medicaid coverage; 5. The ability to conduct long-term follow-up of patients is unclear and; 6. CDC is prepared to provide quality control materials but if a large number of states implement simultaneously, the supply could become scarce.

Newborn screening programs' ability to build on current infrastructure and multiplex with SCID screening makes the screening methodology relatively inexpensive to implement, with an expected incremental cost of 10 cents and \$5. Additional costs would be incurred for second-tier testing, including determining SMN2 copy number., as there could be additional costs for hiring full-time personnel or purchase equipment to do second-tier testing.

Most state newborn screening programs (70%) have not determined their screening approach. Of the remaining, 19% indicated they would not attempt to identify and 11% indicated the method used would identify carriers.

A. Discussion

Dr. Kelm asked whether there are any known or potential adverse effects associated with nusinersen. Dr. Kemper said he knew of none except for the effects of repeated lumbar punctures. Dr. Kelm noted

that published information indicates increased levels of urine protein and wondered whether this is a significant issue. Dr. Kemper said that would not typically be considered a serious adverse effect. This was not reported in the studies reviewed, but was an adverse of effect of the class of drugs.

Dr. Shone pointed out that state programs said they may need up to three years to obtain authorization, another three years to obtain funding and an additional three to implement SMA screening — a total of nine years. Dr. Kemper said that many states may not know until they learn more about the new screen how difficult it will be to implement, and answers may change once they learn more. However, the evidence review’s limited (nine-month) time frame limits the ability to explore these issues. In addition, the survey cannot be modified. Mr. Ojodu pointed out that some states may be able to take some of the necessary steps simultaneously. Dr. Shone said that states consistently identify cost and the need to identify funding sources as barriers to implementation. He suggested that the Committee consider these barriers in addition to other newborn screening concerns such as timeliness, cutoffs, etc. when discussing challenges newborn screening programs face. Dr. Lam said these data are being delivered by states that are expressing their intentions, many of which are based on past experience but do not reflect future developments in a rapidly evolving area of research. She added that some states are able to start screening for SMA more rapidly than they could for other conditions, in some cases, within a year, in part because it can be multiplexed with SCID.

Ms. Saarinen pointed out that a treatment’s desired outcome can be very different for a family than it is for a researcher or a clinician; it is a subjective determination, not an absolute. Dr. Tarini agreed, saying that it is hard to define “significant benefit” — whether it means simply survival, improvement or the achievement of normalcy. Different people may weigh these benefits differently. She also reminded the Committee that its job is to determine the incremental benefit of newborn screening compared to identifying infants with SMA clinically.

Dr. Shone said he disagreed with the idea of adding a disorder to the RUSP to create a population of children who screen positive for the disease and can be used to evaluate potential treatment. Dr. Greene predicted that, despite the rapid production of research data, it will take decades to know whether treating a baby at several days or several months after birth will be of incremental benefit.

VII. Committee Report: Newborn Screening for Spinal Muscular Atrophy (SMA)

Beth Tarini, M.D., M.S., FAAP

*Associate Professor and Division Director
General Pediatrics & Adolescent Medicine
University of Iowa Hospitals & Clinics*

Dietrich Matern, M.D., Ph.D.

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Dr. Bocchini explained that Dr. Tarini and Dr. Matern served as Committee representatives on the ERG to review its work and develop a report to the Committee regarding the evidence review of SMA and to help lead the Committee’s discussion.

After reviewing the information covered in earlier presentations, Dr. Tarini noted there is still much to be learned about the benefits of nusinersen. She referred to a chart that Dr. Kemper presented on milestone scores from several sets of infants enrolled in studies of nusinersen, noting that limitations of these studies include a small number of study subjects, subjects are followed for a limited period of time, and some are at different stages in the trials and therefore haven't reached the endpoint. She also pointed out that the case mix comparison between each group is not fully known and that it may not be possible to determine which outcomes are driven by disease severity and which by the efficacy of treatment. She also noted that the therapy is expensive, reportedly costing \$125,000 per vial, per dose.

She and Dr. Matern debated what types of results would represent significant benefit and decided that this would encompass survival and improved neuromuscular development and that, when taking these two outcomes into consideration, there was moderate certainty of significant benefit. If the significant benefit had been defined as normal neuromuscular development and survival, they felt that the data showed there was low certainty of significant long-term benefit. There is no way to determine how far each child was from developing normally.

Dr. Matern discussed various aspects of feasibility and readiness. The evidence presented indicates SMA screening is feasible and can be multiplexed. He explained that the real-time PCR assay detects 95 percent of all SMA cases; to detect the remaining 5 percent additional testing would have to be done. Dr. Matern said that he and Dr. Tarini struggled a bit over the definition of readiness but agreed with Mr. Ojodu's finding that "ready" means the ability to implement screening within a year after the state authorizes the test and when funding is available.

He concluded, based on his and Dr. Tarini's review that: 1. The net benefits of SMA screening are moderate; 2. The rate of feasibility is high and; 3. Many states are or could be developmentally ready (within one to three years) to implement. They also decided to rate SMA as a B2 using the decision matrix.

Dr. Matern does not think it is necessary to wait for peer-reviewed guidelines to be published for management of specific SMA types since a draft has been developed and submitted for publication. Dr. Matern also pointed out that the RUSP has core conditions and secondary targets that could lead to questions regarding whether the core condition is SMA due solely to homozygous deletion or to all forms of SMA caused by SMN1 mutations or other variations. Otherwise, other secondary targets would be all cases that are not homozygous. He added that states that make the decision to add SMA need to stipulate clearly that they are not looking for all SMA types because 5 percent will go undetected.

With regard to treatment, the evidence primarily focuses on treatment for type 1 SMA, which makes up 40 percent to 60 percent of the cases, but late-onset and non-classic forms of disease should also be considered because these cases are likely to benefit from treatment as well. Follow-up protocols are also needed to determine when to start treatment and it has been reported those are coming soon.

In terms of coverage for patient costs, discussions with pediatric neurologists who see patients indicated that some insurance plans require regular updates on the effect treatment is having to determine whether it should be covered on an ongoing basis. As a result, treatment guidelines would be welcome because not every center can do relevant HINE, CHOP INTEND or other developmental milestone studies and there should be some sort of agreement regarding what is necessary to justify treatment.

He concluded by saying that he and Dr. Tarini recommend that the Committee recommend to the Secretary of HHS that newborn screening for SMA caused by homozygous deletion in exon 7 in SMN1 be added to the RUSP as a core condition, with a B2 rating on the decision matrix.

A. Discussion and Vote

Dr. Powell asked Dr. Matern to clarify what he meant when he said the most benefit would be for type 2 and type 3 SMA. Dr. Matern explained that these are later-onset cases and that, since they are milder, may be easier to treat than classic cases. He cautioned, however, that not much is known about the effect of treatment in pre-symptomatic babies after 12 months of treatment — assuming they are type 1 cases with two *SMN2* copies. No studies have been conducted on infants with pre-symptomatic SMA with three *SMN2* copies. Dr. Swoboda, an audience member, offered that in her clinical experience those with three copies have been completely rescued (developing normally) whereas those with two copies are not responding as uniformly. She also offered that people with three copies are also more likely to develop type 2 SMA whereas those with two copies are more likely to develop type 1, but overlap does occur. Dr. Kemper cautioned that copy number should not be conflated with SMA type. Dr. Matern pointed out that the number of *SMN2* copies is not entirely predictive and that the screening test is more of a risk stratification. Dr. Kemper also reminded the Committee that it could not base its findings on unpublished study results.

Dr. Shone said, since long-term benefits of treatment cannot be assessed at this time, neither can the potential harm of treating people. Dr. Matern concurred that the long-term benefits of treating babies that are homozygous and may have just two *SMN2* copies is not clear and this warrants an honest discussion with parents so that they can choose whether to pursue treatment. Dr. Kemper confirmed that improvement in mortality during the first year of life through treatment seems clear but development outcomes are not, in part because of the ways they have been reported. In terms of treatment, Dr. Kelm reported that the FDA's drug review of nusinersen noted that nusinersen is known to accumulate in the kidneys but there is no long-term data on renal toxicity, a known issue in connection with oligos.

Dr. Tarini said that this discussion raises the issue of deciding whether the Committee should consider mortality separately from quality of life issues. Dr. Parisi asked both Dr. Tarini and Dr. Matern if mortality is considered in their rating of SMA screening and if not, would including it change the rating. Dr. Matern said the rating was driven primarily by the availability only of short-term data but he believes that evidence of maintenance or improvement of motor milestones at two or three years of life could have warranted changing the SMA screening rating to A1.

Dr. Wicklund pointed out that the Committee had originally decided only to recommend that conditions rated A1 be recommended for addition to the RUSP but Dr. Bocchini said that this was less of a rule and more a guideline. He added that other conditions have had a B rating, for example MPS1.

Dr. Tarini pointed out that this discussion shows that decision-making process should be revisited later but not just for the purpose of deciding whether any condition should be removed but to examine the decisions the Committee made to see whether it anticipated correctly in making its decisions. Dr. Bocchini pointed out that the Committee did just that for critical congenital heart disease recently and for SCID and suggested that a workgroup could examine a potential approach to revisit and re-evaluate decisions that have been made and implemented. Dr. Berry suggested that a conditional approval approach be considered whereby the screen is implemented on a provisional basis and subject later to a

final decision based on subsequent investigation. Dr. Brosco pointed out this approach could be difficult for states, to introduce a screen but then halt its use. He thought it unlikely that most states would be willing to do that.

Dr. Shone agreed and added that he thought the decision-making process in this case was being rushed and warranted the presentation of more data. Dr. Matern pointed out that there are no false positives in screening for babies who are homozygous for the SMN1 deletion and it has been established that there is successful treatment. Dr. Swoboda, an audience member, offered that interim findings of a study [unpublished], with about two-and-a-half years of data thus far, show the benefits of treatment and the plateaus and declines in motor development could be attributable to various factors such as the development of unrelated illness, which can be exacerbated by the condition. Ms. Scott reminded the Committee that it is bound by the evidence in the evidence-based review conducted. Dr. Bocchini added that unpublished data the Committee is made aware of do serve as indirect evidence.

Dr. Bocchini entered a motion on whether to approve Dr. Matern's and Dr. Tarini's recommendation to recommend to the Secretary of HHS the addition of Spinal Muscular Atrophy due to homozygous deletion of exon 7 in SMN1 to the Recommended Uniform Screening Panel.

Voting in favor: Dr. Berry, Dr. Bocchini, Dr. Brosco, Dr. Matern, Dr. Parisi, Dr. Powell, Ms. Saarinen and Dr. Tarini.

Voting against: Dr. Kelm, Dr. Mistry, Ms. Scott, Dr. Shone and Ms. Wicklund.

Dr. Baker and Dr. Cuthbert recused themselves.

Dr. Bocchini announced that the motion passed with eight in favor and five against. There were no abstentions. A letter containing this recommendation will be sent to the Secretary of HHS. Dr. Bocchini thanked the Evidence Review Workgroup for completing its first nine-month evidence review, which he deemed to be successful.

VIII. Follow-Up and Treatment Workgroup Report: The Role of Quality Measures to Promote Long-Term Follow-Up of Children Identified by Newborn Screening Programs

Jeffrey P. Brosco, M.D., Ph.D.

Chair, Follow-up and Treatment Workgroup

Dr. Brosco provided an update on the report he described on the Follow-Up and Treatment Workgroup's behalf during the August and November 2017 meetings. He reminded the Committee that the report was drafted in response to a charge from 2016 to focus on quality measures as a way of assessing and driving long-term follow-up and a draft of the report has previously been presented to the Committee. The report describes quality measures, provides case studies and identifies gaps and potential next steps. The Workgroup has completed its work on the report and is asking if there is an informal consensus among Committee members to move forward with the dissemination plan. This involves posting the report on the Committee's website, encouraging other organizations to highlight it to their constituents and pursuing publication of the report's 3-page executive summary. Possible next steps are: 1. Encouraging stakeholders to participate in long-term follow-up of newborn screening, using

existing family-focused and parent-based networks; 2. Identifying a core set of quality measures and associated data resources to ensure that newborn screening is an identified population and; 3. Ensuring that this is included in electronic medical records and other data sets.

Dr. Bocchini said he thought the Workgroup had come up with an appropriate plan and asked whether there was a general consensus on the part of the Committee to this effect. He noted a large number of Committee members nodding to indicate assent and heard no objections; as a result, the report will be posted on the Committee's website and the Workgroup will pursue next steps as outlined. Both Dr. Brosco and Dr. Berry praised Dr. Alan Zuckerman for the enormous amount of time and expertise he put into this project.

IX. New Business

Due to time constraints, the portion of the meeting that would have been devoted to new business was not conducted.

X. Adjournment

Dr. Bocchini thanked all who attended for their enthusiastic participation during this shortened meeting.

The next meeting will be held May 10-11 at HRSA's headquarters in Rockville, Md.