Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Minutes of February 10-11, 2022

Virtual Meeting

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Association of State & Territorial Health Officials
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Forthcoming

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Genetic Alliance
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DAY ONE: Thursday, February 10, 2022

Welcome, Roll Call, Committee Business

***Cynthia M. Powell, MD, MS, FACMG, FAAP*, Committee Chair**
***Mia Morrison, MPH*, Designated Federal Official, Health Resources and Services Administration (HRSA)**

Dr. Cynthia Powell welcomed participants to the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) meeting and conducted the roll call.

Committee members in attendance were:

- Dr. Kamila Mistry (Agency for Healthcare Research & Quality)
- Dr. Kyle Brothers
- Dr. Jane DeLuca
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Michael Warren (Health Resources & Services Administration)
- Dr. Jennifer Kwon
- Dr. Shawn McCandless
- Dr. Melissa Parisi (National Institute of Health)
- Dr. Chanika Phornphutkul
- Dr. Cynthia Powell (Chairperson)
- Dr. Scott Shone

Organizational representatives in attendance were:

- American Academy of Family Physicians, Dr. Robert Ostrander
- American Academy of Pediatrics, Dr. Debra Freedenberg
- American College of Medical Genetics & Genomics, Dr. Max Muenke
- American College of Obstetrics & Gynecologists, Dr. Steven Ralston
- Association of Maternal & Child Health Programs, Sabra Anckner
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Department of Defense, Dr. Jacob Hogue
- Genetic Alliance, Natasha Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Gerard Berry

Dr. Powell welcomed two new Committee members: Dr. Jennifer Kwon and Dr. Chanika Phornphutkul. Dr Kwon is Director of the Pediatric Neuromuscular Program at the University of Wisconsin. Dr. Phornphutkul is a professor of Pediatrics and Pathology and Laboratory Medicine and Genetics at Brown University and Director of the Division of Human Genetics at Hasbro Children's Hospital.

There will be two Committee announcements that will soon be posted in the Federal Register. One is a call for nominations for voting Committee membership and the other is for nominations for organizational representatives. In July 2021, HRSA received a nomination package for Krabbe disease, also known as globoid cell leukodystrophy, which was first nominated in 2007 but was not recommended to the Recommended Uniform Screening Panel (RUSP). In October 2021, the National CMV Foundation submitted a nomination package for congenital cytomegalovirus (cCMV). The Nomination and Prioritization Group is reviewing both nominations and Dr. Powell will keep the Committee informed of next steps.

Dr. Powell reported on updates to the Committee processes. At the November 2021 meeting, the Committee approved updates to the condition nomination package. She advised nominators to use the version of the nomination package that is now on the ACHDNC website and invited those who are working on nomination packages to reach out to her or to Mia Morrison for technical assistance. During the Committee's review on updates to the nomination, evidence-based review, and decision matrix processes, the Committee received several public comments addressing the potential for the number of condition nominations to outpace the Committee's review capacity. Dr. Powell has therefore determined that review capacity will be an area of focus for the coming year.

A Committee member moved for a vote to approve the minutes of the November 2021 meeting. The motion was seconded, roll was called, and the motion passed unanimously.

Overview of New ACHDNC Resources

***Cynthia M. Powell, MD, MS, FACMG, FAAP*, Committee Chair**

Dr. Powell reminded the Committee that their 2019 review of Committee processes identified a critical recommendation to develop new consumer-friendly resources. These new resources were developed in consultation with members of the Evidence-based Review Group and newborn screening experts and are now on the ACHDNC website. In addition to a new page on the history of ACHDNC, there are six new or updated website pages describing Committee processes. Dr. Powell briefly reviewed the new content in each page:

1. **Nominate a Condition** includes a new nomination form with fillable and standard PDF versions and new resources to explain Committee processes.
2. **Condition Nomination Review** includes an easy-to-follow, downloadable graphic depicting the nomination and review process, including a timeline of how a nomination moves through the process.
3. **Nominate a Condition FAQs** provides resources for groups nominating a package or for those interested in learning more about how a condition is added to the RUSP.
4. **Key Questions Considered by the Committee** provides a concise overview of the information the Committee reviews in a nomination package.
5. **Sample Questions Addressed in an Evidence-based Review** provides examples and explanations of the overarching topic areas that are addressed in an evidence-based review, including key questions under each topic.

6. **Committee Approach to Evaluating the Condition Review Report** is based on the decision matrix guidance approved by the Committee at the November 2021 meeting and provides an explanation of how the decision matrix is used to assign a rating to the nomination condition.

Committee Discussion
***Cynthia M. Powell, MD, MS, FACMG, FAAP*, Committee Chair**

- A Committee member suggested that it would be interesting to pool responses from applications on the potential harm of false positives and the uncertainty that early screening can create. Dr. Powell responded that there is research being conducted on this topic and added that it could be difficult to capture this information from applications.

Public Comments

Joseph Muenzer
Dr. Joseph Muenzer is a pediatric geneticist and researcher at the University of North Carolina at Chapel Hill with more than 35 years of experience in the diagnosis, management, and treatment of patients with Mucopolysaccharidosis Type II (MPS II). The lack of newborn screening for MPS II, the rarity of the disease, and delayed diagnoses have made it difficult to demonstrate the effectiveness of early intervention. However, Dr. Muenzer's clinical experience with siblings indicates that a child with MPS II who is treated with ERT before onset of significant disease, typically before one year of age, will have dramatically improved outcomes as compared to a sibling who is diagnosed and treated later. Based on the rarity of MPS II, the available treatment to prevent disease progression, and his studies that indicate improved outcomes with early intervention, Dr. Muenzer strongly supports the addition of MPS II to the RUSP.

Avram Joseph
Mr. Avram Joseph is Vice-President of the MPS Superhero Foundation and father of a son with MPS II. When his son was born in 2013, he was screened for genetic endocrine hemoglobinopathy, immunology, and other metabolic conditions. In 2016, after constant challenges, his son was diagnosed with MPS II, a disease that is known to impact a child's ability to walk, talk, and eat independently by the age of 10, and is also known to take lives by the early teenage years. MPS II can be treated with early intervention of ERT administered on a weekly basis. Mr. Joseph's son missed nearly 165 infusions of ERT that may have slowed down the clinical progression of the disease. He said that the Committee's decision today will be too late for his son but not too late for someone else.

Kim Stevens
Ms. Kim Stevens is mother to a son who was diagnosed with MPS II when he was two-and-a-half years old. By the time he was diagnosed, her son had seven surgeries and met with five specialists who did not identify the disease. MPS II was first considered during a visit to an ear, nose, and throat doctor who recognized signs of the disease. Although her son was diagnosed very late and a lot of damage had already been done, the treatment he received has given them time. She wonders what his life would be like if he had received earlier treatment. Her hope is that other children can receive their diagnoses at birth and receive treatment immediately.

Barbara Burton

Dr. Barbara Burton is a professor of pediatrics at Northwestern University and has been a practicing clinical and biochemical geneticist for more than 40 years. When ERT became available in 2006, she treated seven sibling pairs in which an older brother's MPS II diagnosis led to the younger sibling's earlier diagnosis and treatment. In each of these sibling pairs, she found the burden of disease to be significantly less in the younger siblings. In three of the sibling pairs, pre-symptomatic treatment was started within the first three months of life. Today, at the ages of three, four, and 10 years, none of these younger siblings has required any of the surgical procedures that their older siblings needed, nor do they have any evidence for cardiac disease or joint restriction that their older brothers had. They are essentially physically indistinguishable from healthy children, despite the fact that they carry the same severe neuronopathic phenotype. Dr. Burton also treated two adult cousins with attenuated MPS II who received ERT in their late 20s. One died at age 40 of respiratory failure and the other died at age 36 from post-operative complications following aortic valve replacement surgery. In 2006, their younger cousin was diagnosed and treated soon after birth. He is now 15 years of age and is a healthy, normal-appearing adolescent of normal height with no evidence of cardiac disease or abnormal pulmonary function who is currently a high school football player. Dr. Burton would like this outcome to be available to all children and strongly recommends adding MPS II to the RUSP.

Amy Cherstrom

Ms. Amy Cherstrom is a mother of three sons, two of whom have been diagnosed with MPS II and are treated by Dr. Burton. Although her eldest son does not have MPS II, her second son was diagnosed at the age of two and began ERT treatment soon after. Because of her second son's diagnosis, when Ms. Cherstrom's newborn son went into respiratory distress soon after birth, he was able to receive a diagnosis almost immediately and began ERT at three months of age. While her second son has had numerous surgeries and therapies, communicates with gestures, and attends a specialized school, her youngest son has had a vastly different experience and is thriving at school. Ms. Cherstrom asked the Committee to provide other children with the newborn screening that would give them the opportunity to not only survive but thrive.

Nicholas DiTommaso

Mr. Nicholas DiTommaso was diagnosed with MPS II at the age of 10 and has an attenuated version of Hunter syndrome, which has given him the opportunity to speak for all of those who do not have the same advantage. It took three years for him to receive a diagnosis for something that could have been screened at birth. Even with an attenuated case of Hunter syndrome, treatment has changed his life in many ways—he feels more energy and many of the degrading effects he experienced early in his life have been slowed or stabilized. He said that the impact of treatment cannot be understated. There are irreversible negative impacts of MPS II that take hold before many children show enough symptoms for a diagnosis. Newborn screening would help prevent these degenerative impacts and improve the quality of life for many children, providing an opportunity for them to attend college, enter the workforce, and contribute to the world. ERT is a life-altering treatment that is not being used to its fullest potential and the resources that are invested in the diagnostic journey toward MPS could be applied to newborn screening. He asked the Committee to consider the opportunity to make this difference.

Matthew Ellinwood

Dr. Matthew Ellinwood is the Chief Scientific Officer at the National MPS Society and has been active in MPS research for more than 20 years. He is a co-nominator for the inclusion of MPS II on the RUSP and has served on the technical expert panel reviewing the nomination. The goal of clinical research is to develop both an effective therapy and a means of early diagnosis. Currently, there is a need to unlock the full benefits of clinical progress to children with MPS II, which can only be accomplished by the Committee. The National MPS Society and its allied communities are committed to supporting all newly diagnosed MPS II infants and stands ready to ensure that MPS II patients are well-treated and supported after their diagnosis. In addition to his public comment, the community has provided approximately 3,050 signatures in support of this nomination—representing individuals with MPS II, their families and extended families, friends, community members, researchers, industry partners, clinicians, and members of the allied health professions. A child born with MPS II deserves to receive a diagnosis at birth. Waiting for a diagnosis to be apparent is waiting too long and will result in irreversible damage. In recent years, the nation has become mindful of disparities in health and access to health care. Providing newborn screening for MPS II will ensure that every child has an opportunity to lead as normal and healthy life as possible.

Mark Dant
Mr. Mark Dant is Board Chair of the Washington DC-based EveryLife Foundation for Rare Diseases and parent to a son with MPS I. His son was diagnosed in 1991 at the age of three-and-a-half, many years before treatment was available and newborn screening was possible. His son received his first infusion 24 years ago, making him the world's longest ERT-treated patient. MPS I was added to the RUSP in 2016 and has since helped provide countless children with an opportunity for a fuller life. Elaprase does not cross the blood-brain barrier (BBB) and will therefore not treat cognitive decline in severe forms of MPS II. Aludurazyme, the treatment for MPS I, also does not cross the BBB, but still results in greatly improved patient outcomes and quality of life. There is no reason to allow infants born with MPS II to embark on a long diagnostic odyssey before treatment when they can receive an early diagnosis and treatment before irreversible damage is inflicted. Children with attenuated Hunter disease may not show signs of their disease for several years, yet the damage continues and may be lifelong and irreversible. Last year, his son was married despite his 34-year journey through surgeries and treatment. Those who are diagnosed at birth will not have to endure the pain his son endured. He asked the Committee to vote to include MPS II to the RUSP.

Newborn Screening for Mucopolysaccharidosis Type II: A Systematic Review of the Evidence (Part 1)

Alex R. Kemper, MD, MPH, MS, **Lead, Evidence-based Review Group**
Jelili Ojodu, MPH, **Member, Evidence-based Review Group**
Lisa A. Prosser, PhD, **Member, Evidence-based Review Group**

Dr. Alex Kemper first provided an overview of MPS II. MPS II is a lysosomal storage disorder due to dysfunction of the enzyme iduronate-2-sulfatase (IDS) that is caused by mutations in the *IDS* gene leading to an accumulation of two glycosaminoglycans (GAGs). It is either classified as severe (i.e., neuronopathic) or attenuated (i.e., non-neuronopathic). Approximately 60 percent of individuals with MPS II have the severe phenotype, but the phenotypic expression is highly variable leading to a broad spectrum of involvement.

Dr. Kemper then presented the major findings from the Evidence-based Review Group's evidence review. The data informing their understanding of the disease course and epidemiology originate from the Hunter Outcome Study, which is an effort established in 2005 to capture data from 29 countries on patients who are untreated or who received idursulfase (i.e., ERT). It also includes retrospective data on patients who died prior to entering a study. The Hunter Outcome Study includes multiple studies of different subpopulations and analytic approaches.

Studies show that the disease course of MPS II commonly includes cardiac valve thickening, splenomegaly and hepatomegaly, obstructive sleep apnea, reduced pulmonary function, skeletal disease and progressive joint stiffness, and behavioral problems and cognitive impairment. In its severe form, the disease course also includes intellectual disability and more significant behavior problems. One Hunter Outcome Study found that the median onset of symptoms was one-and-a-half years of age and the median diagnosis was not quite three-and-a-half years of age, indicating a gap between symptom development and diagnosis. Another study followed MPS II patients into adulthood, finding that the rate of survival to 21 years of age was 52 percent in those treated with ERT at any age and nine percent in those not treated. A recent epidemiological review reported a prevalence range between 0.13 and 2.16 cases per 100,000 children. After excluding outliers, the prevalence narrows to between 0.26 and 0.64.

Diagnosis is based on confirmation of low IDS enzyme activity, as well as normal enzyme activity in at least one other sulfatase to rule out other conditions, and confirmation of elevated urine GAG levels. A molecular diagnosis can support these tests but is not necessarily confirmatory. There are more than 700 variants of the *IDS* gene and more significant deletions can predict the more severe form of MPS II. Some individuals may have borderline low IDS or elevated GAG that creates diagnostic uncertainty. For these individuals, the current recommendation is for follow-up every six to 12 months for typically up to two years.

Screening is based on IDS enzyme activity in dried blood spots either through tandem mass spectrometry (MS/MS) on slides or through fluorometry with digital microfluidics. There is an optional second tier test using dried blood spots for GAG levels. Screening methods differ across states. Dr. Kemper reviewed the newborn screening program in Illinois, which uses tandem mass spectrometry and began in December 2017. Between 2017 and 2021, there were 546,000 newborns screened, of which 71 were referred. Nine of the referrals were confirmed with MPS II, 43 showed biochemical pseudodeficiency, nine were normal, five were referred for follow-up, and five were lost in follow-up process. Dr. Kemper highlighted an interesting case in which a newborn positive screen led to additional diagnoses in a two-year-old brother, the maternal great uncle, and the maternal grandfather.

He then reviewed the newborn screening program in Missouri, which uses plate reader fluorometry and began in 2018. In 2020, there were 68,640 newborns screened, of which 11 were referred. One referral was confirmed with MPS II, two had biochemical pseudodeficiency, one was normal, five were in follow-up, one died before referral, and one declined further testing. Additionally, New York is conducting a pilot of MS/MS in a number of select hospitals. Taiwan has two different newborn screening programs using MS/MS. Although the number of MPS II cases per 100,000 screened has a narrow range between 1.5 and 1.6 for the two newborn

screening programs in the United States, Taiwan has higher numbers ranging between 2.9 and 4.1. Dr. Kemper pointed out that the case detection rate from newborn screening in Illinois and Missouri is higher than the expected clinical detection rate, which is common in newborn screening because it identifies cases that may not have otherwise come to attention.

The standard treatment for MPS II is ERT using idursulfase. It is a weekly infusion that is administered over several hours. Adverse effects are generally related to infusion reactions and can be managed by slowing down the rate of infusion or administering antihistamines or corticosteroids. Some individuals can develop antibodies to ERT, which do not seem to interfere with the overall effectiveness of the treatment. The brand name of idursulfase is Elaprase, which was approved by the Food and Drug Administration (FDA) in 2006 indicated for patients with Hunter syndrome. Elaprase has been shown to improve walking capacity in individuals aged 16 months to five years of age. The safety and efficacy of Elaprase have not been established in patients younger than 16 months of age, raising the issue of a lack of established efficacy for infants identified through newborn screening. Dr. Kemper reminded the Committee that FDA standards for establishing effectiveness are high and that research has shown effectiveness of early versus later treatment.

Dr. Kemper briefly reviewed other therapies for MPS II. Hematopoietic stem cell transplantation (HSCT) is a potential therapy but there is currently no evidence of clear benefit on neurologic outcomes and there is a risk of mortality. There are other investigations for intrathecal and intraventricular versions of ERT, a modified version of ERT that has been enhanced to cross the BBB, and gene therapy. However, none of these have been approved for use in the United States.

There are no cohort studies that have evaluated early idursulfase treatment versus treatment after clinical identification. Therefore, the Evidence-based Review Group reviewed practice guidelines from the American College of Medical Genetics and Genomics Therapeutics Committee as guidance for timing of intervention. These guidelines specify that all individuals with severe MPS II or who are predicted to have severe MPS II warrant ERT prior to signs or symptoms, individuals with signs or symptoms with attenuated or severe MPS II warrant ERT, and individuals with attenuated MPS II not showing signs or symptoms do not warrant ERT.

The third recommendation to not treat individuals with attenuated MPS II with no signs or symptoms was made with strong, differing perspectives. Dr. Kemper reiterated that newborns are not likely to show signs or symptoms of the disease and it can be challenging to predict what the phenotype would be. The technical expert panel strongly recommended ERT for all patients with MPS II, highlighting that GAG accumulation leads to progressive involvement regardless of phenotype. However, ERT does not reverse damage cause by GAG accumulation. The technical expert panel suggested that parents make informed choices about when to start treatment. Data from the newborn screening programs showed that at least five of seven cases identified started ERT in Illinois and three severe cases of MPS II started ERT in Missouri (one of whom also received HSCT and died due to transplant-related complications).

Dr. Kemper reviewed studies comparing early versus later ERT treatment. One study under the Hunter Outcome Study stratified 482 participants by age in which ERT began (under 18 months, 18 months to five years, and over five years). As expected, urine GAG levels decreased across

all participants after ERT. Liver size was decreased with faster reduction of hepatomegaly in those who began ERT earlier. After eight years of ERT, those without cognitive impairment who received earlier ERT showed greater increases in walking distance (using the six-minute walk test) than those who received later treatment. Another study followed eight diagnosed infants treated with ERT in the first year of life. The researchers conducted follow-up assessments between 20 months and five-and-a-half years of age and, although there is no comparison group, found that the children had normal growth, minor joint impairment, improved development, and decreased hepatosplenomegaly.

Dr. Kemper reviewed a series of sibling studies describing a total of nine sibling pairs, in which an older sibling diagnosed with MPS II receives later ERT and the younger sibling receives an earlier diagnosis and earlier treatment. In each sibling pair, the younger sibling shows mild to no signs or features of the disease as compared to their older sibling. One of these studies compared an older sibling who began ERT at just under four years of age to a younger sibling who received ERT at just over one year of age. The younger sibling had much improved outcomes as compared to his older sibling. Although he did have significant behavioral involvement, he was still doing much better in terms of ambulation and activities of daily life. Dr. Kemper pointed out that at age 11, the older sibling had limited ambulation that required assistance. Comparatively, the younger sibling at age 12 was fully ambulatory. Dr. Kemper noted that the dramatic difference in walking may be an interesting point to consider in Committee deliberations.

In summary, idursulfase is associated with improvements in the somatic component of MPS II, is associated with decreased risk of mortality by adulthood, and is well-tolerated. Although there are no prospective or retrospective cohort studies comparing ERT in the first year of life to later treatment, sibling cases provide indirect evidence of benefit.

Dr. Lisa Prosser reviewed the projected population-level outcomes of MPS II in newborn screening compared with usual case detection in the absence of screening. The modeling approach for this projection is based on screening outcomes for an annual cohort of 3.6 million newborns in the United States. The approach considers screening outcomes, cases of diagnosed MPS II, and false positives as compared to the number of projected confirmed cases of MPS II in the absence of newborn screening.

There are insufficient data from MPS II cohort studies to model long- and short-term outcomes because standardized outcome measures would have had to been used at comparable ages and stratified by age of diagnosis (a limitation for many MPS II studies). Sibling studies are informative but not sufficient to inform modeling. Dr. Prosser highlighted that this insufficiency is not related to evidence of benefit but of the evidence needed to quantify the magnitude of incremental benefit potentially associated with early identification, diagnosis, and treatment.

The model is based on a systematic approach to decision-making under conditions of uncertainty with the goal of projecting *ranges* of short-term outcomes and to provide the decision-maker the ability to identify which alternative is expected to yield the most health benefit. It is an approach to evidence synthesis that reflects the robustness of the evidence base in general.

Dr. Prosser reviewed the model outlining the different potential outcomes across both newborn screening and clinical identification, as well as the parameters used to define the outcomes. These parameters represent the combined data from the Illinois and Missouri newborn screening programs. Using these data, the probability of a positive screen is 13 per 100,000 (range of 10.3 to 16.1). The number of MPS II diagnoses after a positive screen is 1.6 per 100,000 (0.9 to 5.9). The probability of a false positive is projected to be 8.7 per 100,000 (3.5 to 9.5). The probability of those lost to follow-up after a positive screen is 1.1 per 100,000 (0.9 to 2.4). The rate for confirmed MPS II under clinical identification is 0.67 per 100,000 (not including outlier studies) with a range of 0.13 to 2.16 (including outlier studies).

The number of positive screens is projected to be 467 per year (range of 370 to 580) for the United States cohort of 3.6 million newborns. MPS II diagnoses using newborn screening is projected to be 57 (42 to 59) as compared to 24 (5 to 78) MPS II diagnoses per year through clinical identification. The projected number of diagnostically uncertain cases needing follow-up after screening is 57 (33 to212), projected false positives is 313 (127 to 343), and projected lost to follow-up is 40 (33 to 85).

In summary, the projections show that newborn screening would identify a greater number of MPS II cases as compared to clinical identification. The number of cases requiring follow-up because of diagnostic uncertainty is similar to the number of MPS II cases diagnosed immediately following newborn screening. These projections have a greater range of uncertainty. This approach to evidence synthesis is the first condition considered by the Committee for which there was insufficient evidence to model long-term outcomes.

Newborn Screening for Mucopolysaccharidosis Type II: A Systematic Review of the Evidence (Part 2)

Alex R. Kemper, MD, MPH, MS, **Lead, Evidence-based Review Group**
Jelili Ojodu, MPH, **Member, Evidence-based Review Group**
Lisa A. Prosser, PhD, **Member, Evidence-based Review Group**

Dr. Kemper reviewed the estimated cost of implementing MPS II newborn screening, which was based on interviews with representatives from the Illinois and Missouri newborn screening programs. Depending on factors, such as the screening technology used, the volume of specimens, the need for additional technician time, the type of assay used, the cost of equipment, and any other potential direct costs, the estimated cost of implementing MPS II screening is between $2 and $6 per infant screened. The number of infants estimated to need second tier testing is small and does not significantly impact cost.

Mr. Jelili Ojodu reviewed the results of the public health impact assessment of MPS II newborn screening. He focused first on the readiness and feasibility of implementing a mandated screening for a new condition. *Readiness* for implementation of a newborn screening program is defined as “ready” if the new condition can be implemented into the existing newborn screening panel within a year, “developmental readiness” if the new condition can be implemented into the existing newborn screening panel within one to three years, and “unprepared” if it would take longer than three years to implement a new condition. *Feasibility* is ensured by having a

validated, established, and available newborn screening test; a clear diagnostic confirmation approach; an acceptable treatment; and a long-term follow-up approach.

The purpose of the public health impact assessment is to understand real-world barriers and facilitators related to the screening and to evaluate its opportunity cost. To conduct this assessment, they developed a fact sheet and hosted a webinar about screening for MPS II for state newborn screening programs; developed a survey to collect feedback from 53 states, territories, and Washington, DC; conducted interviews with the two newborn screening programs that are already screening for MPS II and with three states piloting or preparing to screen for MPS II; and conducted interviews with three additional programs to understand their implementation of recent additions to the RUSP and how that might impact adoption of MPS II screening.

Mr. Ojodu reviewed survey results, which had a nearly 80 percent response rate. Responding states most often indicated that major challenges to implementation included the availability of a validated screening test, increased fees, and administrative issues. The majority of states considered identifying specialists to treat children with MPS II as not a challenge. Of the states that conduct the laboratory testing in-state, an overwhelming majority of responses indicated that the programs had access to appropriate diagnostic services, treatment centers, and specialists available to manage the expected MPS II caseload. An overwhelming majority also indicated that they had, or could obtain within one year, follow-up protocols and a sufficient number of genetic counselors and laboratory technicians. Similarly, of the states that outsource their laboratory testing, an overwhelming majority had, or could obtain within a year, the resources needed to manage the expected MPS II caseload.

Mr. Ojodu reviewed survey results indicating the barriers and facilitators to adding MPS II screening to the RUSP. The majority of states indicated that their focus on other public health priorities, cost for screening, and other ongoing screening programs were major barriers to implementation. An overwhelming majority considered the predicted time needed to screen for MPS II to be a minor barrier. An overwhelming majority of states considered advocacy for MPS II screening to be a major facilitator. Notably, the expected cost benefit of screening was most often considered a facilitator. In terms of readiness for program implementation, 62 percent of the states indicated that it would take one to three years to implement MPS II screening within their existing program and 30 percent indicated it would take longer than three years.

He then reviewed lessons learned from the interviews with the programs already implementing MPS II screening. They highlighted that the use of second-tier GAG tests reduced false positives. They also indicated that the ability to multiplex with other lysosomal storage diseases could be an advantage or a challenge, depending on if a state is already screening for other lysosomal storage diseases or not. Revisions to laboratory information management systems (LIMS) continue to be a challenge that can take between six and 18 months to complete.

Lessons learned from the three additional states suggested that the latest conditions added to the RUSP enabled a number of benefits such as increased fees, recommendations from the Committee, and a readiness tool to help move them from one phase to the next. The challenges of implementing new RUSP conditions included the amount of funding, hiring, and space

needed, as well as the need to update their LIMS. None of the programs interviewed were concerned about the challenges of short-term follow-up or access to treatment.

Mr. Ojodu emphasized that the responses to the surveys were hypothetical and that there is significant variation across newborn screening programs, which could limit generalizability. He summarized that the majority of state newborn screening programs reported that it would take between one and three years to implement MPS II screening, with an advantage for those that already screen lysosomal storage diseases. The most common challenges were the need to increase fees or obtain funding, administrative issues, staffing and laboratory capacity issues, and competing priorities (e.g., the COVID-19 pandemic).

Committee Discussion

***Cynthia M. Powell, MD, MS, FACMG, FAAP*, Committee Chair**

- A Committee member asked if the states currently implementing MPS II screening have received pushback from insurance companies, considering that the FDA drug label indicates its use for pediatric patients aged five and over. Dr. Kemper answered that the Evidence-based Review Group was not able to systematically assess the degree to which insurance covers ERT nor the patient's access to it. Clinical experts in states that provide ERT have labeled it as newborn screening and said that insurance access was not a problem. It is his understanding that sibling studies would not be sufficient to modify the drug label and there was also the practice guideline statement that did not promote the use of ERT in "asymptomatic" MPS II.
- A Committee member asked what is being looked for in children who are moved to follow-up and what are families told about their children's status. Dr. Kemper said that he cannot comment on specific conversations that clinicians have with families but that they would address the issues of slightly abnormal findings with a need to err on the side of caution. There is likely some individual variation among clinicians in how the follow-up is conducted. In general, it is a follow-up around every six months to ensure there is no biochemical abnormality that would point to MPS II.
- A Committee member asked if children lost to follow-up had been included in prediction models for other disorders. Dr. Prosser answered that it is not typically included, but it was included in this case because it was reported. Given the small numbers of diagnosed confirmed cases, any added confirmed case would change the model results.
- A Committee member commented that the estimated cost to screen an infant does not consider the cost of establishing the test, the immense follow-up and education that precedes the test. The Committee member also suggested that the public health survey obtained data on ideal situations and did not necessarily represent the different challenges that will arise.
    - Mr. Ojodu agreed that there is variability in implementation challenges across states, citing that only 20 states screen for all four conditions that have been added to the RUSP since 2015.
    - Dr. Kemper added that the survey instrument was cleared by the Office of Management and Budget (OMB), which takes about 18 months for clearance. Therefore, the survey questions cannot be easily changed. The Association of Public Health Laboratories (APHL) provided some approaches for obtaining

honest appraisals of implementation. The Evidence-based Review Group is open to considering other methods to collect this information.

- A Committee member suggested that the fact that MPS II is not yet an FDA-approved test may create a need for multiplex validation as opposed to multiplex verification and asked if there will be an FDA-approved test to make multiplexing easier. Mr. Ojodu said that there is a possibility of an FDA-approved test but a number of things have to happen before that is available. The states that currently screen for lysosomal storage diseases can conduct traditional multiplex for MPS II.
- A Committee member commented about the disagreement with the practice guidelines about treating children with different phenotypes that resulted in a recommendation for parents to make informed decisions. There is a concern that this will create an equity issue because parents make decisions informed by input from their clinician and this input may vary. Dr. Kemper said that he was surprised that these treatment guidelines differed from that of experts. In his deeper dive of the deliberations that informed the recommendation for parental informed decisions, it was clear that there were different perspectives in offering ERT to all children with MPS II and that this recommendation was developed, not from consensus, but as a way to not automatically begin or prohibit treatment. The technical expert panel had consensus that all children with MPS should be offered ERT. It is not always possible to predict phenotype during follow-up but the sibling studies show a benefit to even children with attenuated MPS II. There will be work needed with individual states about consensus for treatment.
- A Committee member asked for clarification about the differences in pseudodeficiencies, which were quite a bit higher in Illinois than in Missouri, and asked if these cases were added into false positives. Dr. Kemper answered that the differences come from the use of second tier confirmation with dried blood spot GAG. In terms of the model, pseudodeficiency leads to referral and would still be considered a false positive. The second tier confirmation test decreases the number of infants with pseudodeficiency.
- A Committee member shared that the National Institute for Child Health and Human Development (NICHD) is supporting a pilot project to screen for MPS II in North Carolina beginning in April 2022. They aim to screen 140,000 infants over the next two years.
- A Committee member commented that a population-based program will bring much more variation than is seen in sibling studies. There is an issue of equity in terms of children lost to follow-up. The Committee member asked what factors contribute to those lost to follow-up. They suggested that the MPS II community should develop a guideline for treatment because ERT is among the top ten most expensive medications. They also suggested the Committee consider the reasons for the slow uptake of certain recently added conditions across different states. Dr. Kemper agreed that those lost to follow-up is an important area to study because not much is known. He agreed that equity is an issue and there is a risk that when families do not follow-up, there will be greater risk for health disparities.
- An organizational representative asked if any consideration had been given to who will conduct and gather data from longitudinal follow-up, not just on disease progression but any other longitudinal outcomes, and how the interaction between the specialty center, the medical center, and non-clinical entities such as schools, community, and rehabilitation centers would take place.

    - Dr. Kemper said that this is an important question and answered that sibling studies provide helpful information about the kinds of services a child with MPS II will need, based on whether the child was identified from newborn screening or clinical detection. A child diagnosed by clinical detection will likely need more intensive services than a child diagnosed through newborn screening. However, ERT is also a very intensive therapy administered throughout life.
    - Dr. Prosser said there is an outline of the types of outcome measures that would be helpful towards understanding the long-term benefit of early versus later detection.
- An organizational representative commented that ethnic and racial data for people with pseudodeficiencies has been previously requested but was not available. The information is available and it is important to understand the disproportionate impact on certain populations. It is known that false positives cause harm and it is a topic that needs to be explored, especially in terms of equity. An unknown number of pseudodeficiencies will occur and the impact, cost, and expectation for follow-up with other family members of that is unknown. There is a cost associated with educating providers and preparing for patients who may need follow-up for up to two years or longer. Screening results matter for every infant, not just those who are diagnosed. The organizational representative asked federal funders to consider the technical assistance and training that will be needed for implementation.
    - Dr. Kemper reiterated that pseudodeficiency is less of a problem with second tier GAG testing but that children with slight biochemical abnormalities will need follow-up. The cost of short-term follow up is relatively small because it is only a few cases per 100,000. It is correct that the cost estimate does not include this follow-up time. Programs did say that they use the same clinical resources that are used for other, similar metabolic conditions.
    - A Committee member added that clinicians are already taking care of the children who are being followed-up and that the follow-up numbers are small. It will not be a significant problem.
- An organizational representative commented that clinical practices evolve with clinical guidelines. What is relevant in 2018 may not be in 2022. The organizational representative also asked the mechanisms by which cognitive decline is stabilized with ERT if ERT does not cross the BBB. Dr. Kemper answered that some of the enzyme does cross the BBB but it is not a significant amount. A child who has improvements with ambulation or self-care will naturally have some difference in cognitive skills even without dramatic central nervous system (CNS) involvement.
- An organizational representative asked if the cost estimate is made for the laboratory or for the newborn screening program. Dr. Kemper answered that the cost estimate includes the cost of the LIMS, short-term follow-up, and everything included in the program. It is not the cost of the test itself but of the newborn screening process. Referral numbers do not add significant costs.

Committee Report: Newborn Screening for MPS II

***Jane M. DeLuca PhD, RN, CPNP,* Committee Member**
***Shawn E. McCandless, MD,* Committee Member**

Before introducing Dr. Jane DeLuca and Dr. Shawn McCandless, the two Committee members tasked with developing a report and forming a condition rating and an overall Committee recommendation, Dr. Powell presented an overview of the decision matrix. She reminded organizational representatives that, unless otherwise directed, the presentation of their report was for Committee members only.

Dr. DeLuca provided a brief review of MPS II and its classifications, prevalence, screening methods, confirmatory diagnosis methods, and treatments. She also reviewed the evidence base for the benefits of early versus later treatment.

Dr. McCandless provided an overview of projected outcomes with implementation of newborn screening for MPS II and urged the Committee to consider the ranges of estimates. The number of infants expected to have diagnostic uncertainty and need follow-up is similar to the number of infants expected to have a positive screen and confirmed diagnosis. The expected number of infants with a positive screen lost to follow-up is significant. The false positives are mostly pseudodeficiency and can be identified through confirmatory testing.

The benefit of treatment is relatively evident. ERT may modestly prolong life, although the data on survival co-mingles severe and attenuated phenotypes and is therefore challenging to determine. ERT is likely associated with better somatic function and improved quality of life. ERT does not alter CNS outcomes, although it may slow the rate of deterioration. Early initiation of ERT likely maximizes its benefit, although there are few data regarding pre-symptomatic therapy.

The potential harms of the newborn screening process are primarily related to false positives, in particular those with indeterminate results. Dr. McCandless pointed out that GAG analysis is not dichotomous but a continuous variable with a clear normal range, a clear abnormal range, and a "gray zone" in which most indeterminate results would likely fall. The Committee should not ignore the potential impact to those lost to follow-up, including travel time, unrecovered income, monitoring cost, and quality of life. Second tier dried blood spot GAG analysis may reduce false positives by approximately two-thirds. No false negatives have been reported.

As the Committee considers net benefit—the balance of benefit versus harm—it is important to understand that the benefits and harms affect different individuals in the population and there should be consideration for equity and justice. Dr. McCandless and Dr. DeLuca believe that the evidence is challenging to interpret due to the rarity of this disorder, which points to the need for researchers to present their future data in ways that facilitate comparison.

Despite this challenge, the bulk of evidence and the experiences of expert clinicians and families indicate moderate certainty of net benefit. The term "moderate" has been used because, while somatic benefits are evidence, the potential benefit on CNS involvement and mortality are less evident based on currently available data. The potential harms are to families whose children receive an indeterminate status and Dr. McCandless noted that no families spoke on their experience of this harm. The risk for treating patients who will not benefit is extremely low.

Based on the rarity of the disease and the cost of testing, the cost of screening is relatively high compared to other conditions that have been added to the RUSP.

After careful consideration, Dr. McCandless and Dr. DeLuca assigned MPS II with a Category B for certainty of significant benefit, representing moderate certainty that screening would have a significant benefit.

Dr. McCandless summarized what was learned from the feasibility and readiness of MPS II screening. He noted that newborn screening tests are available and appropriate for high-throughput testing and have a proportion of true positives to all positives that is within range of other conditions on the RUSP. They highly recommend second tier testing to reduce false positives. There is evidence that most states could add screening within a period of one to three years without adding significant burden. The marginal screening cost is higher than some conditions recently added to the RUSP but evidence suggests that follow-up resources are thought to be adequate for the demand.

Dr. McCandless and Dr. DeLuca therefore assigned MPS II with a Category 2 for developmental readiness, representing high to moderate implementation across the nation over the next three to four years.

Based on the rating for certainty of significant benefit and developmental readiness, MPS II met the decision matrix criteria for a category rating of B2. Their recommendation was that MPS II be added to the RUSP as a core condition.

Committee Discussion
***Cynthia M. Powell, MD, MS, FACMG, FAAP*, Committee Chair**

- A Committee member asked where the data supporting the statement about better survival rates came from. Dr. McCandless answered that it was based more on expert opinion than actual study data. It is also an assumption because of the improvements in overall health, particularly in respiratory and cardiac issues that can often be a cause of death. Additionally, the patients who receive early treatment and survive longer may potentially benefit from any future therapies. Newborn screening maximizes that potential. He suggested that the same benefit could come from a broader, population-based prenatal carrier testing program. Newborn screening is not necessarily the only solution. He added that newborn screening programs are compulsory. Most families do not realize that it happens until there is an abnormal result. Because of this, it is very important to be confident of benefit. Carrier screening for the same conditions provides the patient and doctor to discuss what is best for the family.
- A Committee member asked for clarification about how weekly infusions would be implemented within a newborn screening program. There is no question of net benefit from ERT but there may be families that may feel suddenly thrown into a lifetime of treatment. By making decisions about a compulsory program, the Committee is being asked to make these decisions for the family.

    - Dr. DeLuca answered that population-level screening does come down to the individual families because it identifies an individual with an abnormal result, whose family needs to be counseled. It was surprising to see the families that were lost to treatment. It is a daunting idea to face a lifetime of treatment and it will be important to develop ways to speak to people therapeutically to meet them on their terms.
    - Dr. McCandless agreed that weekly treatment is likely going be seen as burdensome. There are families who stop the therapy until their child's deterioration is enough that the burden of treatment is outweighed by the perceived benefit of the treatment. The benefit of newborn screening is that families can decide as early as possible to maximize the benefit of treatment.
- A Committee member expressed concern for families that receive a false positive and the potential unequal distribution of harm. Despite this concern, the evidence for years of benefit for families with a true positive outweighs the relatively short-term inconvenience of potential harm. It is a flaw in the system of newborn screening that some families are lost to follow-up. Perhaps these families move to a state with better available care. Some children may have not developed the condition. Ultimately, any other way to identify this condition, either prenatally or in primary care, does not work well. Currently, the only way to obtain the benefits of early treatment is newborn screening.
- A Committee member asked for clarification on two statements made in the presentation—that those who benefit differ from those who may be harmed and the low risk of treating patients that will not benefit.
    - Dr. McCandless said that the technical expert panel also suggested that the people who benefit most are those with the attenuated form of MPS II who will likely have preserved cognition and a longer life with better health and fewer limitations. There will be benefit in somatic symptoms in the most severe forms, but it likely will not change the ultimate outcomes as much. There is a need for meaningful data that can be compared across cases and across different ages.
    - The Committee member added that there is a need to validate the data for MPS II at the same time MPS II screening is implemented.
    - Dr. McCandless acknowledged that the Long-Term Follow-up workgroup has made progress through recommendations that HRSA has responded to and is investing in. There is movement toward the right direction.
- A Committee member asked how to emphasize the need for more data in their recommendation.
    - Dr. Powell answered that the Secretary did ask the Committee to conduct a follow-up evaluation within two years when SMA was added to the RUSP. This is the plan for all conditions on the RUSP.
    - A Committee member added that it would be interesting to follow-up on MPS I and MPS II at the same time because uptake of MPS I has been slow and a follow-up would inform how to improve uptake in the future.

A Committee member moved for a vote to accept the rating of B2 and recommend that the MPS II be added to the RUSP as a core condition. The motion was seconded, roll was called, and the motion passed.

Dr. Powell will prepare a letter to the Secretary with the recommendation from the Committee. She reminded the Committee that the Secretary makes the final decision to accept or not the recommendation. The decision will be posted on the ACHDNC website.

DAY TWO: Friday, February 11, 2022

Guanidinoacetate Methyltransferase (GAMT) Deficiency Evidence-based Review – Phase 2 Update

***Alex R. Kemper, MD, MPH, MS,* Lead, Evidence-based Review Group**
***Lisa A. Prosser, PhD,* Member, Evidence-based Review Group**

Dr. Kemper provided a high-level overview of guanidinoacetate methyltransferase (GAMT) deficiency and an update on the review of evidence. GAMT causes a cerebral creatine deficiency that, left untreated, can lead to global developmental delays, seizures, muscle weakness, and movement disorders. It is an autosomal recessive condition caused by a mutation in the *GAMT* gene that is associated with elevated guanidinoacetate (GUAC), low plasma, and low brain creatine. The pathophysiology of GAMT deficiency is related directly to the low creatine levels, leading to significant and progressive intellectual disability when not treated. The GUAC accumulation also leads to associated disorders such as epilepsy and extrapyramidal disorders.

The estimated prevalence of GAMT deficiency is under 0.2 cases per 100,000 live births. There is a wide range in carrier frequency but it is a rare disorder. There is also a wide range of ages in which an individual is diagnosed, which is a challenge in determining the epidemiology of the disorder. In one study, clinical identification ranged from age two to 29 with a mean age of 12.3 years. Another retrospective study in France evaluating more than 6,000 individuals identified seven cases, most of whom showed signs before two years of age. However, only one case was diagnosed before the age of two and three cases were diagnosed after the age of 10.

Diagnosis through newborn screening is based on tandem mass spectrometry screening for elevated GUAC and low creatine soon after birth and other conditions need to be ruled out. For example, arginase deficiency can also cause elevated GUAC. In the United States, screening for GUAC deficiency began in New York in October 2018 using laboratory developed tests. Screening began using a two-tiered test, first to look at GUAC and creatine with injected tandem mass spectrometry and then second to measure GUAC by high-performance liquid chromatography (HPLC). The second tier screen was discontinued in September 2021. The GAMT gene is sequenced as part of the referral process but it is not a critical component of diagnosis. In 2021, the New York program screened 211,242 infants, of which 78 (37 per 100,000) were borderline, six were referred (3 per 100,000), one positive was identified (0.47 per 100,000), and three were false positives and another two were likely false positives.

Dr. Kemper reviewed Utah's screening program. Utah is a two-screen state and screening for GAMT deficiency began in June 2015 using laboratory developed tests. From 2015 to 2019, their first tier screen was based on GUAC and creatine using a derivatized assay. The second tier GUAC and creatine re-test used liquid chromatography tandem mass spectrometry. From 2019 to present, their first tier used a non-derivatized method and their second tier is sent out. Since adoption of the current approach, the Utah program has screened approximately 78,477 infants. One case received a second tier test and was referred and identified (1.3 per 100,000).

Treatment is supplementation with ornithine to minimize buildup of GUAC, creatine to replace the creatine not being generated, and sodium benzoate. Additionally, there is a dietary restriction of arginine. These supplements are available over-the-counter, making treatment readily available and less expensive. Ideal timing of treatment is uncertain but experts recommend supplementation from two to four weeks of age, with serum monitoring over time.

Dr. Kemper reviewed studies investigating effectiveness of early treatment. In one case series of 48 subjects, diagnosis occurred at a median age of 51 months, ranging from prenatal to 34 years of age. Increased age at the start of treatment was associated with greater severity of intellectual disability. Those who were treated before one month of age showed no developmental delay after a period of treatment, ranging from 14 months to seven years. Another case report described a subject who began treatment at 28 months of age and showed persistent intellectual disability at six years of age. In contrast, another case report described a subject who was diagnosed early based on family history and treated at eight days of age, with normal development at 12 months of age.

Dr. Kemper then reviewed sibling studies. In one study, an older sibling was treated at 10 months of age and had delayed speech and fine motor skills at age six. The younger sibling was diagnosed prenatally and was normal at 42 months of age. Another sibling study reported an older sibling who was diagnosed at two years of age after presenting with significant developmental delay and seizures. The younger sibling began treatment at 22 days of age and is reported to be developmentally mobile at 14 months of age. In a cousin study, an older cousin began treatment around three years of age, had an unclear period of treatment, and still showed significant intellectual impairment but improved seizure frequency. The younger cousin was evaluated at five months of age and showed normal development at 16 months of age. Given the rarity of GAMT deficiency, these sibling and cousin studies will provide the best evidence for the benefit of early treatment.

The Evidence-based Review Group is currently focused on reviewing screening and treatment to find comparisons of early to later identification. They will also be comparing projected outcomes from GAMT deficiency newborn screening for all newborns in the United States with usual case detection in the absence of screening. The modeling will be similar to that of MPS II in terms of screening outcomes and the inability to model long-term outcomes. The public health impact survey will be conducted to assess the readiness and feasibility of newborn screening for GAMT deficiency. The APHL coordinated a webinar that was held on January 14, 2022 and the survey will open next week. APHL will then conduct in-person interviews with programs that have adopted GAMT deficiency screening as well as those that are not currently conducting the screening.

Committee Discussion
***Cynthia M. Powell, MD, MS, FACMG, FAAP*, Committee Chair**

- A Committee member asked about New York's sequencing process and the five false positives that were found and other variants of uncertain significance. Dr. Kemper answered that the sequencing is embedded in their newborn screening process and he will follow up with details about the false positives.

- A Committee member asked if the flow injection analysis is the standard for tandem mass spectrometry and if every state laboratory would already have the equipment to conduct it. Dr. Kemper confirmed that it was standard and that it was an easy addition to existing tandem mass spectrometry screening.
- A Committee member asked if the treatments available over-the-counter would be considered nutritional supplements by insurance companies and therefore not covered. It would be helpful to know what the cost burden would be on the family.
    - Dr. Kemper answered that there is the issue of cost and coverage but there is also an issue of quality. If families opt to buy over-the-counter or online, there will need to be standards so that that they can be reassured that they are receiving the highest quality supplements.
    - Dr. Powell added that the cost of over-the-counter supplements can be minor for some families but a burden for others. It will be an important topic to discuss.
- A Committee member asked if there was time to ask the nominators of this package if there can be an update on the long-term outcomes from the case reports. Dr. Kemper said that this was a good recommendation.
- A Committee member asked if the reason that the second tier assay was discontinued in New York and was transitioned to being sent out in Utah was a result of the low number of infants being too burdensome to maintain. Dr. Kemper confirmed that this was the reason.
- A Committee member asked if there will be a more detailed report with information from the newborn screening programs outside of the United States. Dr. Kemper confirmed that this information will be included in the final report.
- A Committee member asked if the newborn screening technology will pick up other types of creatine deficiencies as a secondary finding. Dr. Kemper answered that this was a question for the technical expert panel but the focus is on GAMT deficiency and then measuring the GUAC and creatine ratio.
- An organizational representative suggested that there is a difference in the flux that exists in the utilization of arginine through a normal pathway versus a pathway that involves entry into the mitochondria for biosynthesis. It may cause problems for some infants and may cause false negatives. Dr. Kemper said he will follow up on this question.

ACHDNC Condition Review Capacity – Initial Discussion

***Cynthia M. Powell, MD, MS, FACMG, FAAP*, Committee Chair**

Dr. Powell asserted that, as technology for newborn screening and treatment of rare, heritable disorders advances, there is a possibility that the number of condition nominations will outpace the Committee's capacity to review nomination packages and conduct evidence-based reviews. In August 2021, the Committee began to explore this potential scenario, discussing the equity of the nomination process and the timeline and approach for conducting evidence-based reviews.

Currently, the Committee has the budget and capacity to conduct two rigorous evidence-based reviews per year. Additionally, most states would not be able to keep pace with implementation of multiple newborn screening conditions added to the RUSP. The Secretary recommends that every state screens for conditions included on the RUSP because of the expertise of the

Committee and the Evidence-based Review Group and the rigor of their evidence-based review and informed decision-making processes.

Dr. Powell stated that a key strategy to meet this challenge will be to develop criteria for prioritizing the review of nomination packages. She will convene a workgroup comprised of current and former Committee members to discuss this strategy. Dr. Powell asked the Committee to provide their initial thoughts on potential criteria for prioritization, what the prioritization process might look like, if there were factors that might make a condition not ideal for prioritization, and if there should be more than one Nomination and Prioritization (N&P) workgroup.

Committee Discussion
***Cynthia M. Powell, MD, MS, FACMG, FAAP*, Committee Chair**

- A Committee member asked how the N&P workgroup is formed. Dr. Powell answered that it is a standing workgroup comprising four Committee members and the Committee Chair, representing a wide range of expertise across clinical care, primary care, laboratory, and ethics. A nomination package is first reviewed by HRSA for completeness, then it is sent to the workgroup for review to identify any outstanding questions that need answers before submitting the package to the full Committee to determine if the package is ready for a full evidence review.
- A Committee member commented that there are prioritization processes in other health care settings that are focused on triage, such as in the military or for the COVID-19 pandemic. However, a prioritization framework based on triage might not work well with nomination packages because it is only through rigorous evidence review that the capacity for helping the highest number of children can be evaluated. For that reason, it would also be difficult to prioritize based on the commonality of a condition or the potential benefit of treatment. One solution might be to vote on prioritization after an evidence-based review. This would require scaling-up resources to conduct more evidence-based reviews and perhaps a requirement that only one review of evidence be conducted at each Committee meeting. Another approach might be a first-come, first-served approach, acknowledging that there is no meaningful way to prioritize conditions. Dr. Powell said that there had been discussion of the N&P workgroup conducting a more detailed review before making a recommendation. The challenge with this solution was that workgroup members volunteer their time and adding to that burden may become difficult. Another challenge was that the Newborn Screening Saves Lives Act was not passed and the Committee is currently operating as a discretionary committee with a few members short.
- A Committee member commented that some nominated conditions may only take a few weeks for the N&P workgroup to review and others may take a few months. HRSA could develop the critical components for the N&P workgroup to focus on, but then the Evidence-based Review Group will carry a larger burden. There may be a need for multiple Evidence-based Review Groups and an evaluation of the evidence-review process. There is also concern that many states need more than three years to implement screening for a new condition when the Committee's evaluation of capacity suggest that implementation will only take one to three years. There may be a need for an evaluation of submission criteria to the N&P workgroup.

- A Committee member suggested a process for scaling-up resources to meet the times in which there is a backlog of nominations and a shift from volunteer work to more of a job responsibility.
- A Committee member commented that a first-come, first-served approach may reward nominators with better resources. An obvious criterion should be a benefit of treatment that starts in infancy, although the evaluation of that can be challenging.
- A Committee member suggested that there is an obligation to not use a first-come, first served approach because there are clear criteria for measuring the impact of a screening program. One possibility is to objectify these criteria as an upfront measure so that a nominator can provide supportive data in the nomination package. It may not be a completely objective process, but it could help indicate nominations that may have higher impact than others. Nominators should also be asked to provide an argument for newborn screening as the most appropriate method of identifying a condition. Newborn screening is not the solution to every childhood condition. Another Committee member commented that education about and criteria for more complete data in nomination packages would be very helpful.
- An organizational representative commented that equity is a critical issue that needs to be addressed. There should not be an assumption that every nominator has the same level of resources for developing a nomination package. If an advocacy group or community is less resourced, then the condition they are advocating for may never move to the front of the line. There should also be clarity for whether the Committee is setting an expectation that it will meet the pace of treatments available.
- An organizational representative emphasized that states do not get funded to implement two conditions a year. Once a recommendation is made, the Committee's work is complete and the states and program jurisdictions begin the daunting work of implementation. One possible approach for prioritization is having two deadlines a year for applications instead of a rolling deadline. Although this may become a race to push nomination packages and potentially creates equity issues, it also provides a process for comparing packages for prioritization. Additionally, newborn screening is not necessarily the solution for the diagnostic odyssey; there are other paths. Another Committee member agreed that a deadline instead of a rolling process for submissions would be helpful.
- An organizational representative said that another consideration is that the lack of adoption by some states is sometimes not about capacity but about choice. The APHL survey might consider adding a question for if a state wants to screen for a condition.
    - A Committee member commented that screening programs do not make the choice whether to implement screening or not. Rather, the system in place in their state has criteria conducive to rapid or slow implementation. There is readiness in the form of procurement, staffing, facility management, and construction that precedes the readiness for implementation. Additionally, there are growing legislative requirements for implementation, such as North Carolina's requirement to implement screening within three years of an addition to the RUSP. These are the burdens that the Committee should consider.
    - The organizational representative responded that there are examples of states that deliberate and decide not to screen.

    - Another organizational representative commented that universal newborn screening is meant to reach every newborn and be equitable. In reality, if implementation decisions are being made at the state-level, then it is challenging to consider newborn screening equitable.
    - Another organizational representative suggested that newborn screening does create a more equitable situation but that it is important to consider equity at every step to ensure that nothing is being done to create inequity. Newborn screening is not a federal mandate and every state has a process for adding conditions to their panel, some of which includes additional evidence review and an advisory committee.
- An organizational representative suggested that HRSA should consider cross-functionality with NIH and CDC and other federal agencies to link efforts for pilot studies, implementation, long-term follow-up, and education campaigns.
    - A Committee member agreed that federal coordination is important but said that coordination would not represent one mission. Every agency has a different mission, different funding, and different functions. Although there is some coordination now, more can be done to improve federal partnerships.
    - Another Committee member responded that there are legislative parameters to consider in terms of timing and budgeting for the review processes that should be considered when thinking about federal partnerships.
- An organizational representative emphasized the importance of considering equity and justice in terms of the large burden already placed on a scarcity of genetic professionals. Additionally, the more screening that is conducted, the more false positives there will be and that is an additional burden on both clinicians and patients.
- An organizational representative commented that equity becomes even more of an issue when screening moves from newborn screening to carrier screening. The uptake of carrier screening is not universal and the only way to reach a full population at this time is newborn screening. Additionally, the burden on programs becomes exponential with each condition added to the RUSP. Although some programs may not be as burdened with an addition to a multiplex, most programs have to consider additional resources, space, and personnel. These programs are state-based and the salaries are not equitable to industry, which creates shortages. Another organizational representative added that the pandemic compounded these shortages.
- An organizational representative commented that addressing equity is challenging because of the expense of screening and disparities in genetic analyses. If the Committee makes equity a priority issue, it will be important for the Committee to increase awareness of this priority to acknowledge all areas in which inequity exists.
    - An organizational representative agreed that the challenge of equity is an issue across the system and families are at the center of that system. The Committee and any workgroups should consider the different processes that can be affected by equity.
    - Another organizational representative added that it is not inherently easier to sequence the genetics of one person versus another. It is a choice to focus on certain populations. As a result, it can be a surprise when a disease presents differently in different populations.

Dr. Powell thanked the Committee for their input and reiterated that she will form a workgroup and keep the Committee apprised of the process.

Public Comments

Heidi Wallis

Ms. Heidi Wallis is the Executive Director of the Association for Creatine Deficiencies and parent to two children with GAMT deficiency. She answered some of the questions that were asked during Committee discussion. In response to the question about cost, the association conducted a study on the cost of treatment for GAMT deficiency that is based on the CDC growth chart and recommended dosage of each supplement. For example, at two years of age, the cost of supplementation is $31.50 a month. The cost does increase as the child grows. Her daughter was diagnosed with GAMT deficiency when she was five years old. She is now 18 years old and the cost of emergency and specialty care has far outweighed the cost of supplements. In their community, half of families have been able to obtain coverage for supplements through insurance or state coverage. In response to the question about screening cost, she clarified that the Utah screening program screens for GAMT using a lab developed kit for flow injection analysis, not an FDA kit. The association worked with Utah to evaluate cost of implementation and estimated the cost per screening at $0.19, which includes labor and follow-up for repeats. In response to the question regarding Utah's decision to send out the second tier test, when Utah brought tandem mass spectrometry in-house, ARUP Laboratory had already been conducting the amino acid acylcarnitine screen and it remained there. In terms of whether GAMT screening would identify other creatine deficiencies, there is no conclusive evidence for identifying the two other X-linked creatine transporter deficiencies. In response to the question about false positives, more information can be found in a published study called "Prospective Identification by Neonatal Screening of Patients with Guanidinoacetate Methyltransferase." Additionally, there are some studies on outcomes of earlier versus later diagnosis and a sibling study that is currently being conducted that should be complete by the next Committee meeting. Ms. Wallis shared some personal experience about living with GAMT deficiency. Her older child was diagnosed at age five-and-a-half and experienced significant developmental delays. In contrast, her younger child was diagnosed from newborn screening and experienced typical development. She believes there is an obligation to move a condition forward to the RUSP if there is evidence supporting newborn screening. The idea of asking states whether they will choose to implement the screen or not as a criteria for moving the condition forward is upsetting.

Megan Pesch

Dr. Megan Pesch is an assistant professor at the University of Michigan and President-elect of the National CMV Foundation and mother of a daughter with congenital cytomegalovirus (CMV). The foundation submitted a nomination package for the inclusion of congenital CMV on the RUSP in fall 2021. Congenital CMV affects one in 200 infants in the United States and is associated with hearing loss, cerebral palsy, and other neurodevelopmental disabilities. Her daughter did not have symptoms at birth and was diagnosed at four months of age, missing the ideal window for treatment with antiviral medication. Congenital CMV cannot be diagnosed based on clinical presentation in the majority of infants who have it. Early treatment is an option for severely-affected infants and hearing loss monitoring can provide an opportunity for hearing loss treatment. She is in favor of universal screening for congenital CMV and looks forward to the Committee's deliberations on the nomination package.

Dylan Simon
Mr. Dylan Simon is the Associate Director of Policy for the EveryLife Foundation for Rare Diseases, a nonprofit that is dedicated to empowering the rare disease patient community and advocating for impactful, science-driven legislation and policy towards life-saving diagnosis, treatment, and cures. The foundation is currently dedicated to the passage of the Newborn Screening Saves Lives Reauthorization Act. The legislation passed the House in June 2021 but it has been held at the Senate judiciary on a proposed consent amendment for more than two years. The foundation will convene more than 1,000 rare disease committee members on Capitol Hill later in February 2022 for Rare Disease Week to seek support for the legislation. Following its passage, the foundation will continue to work with the rare disease community to ensure the impact of the legislation on patient communities is well-understood by policymakers. The foundation also remains focused on shortening the time between nomination to the RUSP and screening at the state level. They are also focused on legislation to require states to implement screening for conditions on the RUSP within a specific timeline. This legislation has already passed six states and similar legislation is underway in additional three states. Finally, Mr. Simon highlighted that the *JAMA Network Open* published an article titled "Expert Evaluation Strategies to Modernize Newborn Screening in the United States," which evaluates the opportunities and challenges in the newborn screening system and proposed modernization.

Beth Vannoy
Ms. Beth Vannoy is parent to a child with metabolic disorder MCADD, or medium-chain acyl-CoA dehydrogenase deficiency, and founder of the nonprofit Minutes Matter MCADD. Her goal is to ensure that all newborns receive timely screening for a chance to live health productive lives. There is work to be done for ensuring the timely return of screening results for extremely time-sensitive disorders such as MCADD. Ms. Vannoy shared three patient stories that illustrated the very short amount of time in which an infant progressed from healthy into a metabolic crisis. The infants died within days and the newborn screening results often came only one day after. Ms. Vannoy said that a solution must be found to prevent these losses of lives.

Mena Scavina
Dr. Mena Scavina is a neurologist at Children's Health in Delaware and program advisor to Parent Project Muscular Dystrophy. As an advocate for the inclusion of Duchenne muscular dystrophy (DMD) on the RUSP, she shared her experience with families that have two or more children with DMD. Newborn screening for DMD would provide parents with valuable information on carrier status towards family planning. Family members of childbearing age can also be tested to determine their carrier status. DMD often has a delayed diagnosis and there are recent treatment options to change the course of disease and improve quality of life. The diagnostic odyssey for DMD is expensive and often involves unnecessary testing and treatment. She looks forward to the Committee's review of the DMD nomination package.

Health Equity in Newborn Screening

***Sikha Singh, PHS, PMP,* Deputy Director, Newborn Screening and Genetics, Association of Public Health Laboratories**

Ms. Sikha Singh presented results of a preliminary analysis of the NewSTEPS quality indicator dataset on healthy equity in newborn screening. NewSTEPS is a newborn screening technical assistance and evaluation program of APHL that provides technical assistance for newborn screening laboratories and follow-up programs. One of the goals of NewSTEPS is to provide a centralized website and data repository with the intent of performing data-driven outcome assessments. Research shows that ethnic and racial minority groups in the United States experience disproportionately high rates of illness and death across a range of health conditions Her presentation was based on health equity data entered into the data repository between 2011 and 2021.

Across this time period, the data repository contained over 29,000 cases entered by 46 state newborn screening programs. These data were not entered uniformly across all states because data entry into the repository is voluntary and states entered memorandums of understanding with APHL at different time points across the past several years. Of the 35 core conditions on the RUSP, 16 are classified as time-sensitive. Additionally, all of the secondary conditions are classified as time-sensitive. Of the nearly 30,000 cases that were analyzed, 3,904 were classified as time-sensitive. Across race and ethnicity, 39 different race groupings were reported and about a third of cases did not report race/ethnicity, indicating that the process to collect race/ethnicity information should be improved.

They analyzed timeliness in 22,199 cases that were detected by initial specimen and condensed that data into seven categories by race. They found no significant differences across race and timeliness of birth to collection, birth to receipt by laboratory, and birth to recording. This may be indicative of the relative uniformity of screening across the country as an opt-out and public health surveillance program. However, there were significant differences between the reported racial categories in timeliness from median birth to diagnosis and in birth to intervention. For example, timeliness from birth to diagnosis was significantly different in Black/African American infants as compared to Native American, Asian, and White infants. There were significant differences in timeliness from birth to intervention between Black/African American infants and all other races.

They then analyzed time-critical cases and found fewer significant differences and timeliness for nearly all categories from birth to diagnosis, and birth to intervention. The reason for this finding may be that time-critical cases have a fairly straightforward directive and there is less subjectivity about what action to take next. Additionally, time-critical conditions are relatively pan-ethnic, with no dominant race affected disproportionately. They analyzed time-sensitive disorders by race and found significant differences across racial categories except Pacific Islander, which is a very small population. There were significant differences in time-sensitive disorders between Black African American infants and all other races.

They conducted an analysis that was stratified by specific disorder. Cystic fibrosis was found in significantly more White infants than all other races, which is not to say that other races are not impacted. White babies were being diagnosed and receiving interventions from days to weeks before Black/African American, Asian, and other mixed infants. This finding may be attributed to misconceptions about cystic fibrosis and disparities in access to diagnosis and care.

Conversely, hemoglobinopathy was found in significantly more Black/African American infants, with diagnosis and intervention occurring more rapidly than in other infants. However, there were no significant differences between Black/African American infants and White infants for timeliness in birth to diagnosis nor in birth to intervention. This might be attributed to a lack of communication of urgency about this specific disease or differences in access to timely clinical care.

Finally, they analyzed congenital hypothyroidism, which is pan-ethnic and not time-critical but requires a prolonged treatment process. They found significant differences in timeliness from birth to diagnosis and from birth to intervention between White, Black/African American, Asian, and other mixed infants.

Ms. Singh reiterated that the limitations of this dataset were completeness and uniformity of data. Further, race and ethnicity may have been based on the mother and not the infant, but almost certainly not the father. There appear to be differences in timeliness across race, most notably in time-sensitive conditions. There is a need for more complete race data, as well as more harmonized diagnosis and intervention date definitions across programs.

Committee Discussion
***Cynthia M. Powell, MD, MS, FACMG, FAAP,* Committee Chair**

- Dr. Powell asked if cases were separated based on urban and rural home areas. Ms. Singh answered that they do not have that level of information.
- An organizational representative commented that potential confounding variables need to be considered before drawing conclusions or addressing what to correct. Socioeconomic factors may be driving social disparities. Ms. Singh agreed and referenced the wealth of research that supports the role of social inequities. This was a preliminary analysis and it would be helpful to link these data to vital records to add a layer of information
- An organizational representative asked if they plan to publish these data. Ms. Singh said they do hope to work with HRSA to publish this analysis.
- An organizational representative commented on the need to understand the delay in time to intervention, which may be a systems issue, and asked what is needed to obtain the data needed to further this analysis. Socioeconomics play a role, but there are other factors involved in racial disparities. Ms. Singh answered that connecting vital records to their data would be very helpful and make it easier to states to enter data into the repository. There may also be benefit for collecting data from other HRSA-funded projects, such as access to genetics data or national data centers. There are efforts in which newborn screening programs reach out to families to help bridge the gap in access. For instance, the early hearing detection program does a great job finding those lost to follow-up to determine whether they were lost due to issues such as insurance coverage, access, or literacy.
- A Committee member asked if there was any information on insurance coverage in their data because people on Medicaid can have a harder time scheduling follow-up visits due to lower reimbursement rates. In 2013 and 2014, Medicaid was required to reimburse at the same level as Medicare, which resulted in increased coverage for people on Medicaid.

The challenge is an institutional issue, not an issue with individual providers. Ms. Singh said this information was not in their repository.

- A Committee member asked if the repository data comes from case data rather than routine data collection. There is also concern for data integrity, for instance, different states may combine race and ethnicity under one metric or separate it. Ms. Singh answered that they collect three large sets of data. These include public data from the newborn screening programs and quality indicator information that is aggregated across time to birth, collection, receipt, reporting, diagnosis, and intervention, for which intervention and diagnosis are well-defined. The third set of data is case data, populated from the dried blood spot card. This is where connecting to vital records becomes important in terms of uniformity and objectivity.
- An organizational representative reiterated that not every program is reporting to this repository and that the programs that do are actively working on timeliness with APHL. If data were available from all programs, the timeliness may be significantly worse. There are plenty of data indicating that race is a primary factor to health disparities when everything else is excluded. There is no reason to think that the newborn screening program is not influenced by the factors that are known to impact infant health outcomes.
    - Ms. Singh agreed and added that the data came from 46 states, which was a fairly good representation. However, not every state entered data for the entire decade. Additionally, it was not certain that states that did not provide data are not also working on timeliness.
    - Another organizational representative agreed that race is a primary consideration but that other factors can help identify indirect solutions.

New Business

***Cynthia M. Powell, MD, MS, FACMG, FAAP,* Committee Chair**

Ms. Natasha Bonhomme said that Genetic Alliance, in partnership with the CMV Foundation, is convening a workgroup to bridge the CMV community with the newborn screening community. The first meeting will be in March 2022.

Dr. Powell thanked Committee members and said that the next Committee meeting will take place virtually on May 12-13, 2022.

Adjourn

Dr. Powell adjourned the Committee meeting at 1:30 P.M.