Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Minutes of February 9-10, 2023

Virtual Meeting

Table of Contents

Committee Members

Kyle Brothers, MD, PhD
Endowed Chair of Pediatric Clinical and Translational Research
Associate Professor of Pediatrics
University of Louisville School of Medicine

Ned Calonge, MD, MPH (Chairperson)
Associate Professor of Family Medicine
University of Colorado School of Medicine
Term End Date: June 30, 2026

Michele Caggana, ScD
Deputy Director, Division of Genetics
New York State Department of Health

Jannine D. Cody, PhD
Professor, Department of Pediatrics
Director, Chromosome 18 Clinical Research Center
University of Texas Health Science Center
Founder and President
The Chromosome 18 Registry & Research Society

Jane M. DeLuca PhD RN
Associate Professor
Clemson University School of Nursing
Metabolic Nurse Practitioner
The Greenwood Genetic Center

Ashutosh Lal, MD
Professor of Clinical Pediatrics
University of California San Francisco School of Medicine
Benioff Children's Hospital

Jennifer M. Kwon, MD, MPH, FAAN
Director, Pediatric Neuromuscular Program
American Family Children's Hospital
Professor of Child Neurology
University of Wisconsin School of Medicine & Public Health

Shawn E. McCandless, MD
Professor, Department of Pediatrics
Head, Section of Genetics and Metabolism
University of Colorado
Anschutz Medical Campus
Children's Hospital Colorado

Chanika Phornphutkul, MD, FACMG
Professor of Pediatrics and Pathology and Laboratory Medicine and Genetics
Director, Division of Human Genetics
Department of Pediatrics, Brown University
Hasbro Children's Hospital
Rhode Island Hospital

Ex-Officio Members

Agency for Healthcare Research & Quality
Kamila B. Mistry, PhD, MPH
Senior Advisor
Child Health and Quality Improvement

Centers for Disease Control & Prevention
Carla Cuthbert, PhD
Chief
Newborn Screening and Molecular Biology Branch
Division of Laboratory Sciences
National Center for Environmental Health

Food & Drug Administration
Kellie B. Kelm, PhD
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health

Health Resources & Services Administration
Michael Warren, MD, MPH, FAAP
Associate Administrator
Maternal and Child Health Bureau

National Institutes of Health
Diana W. Bianchi, MD
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Acting Designated Federal Official

LCDR Leticia Manning, MPH
Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau

Organizational Representatives

American Academy of Family Physicians
Robert Ostrander, MD
Valley View Family Practice

American Academy of Pediatrics
Debra Freedenberg, MD, PhD
Medical Director, Newborn Screening and Genetics, Community Health Improvement
Texas Department of State Health Services

American College of Medical Genetics & Genomics
Robert Best, PhD
Interim Chief Executive Officer

American College of Obstetricians & Gynecologists
Steven J. Ralston, MD, MPH
Chief of Obstetrics
Howard University Hospital

Association of Maternal & Child Health Programs
Karin Downs, RN, MPH
Maternal and Child Health Director (retired)
Massachusetts Department of Public Health

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

Association of State & Territorial Health Officials
Scott M. Shone, Ph.D., HCLD(ABB)
Director
North Carolina State Laboratory of Public Health

Association of Women's Health, Obstetric and Neonatal Nurses
Shakira Henderson, PhD, DNP, MS, MPH, RNCNIC, IBCLC
Board Director, Vice President, Research Officer
University of North Carolina Health

Child Neurology Society
Margie Ream, MD, PhD
Associate Professor
Director, Leukodystrophy Care Clinic
Director, Child Neurology Residency Program
Nationwide Children's Hospital
Division of Neurology

Department of Defense
Jacob Hogue, MD
Lieutenant Colonel, Medical Corps
US Army
Chief, Genetics, Madigan Army Medical Center

Genetic Alliance
Natasha F. Bonhomme
Vice President of Strategic Development

March of Dimes
Siobhan Dolan, MD, MPH
Professor and Vice-Chair for Research
Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine and Montefiore Medical Center

National Society of Genetic Counselors
Cate Walsh Vockley, MS, LCGC
Senior Genetic Counselor
Division of Medical Genetics
UPMC Children's Hospital of Pittsburgh

Society for Inherited Metabolic Disorders
Gerard T. Berry, M.D.
Harvey Levy Chair in Metabolism
Director, Metabolism Program
Division of Genetics and Genomics
Boston Children's Hospital
Director, Harvard Medical School
Biomedical Genetics Training Program
Professor of Pediatrics
Harvard Medical School

DAY ONE: Thursday, February 9, 2023

Welcome, Roll Call, Committee Business

***Ned Calonge, MD, MPH*, Committee Chair**
***Leticia Manning, MPH,* Acting Designated Federal Official, Health Resources and Services Administration (HRSA)**

Dr. Ned Calonge 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. Kyle Brothers
- Dr. Ned Calonge (Committee Chair)
- Dr. Michele Caggana
- Dr. Jannine Cody
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention; CDC)
- Dr. Jane DeLuca
- Dr. Kellie Kelm (Food and Drug Administration; FDA)
- Dr. Jennifer Kwon
- Dr. Ashutosh Lal
- Dr. Kamila Mistry (Agency for Healthcare Research and Quality; AHRQ)
- Dr. Shawn McCandless
- Dr. Melissa Parisi (National Institutes of Health; NIH)
- Dr. Chanika Phornphutkul
- Dr. Michael Warren (Health Resources & Services Administration; HRSA)

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. Robert Best
- Association of Maternal & Child Health, Ms. Karin Downs
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State and Territorial Health Officials, Dr. Scott Shone
- Child Neurology Society, Dr. Margie Ream
- Department of Defense, Dr. Jacob Hogue
- Genetic Alliance, Ms. Natasha F. Bonhomme
- March of Dimes, Dr. Siobhan Dolan (Day One)
- National Society of Genetic Counselors, Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Gerard T. Berry

Dr. Calonge introduced new Committee member, Dr. Michele Caggana, and new organizational representative for the American College of Medical Genetics and Genomics, Dr. Robert Best.

Dr. Calonge highlighted two funding opportunities from the Maternal and Child Health Bureau (MCHB) to strengthen newborn screening systems. The State Newborn Screening Systems Priorities Program (NBS Propel) aims to provide screening, counseling, and health care services to newborns with or at risk for heritable disorders. The National Center for Newborn Screening Systems Excellence (NBS Excel) supports state NBS programs and stakeholders nationwide. He also notified the Committee of the nationwide shortage of penicillin VK solution, which can affect children with sickle cell disease. The Sickle Cell Disease Association website posted alternatives to the penicillin VK solution as a resource for families and clinicians during this shortage.

On January 4, 2023, the Department of Health and Human Services (HHS) Secretary Xavier Becerra (the Secretary) approved the addition of guanidinoacetate methyltransferase (GAMT) deficiency to the RUSP. Dr. Calonge emphasized that the addition of GAMT deficiency to the RUSP is a recommendation and does not constitute a requirement for state implementation and he expressed hope that states would take advantage of the two new MCHB grant programs to aid in its implementation. The Secretary requested a five-year report on the state implementation of GAMT deficiency screening, potential barriers to treatment, long-term follow-up, and health outcomes.

Dr. Calonge reminded the Committee of their forthcoming vote to recommend the addition of Krabbe disease to the RUSP and Duchenne muscular dystrophy (DMD) for full evidence review and conveyed the importance of the evidence-based review and decision framework as they deliberate. He acknowledged the value of personal stories and advocacy that families and other members bring to the Committee and expressed gratitude for their personal investments in the process.

A Committee member moved for a vote to approve the minutes of the November 2022 meeting. The motion was seconded, roll was called, and the motion passed unanimously.

Public Comment

Michael Wilson

Mr. Michael Wilson is a 12-year-old boy with Krabbe disease. He tested for Krabbe disease at birth because his brother, born 15 months before him, also had Krabbe disease. His brother did not have symptoms of Krabbe disease until he was 12 months old and was not diagnosed until he was 18 months old. He was therefore unable to receive lifesaving treatment and passed away. Although Mr. Wilson was asymptomatic, he was diagnosed with Krabbe disease at birth and received a stem cell cord blood transplant when he was four months old. Today, Mr. Wilson is an active child who owns three businesses (i.e., running a snow cone stand, lawn-mowing, and car washing), plays sports, and takes electric guitar lessons. He is also the 2023 Ambassador for the Children's Miracle Network and served as a patient designer for the Nike Freestyle Program. He told the Committee that he is proof that treatment can provide children with their best possible lives.

Stacy Pike-Langenfeld

Ms. Stacy Pike-Langenfeld is mother to Makayla, a child with Krabbe disease who died at age 2. Ms. Pike-Langenfeld said that Krabbe disease meets readiness criteria for inclusion on the

RUSP. First, Krabbe disease meets the pediatric onset criteria—90 percent of cases each year fall within the early infantile cohort and must receive treatment within the first 30 to 40 days of life. Second, Krabbe disease meets level of severity criteria as a severe metabolic disease that causes premature death if left untreated. Third, Krabbe disease meets treatment intervention criteria with the availability of hematopoietic stem cell transplant (HSCT). Finally, Krabbe disease meets effective testing criteria—although the evidence for effective diagnosis was lacking in the 2009 RUSP nomination, experts have since identified the testing mechanisms needed to effectively identify the disease. Ms. Pike-Langenfeld urged the Committee to focus their decision on this evidence.

Wendy Tierney
Ms. Wendy Tierney talked about her two daughters, both of whom had been diagnosed with Krabbe disease. Her older daughter, Grace, was diagnosed at five months old after she became symptomatic and was unable to receive treatment. Her younger daughter, Madison, was diagnosed at birth and received a stem cell transplant at five days old. As they got older, Madison hit developmental milestones, but Grace suffered progressively worse symptoms. By the time Madison began preschool at age 4, her sister Grace had died. Madison continued to grow and thrive, excelling academically and socially. She graduated high school with honors and currently attends university to study criminal justice. Ms. Tierney said that as much as they feel pride for Madison's accomplishments, they also feel sadness for the life Grace might have had if she had received treatment. She urged the Committee to recommend the addition of Krabbe disease to the RUSP so that babies and families no longer have to suffer the same tragic outcome.

Lana Grujicic
Ms. Lana Grujicic talked about her son, Nikola, who was diagnosed with Krabbe disease at six months old after the disease had progressed past the point of treatment. Although Ms. Grujicic and her husband were told that their son had no treatment options and would not live past two years of age, they found an expert who helped them set up the right equipment and medications to help Nikola have the best quality of life possible. Today, Nikola is nearly five years old; takes 13 medications daily; and requires breathing treatment, around-the-clock oxygen, suctioning to manage secretions, a wheelchair, and a bath chair. Each year, his medical costs exceed half a million dollars. Ms. Grujicic said that children with Krabbe disease will have no chance of survival without early diagnosis and treatment. Though Krabbe disease is rare, it should not be ignored, nor should the children it affects be treated like they do not matter. She asked the Committee to consider the testimonies from families as the vote for a recommendation.

Karlita Blackwell
Ms. Karlita Blackwell said that her son, Ezra, was diagnosed with Krabbe leukodystrophy at two weeks old. Ezra was able to be diagnosed and receive life-saving treatment because Krabbe disease is included in Missouri's newborn screening program. Today, Ezra is six years old and has the same opportunities that every family hopes to have for their children including education; meaningful relationships; independence; and the chance to feel loved, happy, and safe. Ezra currently attends kindergarten and lives a full and happy life. Ms. Blackwell said that each time another unscreened child in their Krabbe disease community passes away, she is reminded that the death could have been prevented with newborn screening.

Jill Kelly
Ms. Jill Kelly and her husband, Jim Kelly, founded the Hunter's Hope Foundation after their son, Hunter, was diagnosed with Krabbe disease. Though Hunter was healthy as a newborn, it soon became clear that something was wrong. After numerous misdiagnoses, Hunter was diagnosed with Krabbe disease at four months old. He suffered daily from seizures, suctioning, broken bones, nerve pain, and pneumonia. He requires extensive care and has had many trips to the emergency room and the intensive care unit (ICU). Hunter passed away at eight-and-a-half years old. Ms. Kelly said that after the Committee voted against adding Krabbe disease to the RUSP in 2009, 136 children were born with Krabbe disease and died because they were diagnosed too late to receive treatment. She said that Krabbe disease is always fatal without the benefit of newborn screening and emphasized every child with Krabbe disease deserves a chance to live.

Joanne Kurtzberg
Dr. Joanne Kurtzberg is a pediatric transplant physician who pioneered the use of HSCT for the treatment of pediatric patients with Krabbe disease. When her team first began stem cell transplantation for Krabbe disease in the mid-1990s, most of the children they treated were between 3 and 10 months of age, were experiencing multiple manifestations of the disease, and were not helped by treatment. Dr. Kurtzberg and her team had also treated 11 infants who were diagnosed in utero or at birth because of family history, received treatment within the first six weeks of age, and experienced improved clinical outcomes and quality of life. Since then, HSCT has become restricted to infants with early infantile disease or older children with later onset disease. Dr. Kurtzberg recognized some of the challenges that states may experience when adding Krabbe disease to their newborn screening panel. However, there are more than 100 pediatric transplant programs in the United States (US) that have the expertise needed to conduct these transplants and can provide timely referral and comparable outcomes. Advanced planning and referral with these collaborating pediatric transplant programs, whether in or out of state, will help states rapidly refer identified infants. Dr. Kurtzberg also said that diagnostics were available to provide sufficient evidence before transplant. She urged the Committee to vote in favor of recommending the addition of Krabbe disease to the RUSP.

Maria Escolar
Dr. Maria Escolar is Chief Medical Officer of Forge Biologics, a biotech company that has developed a gene therapy for Krabbe disease. She has treated patients with Krabbe disease for the last 20 years and conducted longitudinal research on more than 190 children with Krabbe disease from 49 states. She has also conducted the largest prospective natural history study of long-term outcomes in both infantile and late infantile Krabbe disease, as well as contributed to the development of psychosine as a disease biomarker for infantile onset. Her research showed a clear benefit of early detection and subsequent early access to HSCT treatment. In most of the cases she followed, the transplant was conducted at out-of-state metabolic-focused transplant centers, which were experienced in rapidly confirming diagnosis, obtaining insurance approvals, and counseling families. Newborn screening also provides an opportunity to identify late infantile onset disease that can be monitored and treated to improve outcomes. Dr. Escolar talked about the gene therapy FBX-101 for Krabbe disease. She will present data from the first two newborns with Krabbe disease successfully treated with FBX-101 at the WORLD S*ymposium* in February 2023. FBX-101 was administered after the patients received HSCT, and the results

indicated improved outcomes as compared to untreated Krabbe patients or Krabbe patients treated with stem cell transplant alone. FBX-101 has received designation as a priority medicine by the European Medicines Agency and both fast track and orphan drug designations by the Food & Drug Administration (FDA). Dr. Escolar highlighted an analogous gene therapy for spinal muscular dystrophy (SMA), a condition that the Committee recommended as an addition to the RUSP in 2018. She asked the Committee to consider the same breadth of evidence that supported the adoption of SMA as they consider a vote for Krabbe disease.

Dietrich Matern

Dr. Dietrich Matern talked about the New York newborn screening program, which began screening for Krabbe disease in 2006 with a procedure that was highly sensitive, but not very specific. The subsequent addition of galactocerebrosidase (GALC) enzyme DNA sequence analysis improved specificity, but not sufficiently. The New York screening program was the first to show that psychosine could be measured by dried blood spot as an effective screening strategy. Since then, the Mayo Clinic added psychosine as an integral part of Krabbe screening, and the Kentucky newborn screening program asked the Mayo Clinic to help them fulfill a new legislative requirement to screen for Krabbe. Since the Kentucky program began in 2016, the Mayo Clinic has screened 380,000 newborns and identified two infants with low GALC and elevated psychosine. Both children were diagnosed early, received transplants, and are doing well. Notably, there were no false positives for Krabbe disease in the seven years that the Mayo Clinic has supported Kentucky's Krabbe disease screening. Dr. Matern noted that significant progress had been made in the screening approach and that eight states are currently including psychosine in their strategy, with another two states that are likely to follow. He added that the Mayo Clinic also diagnosed 12 children with Krabbe disease from states not yet screening for it. Unfortunately, they were already six months old at diagnosis and were unable to receive a transplant. He urged the Committee to vote for the addition of Krabbe disease to the RUSP.

Newborn Screening for Krabbe Disease: A Systematic Review of the Evidence (Part 1)

***Alex R. Kemper, MD, MPH, MS,* Lead, Evidence-Based Review Group**

Dr. Alex Kemper presented key points from the full systematic evidence review. Dr. Kemper provided the disease course and epidemiology of Krabbe disease that included the following: an overview of Krabbe disease and clinical findings; the natural history of the disease with a description of signs and symptoms; and the case definition of Krabbe disease; and the prevalence of Krabbe disease.

Dr. Kemper provided a summary of newborn screening and Krabbe disease that included: a description of first-tier screening and second-tier screening; expert panel recommendations for follow-up after a positive newborn screen; diagnostic evaluation of Krabbe disease; a list of published reports on Krabbe disease newborn screening in the US; and current algorithms of newborn screening outcomes for Krabbe disease. Dr. Kemper reviewed the cost of newborn screening from the program perspective, which is estimated to be between $2 and $7 and reflects the cost of equipment, reagents, and laboratory staff. Lastly, Dr. Kemper reviewed key points from the Public Health System Impact Assessment of 34 states.

Newborn Screening for Krabbe Disease: A Systematic Review of the Evidence (Part 2)

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

Dr. Lisa Prosser reviewed the projected population-level outcomes of Krabbe disease newborn screening as compared to clinical presentation. The population-level model was developed using a number of assumptions: 1) the cohort was divided into onset before and after 12 months, 2) identified newborns would receive treatment before the development of overt symptoms, 3) differences in treatment outcomes before or after 30 days were not included, 4) newborns identified with disease markers by 12 months would be symptomatic at time of transplant, 5) probability of mortality due to transplant-related complications within 100 days of transplant was the same whether identified by newborn screening or clinical presentation, and 6) transplant-related morbidity after 100 days of transplant was not included.

Committee Discussion

***Ned Calonge, MD, MPH*, Committee Chair**

- A Committee member asked how the follow-up recommendations were developed for the low- and high-risk patients and whether there were data available to support those recommendations. The member also asked if it was known how many individuals would eventually be transplanted using those strategies.
    - Dr. Kemper answered that the development of the low- and high-risk algorithm was by expert consensus. There was no evidence to inform how many infants were eventually transplanted.
    - An organizational representative added that the low- and high-risk pathways were primarily based on genotype. A genotype associated with earlier onset would need more frequent and more intense follow-up than a genotype associated with an older onset. Those without a clearly associated phenotype would represent a challenge and experts would consider psychosine and GALC levels to develop a reasonable follow-up approach.
- A Committee member asked about the difference in outcomes between infants identified through family history and those identified through newborn screening. Dr. Kemper said that it is difficult to model outcomes comparing family history and newborn screening detection for a rare disease. When he spoke to experts, there was an expectation that families that knew an infant would be born with Krabbe disease might decide to deliver early to expedite treatment. However, this level of granularity was not reported in the data and most of the identified cases were not identified by family history.
- A Committee member asked what plans were in place to revisit the follow-up guidelines to determine their effectiveness. An organizational representative answered that the initial follow-up guidelines from the New York program resulted in very intense follow-up for at-risk individuals and required repeated tests, such as lumbar punctures and nerve conduction studies. These were often daunting for families to follow. The newer recommendations were developed to address those concerns by recommending very close follow-up with high-risk children and loosening follow-up recommendations for low-risk children. The new recommendations have not been in place long enough to observe outcomes, but the team that developed the recommendations is actively discussing how to collect outcomes data to determine whether the recommendations were appropriate.

- A Committee member asked about the number of states participating in the long-term follow-up recommendations. An organizational representative answered that they are in the beginning stages and will have more information in a few months. Historically, it was believed that 90 percent of patients with Krabbe disease had early infantile onset, but the modeling showed that there were more falling into the long-term follow-up pathway than those needing immediate treatment.
- A Committee member talked about the variable outcomes reported in the older literature and asked how to account for evolving technology and outcomes. Dr. Kemper said that there were no current data to answer that question but that there had been significant advancement in knowledge and improvements in transplant treatment. Despite these advancements, there still seems to be variable outcomes. In addition, there are centers of excellence experienced with Krabbe disease that could advance the understanding of evolving technologies.
- An organizational representative asked whether there were any cases in which screen positive children who needed a transplant had difficulties obtaining one because a state did not have resources or because the family's insurance was difficult to work with. Dr. Kemper said that no such case appeared in the literature. Virginia opted not to screen for Krabbe disease because of concern for obtaining treatment within 30 days. There has been no reported case in which a transplant was recommended, and the family wanted it but was unable to.
- An organizational representative suggested being careful when assessing data about access to treatment because a Committee recommendation for universal screening would inherently affect access.
- An organizational representative suggested that the largest data gap from the evidence review was the long-term benefits and harms of screening, as well as the diversity in response to HSCT. Families spoke during public comment about treatment outcomes that range from no disability to more profound disability.
- An organizational representative said that long-term follow-up is an issue with all RUSP conditions and will likely continue to be, but that status quo was not an acceptable outcome.

Committee Report: Newborn Screening for Krabbe Disease

***Shawn E. McCandless, MD,* Committee Member**
***Jennifer M. Kwon, MD, MPH,* Committee Member**

Dr. Kwon provided a brief review of Krabbe disease and its onset, pathophysiology, screening and diagnostic methods, and treatment. She reminded Committee members that their decision was based on the net benefit of screening and the certainty to which this benefit could be assessed. She emphasized that the evidence base for Krabbe disease contained several case reports and series, but that the data were challenging to interpret and that much of the assessment of the value of newborn screening relied on expert opinion. Overall, newborn screening and early treatment for Krabbe disease benefit those with early onset disease and may have benefit for later onset cases.

Dr. Kwon reviewed projected outcomes from the modeling results, specifically highlighting the number of infants projected to be referred to early treatment and the number projected to require

ongoing follow-up. She expressed an opinion that ongoing follow-up and surveillance can also affect families in negative ways that should be considered.

Dr. McCandless summarized the projected numbers comparing referrals, treatment recipients, and deaths between universal Krabbe disease newborn screening and clinical identification. He reminded the Committee that, although there was no evidence for improved quality of life in the evidence-based review, there were parents who spoke about quality of life as a result of treatment. The projected data suggest that approximately 80 percent of infants would benefit from therapy and 20 percent would not. Regardless of residual disability, it was also not clear whether children who undergo therapy would remain stable or experience later deterioration. Between 3 and 4 times as many infants would not be diagnosed with early onset disease and would enter follow-up protocols—many of whom would likely benefit from early diagnosis and treatment, but there are no data to support this assertion.

At a high level, benefits include increased lifespan, more achievement of developmental milestones (with some sustained disability), and treatment-associated mortality in a minority of cases. The potential harms are difficult to assess because of the lack of data, but include premature death as a result of treatment, false positive results, and unnecessary treatment involving compressed timeframes and therapy planning. Dr. McCandless emphasized that if a recommendation to include Krabbe disease in the RUSP were to move forward, it must include psychosine testing before families are given results to minimize the impact of false positives. The largest potential for harm is the psychological and financial burden on families after false positive and indeterminate diagnostic results.

There was moderate to significant benefit to most confirmed infantile onset cases and a potential benefit for uncertain diagnoses and later onset cases. Additionally, it appeared that most states had readiness to implement newborn screening for Krabbe disease within 2 to 3 years, although it was unclear whether states would incorporate psychosine testing. There was limited evidence to address the feasibility of screening, testing, and treatment in state newborn screening systems—although screening is highly feasible, there is less clarity about their potential approach for diagnosis and treatment.

Dr. McCandless summarized that newborn screening for Krabbe disease met criteria for category C1 in the decision matrix. Their recommendation was that Krabbe disease did not meet the threshold for recommending the addition of Krabbe to the RUSP as a core condition.

Dr. McCandless expressed appreciation for the public comments that were presented earlier and said that this recommendation was not intended to minimize the impact of the condition to affected children and their families, nor to imply that treatment was not beneficial. The recommendation was based on the totality of the currently available evidence.

Committee Discussion

- A Committee member asked for clarification on the inclusion of risk of treatment as a harm when treatment was a family choice and not a mandate. The member also asked for context to help assess the projected cost of $2 to $7.

    - Dr. McCandless said the cost was including as a harm was based on an assessment of overall outcomes from the screening program. The projected cost is generally based on additional reagents and technician's time. The upfront cost of a screening program is highly variable and typically ranged from less than $1 to $15. It is more challenging for screening programs to justify higher costs because they are often not in a position to increase their revenue stream without a legislative or regulatory action from the state.
- A Committee member asked for clarification about the diagnostic tests, such as magnetic resonance imaging (MRI) or lumbar puncture, that provide the most value. Dr. Kwon said that MRI and lumbar punctures can be very difficult to interpret. One process to consider as a best practice would be to identify a transplant center with a trusted specialist to interpret those tests and to determine whether the child needs a transplant or not. A neurologist, although very good at interpreting these diagnostics, would not necessarily be the best specialist to determine treatment.
- A Committee member asked what states were currently poised to roll out Krabbe disease screening. An organizational representative said that there were many states with laws in place that require initiation of screening for conditions on the RUSP within a certain time frame. States that may be poised to screen without legislation in place was unknown.
- A Committee member said that any follow-up plan will carry some harm to families in terms of travel and cost and that it is incumbent on providers and experts to recommend a follow-up plan in which the benefits outweigh the harm or to modify it if not. Although families that receive a false positive can experience uncertainty and anxiety for months or years, it was important to separate inherent risk of harm from manageable harm caused by a follow-up plan. It is good that some families may choose not to pursue treatment because it implies that they are engaging in informed decision-making that reflects their values. There is evidence that people tend to inadvertently undervalue the lives of people living with disability. There is also strong evidence that health care providers tend to overestimate the burden that families experience when taking care of a special needs child. There is evidence that HSCT is life-saving and leads to lives that are potentially better than clinicians might assume. The Committee member disagreed with the classification of low net benefit and suggested that it be changed to moderate net benefit because some of the indicated harms were manageable.
- A Committee member added that most of the lost to follow-up occurred in states that did not conduct psychosine second tier testing. There is a large newborn screening community with a wealth of knowledge and experience in Krabbe disease that can help states implement the screen, which is an added benefit. HSCT is not only used for Krabbe disease, but other newborn screening conditions. Some of the data about harms associated with inappropriate treatment may have been based on older data or discussions because there is no evidence of that now. Parents often make the decision to treat too early or not at all and whether that should be considered a harm is debatable. The Committee member added that the child with low psychosine was not a false positive but referred by the newborn screening program.
- Dr. Kwon acknowledged that HSCT was used as a treatment for other conditions but that no transplant center would consider it for an infant under eight weeks of age. The other conditions would not receive HSCT at this young an age.

- A Committee member talked about how the uncertainty of benefit was driven by uncertain levels of psychosine in which patients may become symptomatic later on. There is clear benefit when psychosine levels are high. The potential harms included potential screening policies for later onset cases, but this is a separate group from the early onset infants who need to be treated very quickly. The uncertainty is from the tremendous heterogeneity of the disease, and this is something the medical system needs to address. Krabbe disease is not the only example in which pre-symptomatic genetic traits can be identified.
- A Committee member said that an important influence in the Committee's decision is that psychosine testing has made a significant difference in the number of referred newborns and the number of follow-ups in low-risk cases. Whatever decision the Committee makes should be made on the presumption that psychosine was required for the screening paradigm. Weighing relative risk and benefit is challenging and there can be a degree of subjectivity involved in interpreting data. There are other conditions for which HSCT was the treatment modality that the Committee recommended for the RUSP, although with different parameters. There are also other conditions that the Committee recommended that had uncertain evidence about long-term outcomes and relative net benefit. If the Committee did not recommend that Krabbe disease be added to the RUSP, it was not clear what advice the Committee would provide to nominators about what to improve. The Committee member suggested that there was moderate evidence of net benefit rather than low.
- A Committee member agreed that there was subjectivity in assessing net benefit and that health care providers tended to incorrectly interpret the burden to the family. If the Committee were to move forward with a recommendation to add Krabbe disease to the RUSP, it would have to be with the addition of psychosine as a test because the evidence of its benefit is clear. If the Committee did not move forward with a recommendation, there would need to be an objective path forward for the nominators.
- A Committee member said that they interpreted the follow-up of intermediate levels not as a negative but rather as a way to tell families that there would be action at any first signs or symptoms.
- A Committee member thanked the Evidence Based Review Group, Dr. Kwon and Dr. McCandless, and the families that spoke during the public comment period. It was important to understand that disability is different from quality of life and that it can be easy to become ableist. There is a need to do better in terms of understanding the impact of newborn screening on quality of life and there should be research funding directed towards advancing that knowledge. It is also important to understand the impact on the newborn screening system overall, as well as equity in terms of the availability of providers and treatment. Where one is born and lives should not influence how long one lives. It is also important for the Committee to continue to think about the decision-making framework, which may only work well for conditions with a certain prevalence.
- A Committee member reiterated that there were multiple steps involved in this screening. The addition of a first tier Krabbe screen might not be a barrier, but there are two states that conduct screening without psychosine and it is not clear why. With most labs already screening for lysosomal storage disease, he felt that adding psychosine would not be a heavy lift.

A Committee member moved for a vote to change the rating of Krabbe disease screening from C1 to B1. The motion was seconded, roll was called, and the motion passed eight to six.

A Committee member moved for a vote to recommend to the Secretary that Krabbe disease be added to the RUSP as a core condition. The motion was seconded, roll was called, and the vote was tied seven to seven. The motion was therefore not passed.

Dr. Calonge said that Krabbe disease would not move forward to the Secretary as a recommended addition to the RUSP and recognized the challenging decision-making process for this very serious condition. The Committee will prepare a letter summarizing the evidence that will be helpful should a renomination come before the Committee.

Orientation to Workgroup Sessions

***Ned Calonge, MD, MPH*, Committee Chair**
Dr. Calonge said that, after discussions with the Workgroup Chairs, HRSA, and other colleagues, there would be a change in the Workgroup structure and approach going forward. He believed it will be a more effective approach to have ad hoc workgroups based on specific topics that would provide recommendations for the newborn screening system. He invited members of the public, advocates, and families to provide input into any of the topic-related Workgroups.

DAY TWO: Friday, February 10, 2023

Welcome and Roll Call

***Ned Calonge, MD, MPH*, Committee Chair**
***Leticia Manning, MPH,* Acting Designated Federal Official, HRSA**
Dr. Calonge welcomed participants to the second day of the Committee meeting. Ms. Manning welcomed participants and conducted roll call.

Prioritization and Capacity Workgroup Interim Update

***Alex R. Kemper, MD, MPH, MS,* Project Lead, Prioritization and Capacity Workgroup**
There is an anticipated increase in the number of nominated conditions submitted to the Committee as a result of advances in newborn screening and treatment. The Committee's Nomination and Prioritization Workgroup has a finite capacity for reviewing nomination submissions. No criteria were in place to define the prioritization of multiple simultaneously submitted nominations. Dr. Kemper emphasized that the limited capacity was not currently an issue but that there was a need to develop prioritization criteria and processes in preparation for the future. The prioritization process would follow a set of key principles that considered variables such as prevalence, expected benefits and harms, availability of a valid screen, potential to reduce inequities, and balance in the portfolio. The Workgroup was considering a formal point system to support both transparency and challenging decision-making.

Committee Discussion
***Ned Calonge, MD, MPH*, Committee Chair**

- A Committee member commented on the overlap in the Committee's review of mucopolysaccharidosis type II (MPS II) and GAMT and asked how the Workgroup would address the review of conditions at different stages in the process. Dr. Kemper

answered that there was a set of procedures that were followed for the review of MPS II and GAMT that worked well even though there was overlap. The need for prioritization may arise when the Committee has challenges in reviewing multiple conditions thoughtfully. HRSA decided the number of conditions that could be reviewed simultaneously.

- An organizational representative commented that the issue of equity was an ethical decision. Making a decision about the greatest public health impact when rare diseases were less likely to be nominated should be considered as an issue of equity and should be overtly addressed in the prioritization process. There should also be cognizance that the strength of an advocacy group's voice can also influence the process. It was important to ensure that a formal point system was not a way to quantify something that could not be quantified or to create a sense of objectivity by assigning values and numbers. Thinking about a point system as a tool rather than a rule would be a good approach.
- An organizational representative said that careful adherence to an evidence-based process was essential because it can be very easy for experts to fall into a tautology in which their assumptions were proven by the scoring system they developed. It was also important to not allow the administrative process to override the intent of a publicly transparent prioritization determination. The Committee member asked for clarification on the idea of a balanced portfolio. Dr. Kemper said that the idea of a balanced portfolio was to ensure that the process evaluates not only incremental advances in technology but also novel technologies. This had not been a problem in the past but considering it now would help avoid potential problems in the future.

Public Comment

Samantha Nikirk

Ms. Samantha Nikirk is mother to a two-and-a-half-year-old daughter, Evie, who was born with congenital cytomegalovirus (cCMV). Although Evie had signs and symptoms at birth, she was not diagnosed with cCMV until she was three months old, which was too late to receive the antiviral treatment that would have helped prevent her hearing loss and developmental delays. She currently has multiple lifelong disabilities. Ms. Nikirk provided an overview of cCMV, which affects 30,000 children each year in the US, or 1 in 200 children. It is the primary cause of non-genetic hearing loss, and more children have disabilities related to cCMV than to Down syndrome, fetal alcohol syndrome, spina bifida, and pediatric HIV AIDS. It is also more common than all other conditions on the RUSP. Less than 5 percent of infants with cCMV are identified by clinical observation. Ms. Nikirk said that cCMV should be added to the RUSP because screening must occur before 21 days of life and treatment must be initiated within the first month of life.

Taylor Gerding

Ms. Taylor Gerding is mother to a two-year-old daughter, Ava, who has cCMV. Ava was diagnosed at birth after a neonatologist recognized her symptoms and recommended a cCMV screen. As a result of early screening, Ava was able to receive antiviral treatment and today has only mild hearing and vision loss. Ms. Gerding said that diagnosis at birth is rare—a recent 2017 study showed that less than 10 percent of cCMV cases are identified at birth, despite being symptomatic. She asked the Committee to recommend the addition of cCMV to the RUSP so that all affected infants can receive treatment within the 30 days of birth.

Christina Estby
Ms. Christina Estby is mother to two boys, Samuel and Josiah, who were diagnosed with DMD within weeks of birth as a result of their genetic heritage. Samuel and Josiah received high-dose steroid treatment at 12 and 6 months of age, respectively. They also received specialized medical care and follow-up appointments every six months. They began wearing ankle-foot-orthosis and began physical therapy at 2 years of age—an age in which many boys with DMD have not yet been diagnosed. Ms. Estby said that their diagnostic odyssey took weeks instead of months and years, as is typical for most families affected by DMD. The boys are now 9 and 7 years of age and very active. Ms. Estby said that many promising therapies for DMD are becoming available, making the early identification of DMD increasingly important. Early treatment can halt the progression of DMD before it even starts, and newborn screening could provide an opportunity for all boys with DMD the opportunity to live a long and healthy life.

Niki Armstrong
Ms. Niki Armstrong is the Newborn Screening Program Manager for Parent Project Muscular Dystrophy (PPMD). She provided an overview of key points about DMD, which is the most common pediatric muscular dystrophy, affecting approximately 1 in 5,000 males. Infants with DMD are born with muscle damage that progresses and accumulates over time until the muscle cells are so damaged that they die and are replaced with fat and fibrosis. Once this occurs, there is no way to reverse the damage. DMD is life-limiting with an average age of death in the late 20s. There are currently five treatments for DMD, with another two potential therapies under FDA review. Treatment is most beneficial when provided before there is significant, irreversible muscle damage, but the average age of diagnosis is 5 years of age. Ms. Armstrong asked the Committee to vote to move DMD to full evidence review.

Cara Gagliano
Ms. Cara Gagliano is mother of three sons, two of whom have DMD. Her son Carmine began to show symptoms at 4 years old but was not diagnosed until the age of 7.5, after years of research, concern, and efforts to convince their pediatrician to run tests. By the time Carmine started treatment, his muscles had already suffered irreversible damage. Her younger son Vincent also showed signs of DMD but was able to be diagnosed and start treatment immediately. Ms. Gagliano said that there was a large difference between the two boys and that the earlier treatment provided great benefit to her younger son. She added that no other parent should have to experience the grueling diagnostic odyssey for DMD. Newborn screening for DMD would have huge impact on the lives of affected boys and their families.

Megan Waldrop
Dr. Megan Waldrop is a child neurologist with training in neuromuscular medicine and gene therapy, as well as attending physician and Co-Director of the Muscular Dystrophy and SMA Clinics at Nationwide Children's Hospital in Ohio. The clinic follows 506 individuals with DMD, and the team was a pioneer in the care and treatment of DMD, having conducted both the initial daily prednisone studies and the subsequent efficacy and safety studies. There are currently four available exon skipping drugs and gene replacement therapies in development. Dr. Waldrop conducted the first vectorized exon skipping trial, dosing the youngest ever participant at 7 months of age. The child had the least adverse effects of any other child in the trial and has

continued normal development with a 91 percent drop in creatinine-kinase levels and a 90 percent increase in dystrophin expression. The study indicated a clear age-dependent dosing effect with the greatest benefit in younger children. DMD treatment in infancy has been shown to be both safe and efficacious, which supports the need to include DMD in newborn screening. Early diagnosis and treatment allow affected children to live to their fullest potential.

Paul Melmeyer
Mr. Paul Melmeyer is Vice President of Policy and Advocacy at the Muscular Dystrophy Association (MDA), which serves DMD and Pompe disease, and other rare neuromuscular disease communities, and co-sponsored the DMD nomination in 2022. He asked the Committee to consider the key evidence points. First, the evidence within the nomination package was thorough and adequate to move the nomination forward—after decades of research, the progression of DMD was well understood. Second, pilot studies have tested the validity and reliability of using creatinine-kinase levels as follow-up confirmatory genetic testing to screen and diagnose DMD. Third, there were several FDA-approved treatments available for DMD with a gene therapy anticipated to be approved later this year. Finally, there was a robust network of clinicians prepared to provide comprehensive care to those newly diagnosed through newborn screening. In conclusion, MDA urged the Committee to vote to move the DMD nomination forward for full evidence review.

Dylan Simon
Mr. Dylan Simon is the Director of Public Policy at the EveryLife Foundation for Rare Diseases, a nonprofit organization dedicated to empowering the rare disease community. Yesterday's vote on the Krabbe disease nomination yielded a 7-7 tie that was interpreted as a vote to not move the condition forward to the Secretary. The rare disease community urged the Committee to reconsider this interpretation. It did not yield a no, but rather a need for further clarification of questions raised that could not be addressed by the participating Committee members. The ACHDNC charter states that membership shall not exceed 15 members to ensure that the total number of members is an odd number. While the charter does not explicitly state that this number is to avoid a tie vote, the rare disease community believed that a path forward for further discussion and resolution of this tie would maintain the intention with which the Committee was established. The rare disease community urged the Committee to revisit the vote and consider options to ensure that Krabbe disease receives full consideration. Yesterday's discussion also illuminated critical gaps in the decision-making matrix, and the rare disease community urged the Committee to formalize the data included in the evidence-review matrix. The rare disease community also requests the inclusion of a patient representative as a voting Committee member. The lack of this formal representation reflects a significant imbalance of representation. The rare disease community asked that the Committee formally include an expert member of the nominated disease community to inform the discussion and address any questions that might arise. Yesterday's discussion addressed older data and the perceived negative impacts of a late onset diagnosis when the nomination was for early onset diagnosis. More recent data suggests that the majority of parents were interested in receiving information on a developing disease that could be prevented, treated, or cured. In addition, organizational representatives were vital in the newborn screening ecosystem and silencing their perspectives when it matters the most negated the purpose of their membership.

Education and Training Workgroup Update

***Jane M. DeLuca, PhD, RN, CPNP,* Committee Member Chair, Education and Training Workgroup**

Dr. Jane DeLuca said that the Education and Training Workgroup discussed the proposed change in the existing Workgroup structure and suggested narrowing their original statement of priorities into smaller groups focused on specific and prioritized projects. They considered projects such as 1) fostering community engagement by involving community members in order to steer community priorities into projects; 2) engaging state screening programs to better understand the needs of different groups, particularly among those who are underserved or difficult to reach; 3) accessing the policies and materials across state programs and existing organizations to perform a needs assessment; 4) talking to families about their experiences in screening, including those with positive and false positive results; 5) creating a resource repository. 6) exploring alternative education means such as YouTube videos for different groups, 7) providing education along the continuum of screening to obstetrics to pediatric providers, and 8) preparing education for families and communities about new conditions that would be added to the RUSP.

Follow-up and Treatment Workgroup Update

***Kyle Brothers, MD, PhD,* Committee Member Chair, Follow-up and Treatment Workgroup**

Dr. Kyle Brothers reminded the Committee that the Follow-up and Treatment Workgroup had presented the idea of a blueprint, which would serve as guidance for states after the addition of a condition to the RUSP. The Workgroup identified three elements of the blueprint. The first element was *short-term follow-up*, which would guide state screening programs to develop a plan to assess their program and identify next steps after a screen, such as an algorithm for different levels of biomarkers. The states would also identify the short-term outcome measures specific to the condition.

The second element of the blueprint was *long-term follow-up and treatment*, which would outline a treatment approach for providers, specify the relevant subgroups, and identify standardized terminology. This element would specify the testing, follow-up, and treatment for each subgroup. Nominators for conditions with existing clinical guidelines would not have to outline an approach but rather simply refer to those guidelines.

The third element of the blueprint was *data collection strategy*, such as a data repository or platform in order to assess screening and treatment outcomes.

Laboratory Standards and Procedures Workgroup Update

***Kellie B. Kelm, PhD,* Ex-Officio Committee Member Chair, Laboratory Standards and Procedures Workgroup**

Dr. Kellie Kelm reviewed the three priority topics that the Laboratory Standards and Procedures Workgroup discussed at the last meeting. The first priority area was *best practices for the utilization of second-tier testing,* and the Workgroup talked about drafting a best practices document for states to use when considering the utilization of second-tier testing.

The second priority was a *quick-start guide and project worksheet* for implementation of a condition added to the RUSP. The Workgroup recognized that existing resources were available

(e.g., Association of Public Health Laboratories fact sheets) and that a good start would be to review these resources and identify the gaps in tools and information that states need to support a more rapid implementation.

The third priority was the *evaluation of homocystinuria screening methods*. Although CDC had been working on both first and second tier methods to improve the false negative rate for this condition, information was not yet available to be shared with states.

Committee Discussion on Action Items

***Ned Calonge, MD, MPH*, Committee Chair**

- Dr. Calonge thanked the Workgroups for identifying priority areas for the Committee to consider in terms of what could be achieved within 12 months and the support that might be requested from HRSA. He asked Committee members to discuss the priorities that were presented and identify their priorities.
- There was a discussion about the review, revision, and dissemination of educational materials.
- A Committee member talked about the public comment stories from parents whose doctors had told them not to be concerned when the reality was quite different. Having just-in-time information available would be very helpful. In addition, it was very helpful to know that HRSA and CDC collaborated to align requirements and that grantees were made aware of existing resources. The Follow-up and Treatment Workgroup's idea of a blueprint would be quite useful for nominators, as well as the Committee in terms of having more information available to better assess the evidence.
- A Committee member said that the CDC-HRSA collaboration identified overlapping areas of activities to help both agencies become more strategic about their support for the newborn screening community. A manuscript on the CDC's work on the homocystinuria first-tier screening methods was recently accepted and should be published this year. HRSA's funding opportunities could be helpful to states in implementing new biomarkers for homocystinuria.
- An organizational representative said that the evaluation of educational materials was important, and that one important aspect of the evaluation would be to remember the intention of the resources.
- An organizational representative added that two manuscripts addressing the evidence review for MPS II were accepted by *Genetics and Medicine* and that a manuscript for GAMT was in development.
- An organizational representative talked about the idea of "patients in waiting" as a common phenomenon across the newborn screening system that is often considered a responsibility of the specialist or advocacy group.
- A Committee member said that there needed to be a paradigm shift from the clinical perspective of a yes or no diagnosis toward one that includes the patient in waiting. It was also important to consider how to educate both the next generation of providers and existing providers about this new category. The idea was not limited to newborn screening but extended to population health. There could be collaboration with public health colleagues to address this broadly.

- Dr. Calonge said that he and HRSA would develop a priority list to send to Committee members for feedback on the Committee's 2023 activities and the resources needed to support those activities.

Duchenne Muscular Dystrophy (DMD) Nomination Summary

***Ned Calonge, MD, MPH*, Committee Chair**

Dr. Calonge said that the Committee received a nomination from the Parent Project Muscular Dystrophy in June 2022 to recommend the addition of DMD to the RUSP. He provided a review of the Nomination and Prioritization Workgroup summary and recommendation to move DMD forward to a full evidence review.

DMD is an X-linked neuromuscular disease with progressive muscle damage and weakness associated with highly elevated levels of creatinine-kinase. DMD primarily affects males, although females can be variably affected, and is known to occur in approximately 1 in 5,000 live male births. Diagnosis is based on genetic testing or muscle biopsy and is typically made between 4 to 5 years of age. All individuals with DMD will experience loss of ambulation and upper limb use, followed by progressive pulmonary dysfunction and cardiomyopathy. Irreversible muscle damage begins as early as fetal life and children with DMD often experience significantly delayed milestones. Death related to pulmonary or cardiac disease often occurs in the individual's 30s. Four FDA-approved therapies are available for DMD, and corticosteroids are recommended prior to onset of physical decline—although the optimal age for treatment has not yet been established. Additional therapies were in clinical trial. Treatment management also required a multidisciplinary team to provide specialty care and therapies.

Dr. Calonge reminded Committee members that a nominated condition must meet three core requirements to move to full evidence review: 1) validation of a laboratory test, 2) a widely available confirmatory testing that is sensitive and specific to diagnosis, and 3) a prospective population-based pilot study. DMD did have a valid laboratory test, an FDA-approved screening with creatinine-kinase MM—CK-MM and an available (though not necessarily widely) available confirmatory test with NG sequencing. Prospective population pilot studies had been conducted in New York, North Carolina, and in the Zhejiang province in China.

Because these three core requirements had been met, the Committee must then consider other key factors. Dr Calonge said that DMD is a health condition that is medically serious, with a well-described case definition to help predict a phenotypic range based on population-based screening. Prospective pilot data were available from more than 65,000 newborn screens, with eight confirmed cases, one carrier, and one with a pathogenic variant. First- and second-tier tests were available for DMD, although there were some concerns about analytic validity. The benefits of treatment are significant. There were less data available to quantify the frequency and severity of harms, as well as variants of unknown significance.

The Nomination and Prioritization Workgroup recommended that the Committee should not move DMD forward for evidence review in large part because of the limited evidence on whether detecting cases through newborn screening would result in better outcomes, the lack of published data on treatment benefit, and unclear cutoffs for different ages. Future nominations are welcomed that include additional information on the impact of screening. Dr. Calonge

emphasized that the evidence for DMD newborn screening was expected to evolve and may fill the gaps of uncertainty today.

Committee Discussion

- A Workgroup member said that the public comment session introduced new information about siblings and a clinical trial of pre-symptomatic treatment with corticosteroids that was not considered in their review but would have been very helpful. If more information was released in the near future, it could change their recommendation. In addition, if the number of false positives could be resolved with a second tier or third tier screen, that could also influence their recommendation. The Workgroup member added that lack of an FDA test was not a factor in their personal decision making.
- A Workgroup member added that the timing of testing was considered, specifically whether the first-year screening was the right time for routine screening.
- A Workgroup member echoed that information was introduced during the public comment session that would have been useful to have. The false positive was concerning. There would need to be a reasonable mechanism for addressing this, as well as clarification about how easily false positive cases could close so that families could be quickly reassured. It also seemed that the screening test was not attuned for female carriers and there needed to be clarification on whether that reflected the expectation of the nominators or not.
- A Workgroup member agreed that information from the public comment session would have been helpful to have when additional information was requested from the nominators. The number of false positives was concerning, as were challenges in interpretation of gene sequencing for this large gene. The Workgroup agreed that the situation was fluid and that they were looking forward to additional information from studies concluding in the near future.
- A Committee member said that the biology of the condition lent itself perfectly for newborn screening. An elevation of creatinine-kinase indicated the process of deterioration in the prenatal period. One would therefore assume that early detection would improve outcomes.
- A Committee member said that the data were not perfect, but they never would be. The review of the data showed emerging evidence of benefit for early treatment. DMD was more common than other conditions that the Committee had considered and waiting for evidence to be published would not necessarily improve the outcome of this nomination.
- A Committee member said that there was no question that earlier diagnosis would have positive downstream effects, but that the equity barriers would not likely be solved with early diagnosis because there were other complex factors involved. The data for early treatment that was forthcoming would be better reviewed with another nomination. Starting the full evidence review now would not likely benefit this nomination without those data.
- An organizational representative said that there were other, non-pharmacologic treatments that had been shown to make a difference, such as support services and physical therapy and, started earlier, could delay loss of function. Treatment should be considered in total. In DMD, the symptoms preceded diagnosis by a few years, suggesting that the question should not be about the benefit of pre-symptomatic treatment but rather pre-diagnosis benefit. There was precedence for the benefit of delaying the

progression of disease, such as with Alzheimer's disease. Further, there was a question about whether another first-tier test a few months after the initial test would reduce a number of false positives. These points needed to be investigated by a full evidence review now rather than waiting any longer. Dr. Calonge responded that the idea of pre-diagnosis benefit suggested that there may be another screening approach more appropriate than newborn screening.

- An organizational representative said that it was important to realize that laboratory-developed tests for rare disease were a hallmark of need and that 184 labs providing a confirmatory test was a large number. Additionally, the smaller scale pilot studies inherently had cutoffs that were more conservative in an effort to capture more cases and identify where they would fall in the confirmatory and diagnostic process.

A Committee member moved for a vote to move the nomination for DMD to full evidence review. The motion was seconded, roll was called, and the motion was not passed with a vote of 4 to 9 and one recusal.

Dr. Calonge said that he would provide a letter that summarized the information for the Committee to reconsider the nomination to the RUSP. He urged the nominators to not be discouraged by the vote and to consider resubmission of their nomination. A Committee member asked if there could be an expedited review of another nomination package. Dr. Calonge responded that the nominators had heard the concerns about gaps and could submit a renomination at any time. The advantage was that the Nomination and Prioritization Workgroup had already spent a lot of time reviewing information and would likely be able to provide a timely review of a resubmission.

HRSA State Interoperability Program

Advancing Electronic Data Sharing for Newborn Screening Programs
***Craig Newman, PhD*, Altarum**
HRSA launched the Innovations in Newborn Screening Interoperability Project (INBSI) to work directly with jurisdictional programs to build the foundation for improved data sharing. This was done through technical assistance, training and education on data interoperability, and collaboration between newborn screening programs. The grantee for this program, Dr. Craig Newman discussed interoperability and the ability of systems to exchange information in a meaningful way across boundaries, whether organizational or jurisdictional, so that meaning is not lost when data is shared. Data interoperability in newborn screening is important to provide timely, accurate, and complete screening results; enhanced care coordination; improved quality assurance and health equity; and better communication and transparency between patients, providers, and birthing hospitals. There were still significant barriers to ensuring data exchange between public health programs, but an electronic data exchange had the ability to revolutionize how data is used. To address the current gaps in data interoperability, state public health programs needed resources to evaluate their current infrastructure. To meet this need,

Florida Newborn Screening Interoperability Implementation Activities
***Radley Remo, MPH,* Florida Department of Health**
***Juan Vasquez, MHA,* Florida Department of Health**

Mr. Juan Vasquez talked about Florida's self and readiness assessment, which included staff interviews, focus groups with providers and trading partners, a mapping of current work and data flows, and existing interoperability. The results of the assessment informed opportunities for interoperability and modernization with newer tools and standards. His team then developed recommendations for going forward and matched their goals with leading standards and modernization tools. Mr. Vasquez demonstrated specific components of their readiness assessment and implementation project, highlighting factors such as data validation and anomaly detection to ensure that hospitals receive results that would align with their electronic records.

Interoperability: Utah Newborn Screening
***Andy Rohrwasser, PhD, MBA,* Utah State Department of Health**
Dr. Andy Rohrwasser talked about Utah's efforts to develop an infrastructure for data interoperability in newborn screening. Utah's newborn screening program was considering the addition of between 4 to 10 new conditions and, in order to achieve this, they needed to consider economies of scale and accountability to ensure a long-term follow-up solution. Dr. Rohrwasser emphasized the need to have a scalable, centralized (or distributed) solution that was both automated and can manage ad-hoc situations in order to have a sustainable long-term follow-up solution add a significant number of new conditions to their screening program. He provided an overview of their long-term follow-up data process from the identification of a disorder to notification to primary or specialty care.

Committee Discussion
***Ned Calonge, MD, MPH*, Committee Chair**

- Dr. Calonge thanked the presenters and acknowledged the need for additional funding and model systems.
- A Committee member asked if the integrity systems that was used was an intermediary for exchange in the Florida program from a third-party system and, more generally, how interoperability worked with point-of-care testing. Mr. Vasquez answered that the integrity platform was proprietary at the Florida Department of health but was cloud-based through the Department of Health Infrastructure. It leveraged some advances made in response to COVID-19 testing and reporting.
- An organizational representative said that it was extremely challenging to obtain interoperability in the newborn screening system and encouraged any sharing of information between programs. Texas currently had a process, but it was a delayed process that worked from the back end, such that one could not identify mismatches.
- A Committee member said that it was not only a matter of obtaining funding, but also obtaining buy in from the right people. There was much more attention being paid to interoperability after the COVID-19 pandemic and this was a good time for newborn screening to join that movement.

New Business

***Ned Calonge, MD, MPH*, Committee Chair**
Dr. Calonge invited Committee members and organizational representatives to share new business or announcements. He recognized the challenge of this meeting and extended his heartfelt appreciation for the honesty and courage from organizational representatives and members of the public as they shared their expertise and stories.

Dr. Calonge thanked Committee members and said that the next Committee meeting would be in-person and virtual on May 4-5, 2023.

Adjourn

Dr. Calonge adjourned the Committee meeting at 2:00 P.M. E.T.