Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Minutes of August 30-31, 2022

Virtual Meeting

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Committee Members

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Term End Date: June 30, 2026

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Genetic Alliance
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March of Dimes
Siobhan Dolan, MD, MPH
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National Society of Genetic Counselors
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Society for Inherited Metabolic Disorders
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Harvey Levy Chair in Metabolism
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Boston Children's Hospital
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Professor of Pediatrics
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DAY ONE: Tuesday, August 30, 2022

Welcome, Roll Call, Committee Business

***Ned Calonge, MD, MPH*, Committee Chair**
***Soohyun Kim, 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. Dr. Calonge welcomed Dr. Scott Shone as the new organization representative for the Association of State and Territorial Health Officials and conducted the roll call.

Committee members in attendance were:

- Dr. Kyle Brothers
- Dr. Ned Calonge (Committee Chair)
- 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. Kamila Mistry (Agency for Healthcare Research and Quality; AHRQ)
- Dr. Shawn McCandless
- Dr. Chanika Phornphutkul
- Dr. Melissa Parisi (National Institutes of Health; NIH)
- 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. Max Muenke (Day two only)
- American College of Obstetricians & Gynecologists, Dr. Steven Ralston (Day two only)
- Association of Maternal & Child Health, Ms. Sabra Anckner
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State and Territorial Health Officials, Dr. Scott Shone
- Association of Women's Health, Obstetric and Neonatal Nurses, Dr. Shakira Henderson
- Child Neurology Society, Dr. Margie Ream
- Department of Defense, Dr. Jacob Hogue
- Genetic Alliance, Ms. Natasha F. Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Cate Walsh Vockley

In March 2022, former Committee Chair Dr. Cynthia Powell sent a letter to the Secretary of Health and Human Services (HHS) recommending the addition of mucopolysaccharidosis type II (MPS II) to the Recommended Uniform Screening Panel (RUSP). Dr. Calonge informed the Committee that the Committee received a letter from the Secretary on August 2, 2022, which conveyed acceptance of the recommendation and requested that the Committee submit a report within five years describing MPS II screening implementation, access, cost of treatment for diagnosed infants, and impact on families due to treatment periodicity.

Dr. Calonge provided an update on other RUSP nominations. After the Committee voted to recommend adding guanidinoacetate methyltransferase (GAMT) deficiency to the RUSP at the May 2022 meeting, Dr. Powell submitted a letter of recommendation to the Secretary. The Nomination and Prioritization Workgroup completed their review of the nomination package for congenital cytomegalovirus (cCMV) and concluded that it had insufficient information to move the nomination forward. The Committee received a nomination package for Duchenne muscular dystrophy (DMD) and Dr. Calonge will inform the Committee of next steps. Dr. Calonge will continue Dr. Powell's work to form a workgroup to develop criteria and process for prioritizing the review of nominated conditions and will keep the Committee apprised of this progress at future meetings.

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

Incoming Chair Remarks

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

As the new Committee Chair, Dr. Calonge provided an overview of his professional background in family and preventive medicine, which included 36 years as faculty at the University of Colorado, as well as the positions of Chief of Preventive Medicine for Kaiser Permanente in Colorado, Chief Medical Officer for the Colorado Department of Public Health and Environment, President and CEO of the Colorado Trust, and Associate Dean for Public Health Practice at the Colorado School of Public Health. Dr. Calonge's expertise is in evidence-based medicine and methodology, having served on several advisory roles (including ACHDNC for three years) to translate evidence into evidence-based recommendations for areas such as adult clinical services, public health and community services, genetic testing, immunization practices, and environmental contaminants.

Dr. Calonge's philosophy on screening decisions is that they require the highest level of evidence that is free from politics, special interests, and advocacy; and for which there is an acceptable level of certainty of net benefit. Notwithstanding his position on evidence, Dr. Calonge shared his strong belief in the importance of advocacy as a vital role in evidence-based medicine, particularly in newborn screening, for which it is essential to understand the impact of a newborn condition on the child and families. He shared his view that it is important to have political advocacy to advance the implementation of newborn screening at the state and federal levels.

Dr. Calonge reviewed common criteria for a screening program, which includes the importance and severity of the disease, a recognizable pre-symptomatic stage, reliable screening tests, evidence that treatment results in improved outcomes, and sufficient resources to support diagnosis and treatment in positive screens. He added that these criteria can be simplified into a criterion that evaluate whether a screening program, if implemented under present conditions, would result in sufficient net benefit to justify starting the program, given the level of resources required. He noted, of the five potential outcomes of screening, four could have potential harm. For instance, a false negative could provide false reassurance and delay diagnosis and treatment. A false positive could result in unnecessary and potentially harmful diagnostic tests, treatment, and labeling. An over-diagnosis is a true positive of a disease that would not progress and could lead to unnecessary treatment. There could also be no benefit from early detection, diverting scarce resources from other services.

Dr. Calonge reviewed principles of decision-making when there is significant scientific uncertainty. For instance, there should be a proportional balance between plausible harm and benefit for all individuals. Decision-making should incorporate the values of and informed decisions by individuals. Decisions should also be made with consideration to available resources and be adaptable when new information is available.

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

- An organizational representative talked about advocacy as a continuum and asked Dr. Calonge to clarify his position on advocacy. Dr. Calonge answered that he considers advocacy as something to inform the Committee as it decides how to move forward. It helps elucidate the potential harm of not screening, provides context needed for Committee members to understand why the topic is being considered, and maintains focus on the topic to keep discussions moving forward. Advocates who are on the Committee have made great strides in moving a topic into evidence review. He also believes that advocacy plays an important role in driving forward the resources needed for implementation.

Infant Formula Shortage

The Infant Formula Shortage: Impact, Responses, and Lessons Learned
***Susan A. Berry, MD, FAAP, FACMG,* Professor, Division of Genetics and Metabolism, Department of Pediatrics, University of Minnesota**

Presenting on behalf of the American Academy of Pediatrics (AAP), Dr. Susan Berry talked about the impact of the infant formula shortage and its effect on those who rely on specialty formulas for infants with inborn errors of metabolism (IEM). The recall of several infant formula products manufactured at Abbott Nutrition facilities in Sturgis, Michigan resulted in drastic shortages of many specialty formulas manufactured exclusively at that site. With limited alternatives for specialty formulas, pediatricians became overwhelmed with inquiries from desperate families and had to identify creative substitutions from what was available. Some states temporarily revised their authorized formula requirements, but supply lines remained strained, and families continued to experience stress and concern for their infant's health and wellbeing. Some infants were hospitalized for weight loss and dehydration as a result of

homemade and diluted formulas. Dr. Berry emphasized that medical foods, such as specialty infant formula, are a fundamental responsibility in the care of children identified through newborn screening.

Genetic Metabolic Dietitians International (GMDI) conducted a survey of metabolic dietitians to understand the impact of the formula shortage on patients and clinics. They found that the top barriers for patients were unacceptable taste and inappropriate nutritional profile. Dr. Berry said that many families had to navigate a complex prescription authorization process through their insurance that typically required between one to four weeks before they could obtain their child's prescribed formula.

Dr. Berry reviewed some of the immediate actions that AAP took to address the formula shortage. Soon after the Abbott recall, AAP sent letters to the White House and Congress, urging immediate action and efforts to avoid a future crisis. Additionally, AAP engaged in ongoing communications with the FDA, United States Department of Agriculture (USDA), and CDC to share expertise and conduct regular briefings with the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN).

AAP also developed online educational resources for pediatricians and families that are continually updated as new information emerges. These resources provide guidance for pediatricians to help their patients through the formula shortage, guidance for parents on how to switch to different formulas, information about imported formulas, and safety information warnings against diluting or making homemade formula. AAP also contributed to chapters on formula feeding of term infants, IEM, and federal regulations of foods and infant formula in the latest version of their *Pediatric Nutrition* policy manual. AAP continues to amplify messages through their social media channels to increase awareness of the shortage, to help struggling families with tips for finding formula, and to provide guidance for easing shortages and ensuring that formula is available for all families.

Dr. Berry said that safety is critical for substitution of specialty formulas. Parents of children with conditions that require specialty formulas must work with their medical specialist to find alternatives. NASPGHAN created a resource that categorizes FDA-reviewed formulas by protein type to help pediatricians and families find an interchangeable formula. However, infants may still reject a substitute formula because of taste. Some of the formula shortage has been alleviated by Operation Fly Formula, which was an initiative to import formula brands widely used primarily in Europe and Australia. Dr. Berry concluded by advocating for the passage of the Medical Nutrition Equity Act (MNEA), which would provide more assured access to formula and medical foods on a long-term basis. Current strategies to provide formula will continue to impair delivery, even when shortages are alleviated. AAP will continue to work with the federal government and other partners to help families find the formula they need.

Shortage of Medical Foods for Inborn Errors of Metabolism: The OHSU Experience
***Sandy van Calcar, PhD, RD, LD,* Associate Professor, Department of Molecular and Medical Genetics Graduate Programs in Human Nutrition, Oregon Health and Science University**

Dr. Sandy van Calcar provided her perspective of the formula shortage as a metabolic dietitian who works directly with patients with IEM. Medical formulas treat IEM through eliminating or limiting of the offending substrates in order to normalize metabolism and prevent adverse health effects. They are a major source of energy, protein, and other macronutrients, often administered within the first few weeks of life after a confirmed diagnosis, and typically required throughout adulthood. Even prior to the formula shortage, access to medical food and formulas has been a complicated challenge. Insurance coverage and availability varies widely across states. States may not cover all IEM disorders and may also impose age restrictions, formula selection restrictions, and limited financial coverage.

Dr. van Calcar talked about the formula program in Oregon, which centralizes purchasing, distribution, and financials at Oregon Health and Science University (OHSU). All ages and disorders that require medical foods are covered through mandated insurance coverage and Oregon's Medicaid expansion, Oregon Health Plan. There are no limitations on product selection and the program has wide discretion for prescriptions by OSHU metabolic dietitians. Despite these advantages, there are some challenges, especially with coverage for adults, out-of-state patients, and for individuals with self-funded insurance.

Like the rest of the country, OSHU experienced significant backorders for many products across all of the formula companies that distribute specialized formula for IEM. Despite the restart of production by Abbott and increased production by other companies, there remains significant shortages that will likely continue for the next several months. OSHU responded to the shortage by first prioritizing their patients by age, disorder, and severity; initiating early communications with patients about the shortage; identifying alternatives; and developing transition plans for each patient through taste testing and slow introduction of the new medical foods. They also identified patients who likely would need emergency care to ensure there was sufficient supply to support them through inpatient admission.

Dr. van Calcar talked about the complications that OSHU experienced, including increased family stress and inadequate formula intake, as well as health complications such as inadequate metabolic control and slowed weight gain or weight loss. Although OSHU did not have an increased need for emergency care, Dr. van Calcar is aware that other clinics did. Going forward, she suggested that there is a need to clarify the definition of medical foods, standardize policies and coverage across the United States, reduce barriers to alternative formulas and ingredients, and establish emergency policies for the IEM community. Dr. van Calcar advocated for the passage of the MNEA to help create continuity in how the medical formulas are covered.

The Impacts of the Formula Shortage on the IEM Community
***Sarah Chamberlin,* Executive Director, National PKU News**

Ms. Sarah Chamberlain is a parent to a daughter with phenylketonuria (PKU) and an advocate for improving the health and care for people with IEM through her directorship of National PKU News. PKU News provides resources and support for patients and providers who manage PKU and other IEM disorders. PKU News has also partnered with more than 40 other organizations to advocate for the passage of the MNEA.

Early in the formula shortage, Ms. Chamberlain and other patient advocate organizations launched the metabolicformula.org website in an effort to consolidate communications with the patient community about formula availability and resources. At the end of April 2022, Abbott initiated its Urgent Release Program to make a limited amount of formula stored at Sturgis available on a case-by-case basis to dietitians. Early in June 2022, Sturgis reopened but closed again in mid-June because of a flood. At the end of June, Coram/CVS discontinued their distribution of more than 50 metabolic formulas, requiring patients to start over with the prescription approval process. Sturgis reopened in August 2022, but there is no clear timeline for when metabolic formulas will be available.

The "domino effect" of these events compounded the ongoing shortage, creating additional anxiety and stress about both the supply of metabolic formula and the potential risk of infection from formula available through the Urgent Release Program. Ms. Chamberlain emphasized that not having metabolic formula could lead to acute health effects that require hospitalization, but hospitals were also affected by the formula shortage and did not have the supplies needed to provide treatment. She reminded the Committee that the ACHDNC recommendations are predicated on the ability to treat disorders identified through newborn screening and that any disruption to continuous care would undermine that work.

Ms. Chamberlain said that the metabolicformula.org website grew to include a forum for families to share their stories. She shared some examples of stories illustrating the challenges and stress that the community experienced during the formula shortage. Despite the anxiety and stress, there were positive outcomes from the formula shortage. For instance, there is greater awareness within and outside of the community; greater collaboration between families, clinicians, organizations, industry, and government agencies; increased media attention; and increased action from policymakers. She concluded by talking about the risks of industry consolidation; the need for changes in the supply, regulatory, and reimbursement systems; and the importance of creative solutions to avert future shortages. Ms. Chamberlain said that the crisis in access to formula will not be resolved with supply resumes. There is an opportunity to proactively address pre-approval processes for imported formulas to allow quicker access to medical nutrition and reduce the impact of shortages. Additionally, the MNEA will remove barriers to access and fulfill the promise of treatment to those identified through newborn screening.

***Kathy Stagni,* Executive Director, Organic Acidemia Association**

Ms. Kathy Stagni is a parent to a 33-year-old daughter who was diagnosed at four years of age with propionic acidemia, a parent advocate for the Minnesota Department of Health Newborn Screening Advisory Committee, and the Executive Director at Organic Acidemia Association. Ms. Stagni said that her daughter's source of total nutrition is metabolic formula and that the

formula shortage was one of the most terrifying experiences in her life. Switching formula can be very challenging and can, in some cases, lead to seizures and other medical complications. Communications and support from GMDI were excellent and assured families that they had an additional partner during the shortage. As a support group, the Organic Acidemia Association works with other communities and the government to ensure that a shortage like this does not happen again. Although their work is primarily focused in the United States, they also work internationally with other countries that experience challenges in obtaining metabolic formula.

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

- A Committee member asked how many factories produce specialty formulas and if the challenge was in the consolidation of the manufacturing process. If so, he wondered what the Committee could do to help maintain redundancy in the system. Dr. Berry answered that the manufacturing of specialty formulas is a very small portion of an infant formula company and is typically done at one plant over a short-term basis. Sending the manufacturing of specialty formulas to other plants is not likely considered feasible or cost-effective. This is the way Abbott manufactured their specialty formulas and is likely the way other large companies manufacture theirs. The shutdown of the Sturgis plant resulted in a shortage because it was the only plant in the company that had the ability to conduct specialized manufacturing and handling of specialty formulas. There are smaller companies that only produce medical formulas, but the same challenges apply to them in the overall supply chain. Dr. van Calcar said there were four large manufacturers in the United States, which is very limited.
- A Committee member asked what percentage of formula is distributed through the states versus through insurance. Dr. van Calcar said that the respondents in the GMDI survey represented both those with state distribution and those with insurance coverage, but that she did not know the actual numbers. State programs are quite varied—approximately half purchase formula and distribute it directly to the patient and the other half rely on pharmacies for distribution. Dr. Berry added that the decision on how to distribute the formula is done on a state-by-state basis, and that if a state does not want to invest in direct distribution, then the providers have to work with approval processes.
- Dr. Calonge reviewed his takeaways from the presentations. First, access to specialty formula has been an ongoing problem for at least the last decade and this shortage only amplified a chronic problem. Second, these supply issues affect not only children but also adults, and the Committee's recommendations around newborn screening can actually impact adults with lifelong IEM. Third, stockpiling is an important issue that was considered even before the pandemic created supply chain challenges. For instance, there were public health efforts for emergency preparedness planning that considered an "invisible inventory," or stockpile of a product that could be deployed when needed. Fourth, there might have been an opportunity to mobilize globally with the World Health Organization (WHO). Going forward, there is a need for emergency preparedness planning through collaboration with advocates, leaders, and clinicians to develop a national strategy for addressing formula shortages, especially for medical foods.
    - A Committee member talked about the "invisible inventory" as an important strategic reserve of a perishable item. However, given the current decentralized distribution system, there may be a need for the development of a more

centralized system to support collaboration between different suppliers and payers. This could be a role for the government in the development of an emergency plan with buy-in from manufacturers. The Committee member wondered what the Committee could do to facilitate or support this effort. Dr. Calonge suggested that the topic could be brought forward in future meetings.

Public Comments

Dean Suhr

Mr. Dean Suhr is President of the Metachromatic Leukodystrophy (MLD) Foundation. He talked about the nomination that is in preparation for MLD, for which there is a pilot currently being conducted in New York and Germany. They are currently experiencing challenges in identifying cases but hope to continue interacting with the Committee as they progress through the study. He also spoke about the RUSP Roundtable, an initiative that a number of Committee members and organizational representatives participated in, that brings together a broad range of newborn screening stakeholders to share, learn, and collaborate on timely topics. Some of the topics being considered for the next Roundtable include medical foods dried blood spots policy and public relations challenges, and the changes to the Committee's nomination requirements. He asked the audience to contact him with suggestions for other topics to discuss at the RUSP Roundtable.

Dylan Simon

Mr. Dylan Simon is the Director of Policy for the EveryLife Foundation for Rare Diseases, and he provided an update on EveryLife's newborn screening initiatives. On October 15, 2022, they will hold their fourth annual Newborn Screening Bootcamp that provides attendees with an opportunity to learn about and discuss developments in newborn screening with experts and advocates. There will also be a panel focused on equity in newborn screening that will include research that was recently presented to the Committee. Mr. Simon also talked about their Newborn Screening Modernization Roundtables that convened more than 100 stakeholders to discuss the policy solutions needed to modernize the newborn screening system. There were four overarching goals that were identified: 1) improve and expand federal support and oversight of all components of the newborn screening system; 2) establish a regional lab network to promote efficient processes across state labs; 3) increase access to population-level data; and 4) integrate next generation, evidence-based genomic testing into newborn screening.

Niki Armstrong

Ms. Niki Armstrong is the Newborn Screening Program Manager for Parent Project Muscular Dystrophy (PPMD). On June 29, 2022, PPMD submitted a RUSP nomination package for DMD. The organization has worked for more than a decade to develop the infrastructure needed for a newborn screening program for DMD. They hope that a Committee recommendation to include DMD in the RUSP would remove the diagnostic odyssey and provide identified infants with clinical follow-up, approved therapies, inclusion in clinical trials, and early intervention services.

Robert Thompson Stone

Dr. Robert Thompson Stone is a child neurologist, leukodystrophy specialist at the University of Rochester, and Director of the Leukodystrophy Care Center, where he works with patients and families affected by Krabbe disease. He was the lead author of a publication that provided recommendations for the classification and follow-up of infants who screen positive and recently

developed a family guide to help caregivers navigate through a positive screen. He strongly believes that Krabbe disease should be included in the RUSP. He reviewed a study in which the addition of testing for psychosine led to an 88 percent reduction in testing requirements in early childhood, indicating remarkable progress in the screening algorithm. He said that Krabbe disease is a devastating neurodegenerative disorder that can be significantly impacted by available treatment. With current algorithms and recommendations for risk categories, there is an opportunity to provide this treatment before permanent neurologic injury occurs.

Christin Webb

Ms. Christin Webb is a parent to two children affected by Krabbe disease. At three months of age, their first child began to have symptoms that progressed to an inability to swallow, eat, or breathe on her own. They endured several medical appointments, surgeries, and procedures until they finally discovered that their daughter had Krabbe disease. They were told that she would not likely live to see her second birthday. Ms. Webb talked about how angry she felt when she discovered that her state of Tennessee came close to passing a Krabbe newborn screening program three years prior but decided not to. Three months after her daughter's diagnosis, their newborn son was also diagnosed and was able to receive a transplant and treatment. Ms. Webb's son is now seven and is very active and happy. Ms. Webb expressed hope that the Committee would see the effectiveness of Krabbe newborn screening and consider the devasting alternative.

Committee Discussion

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

- An organizational representative suggested that there needed to be a paradigm shift from one that requires evidence that treating a condition in the pre-symptomatic stage is beneficial to one that provides early screening to those with undiagnosed symptoms. Families talk about their diagnostic odyssey that can last for years when that time could be used for early screening and genetic testing. Dr. Calonge responded that this proposed paradigm would move toward the diagnostic rather than the screening algorithm.
- An organizational representative said that the Committee is not charged with prenatal diagnosis and that using a newborn blood spot screening to solve a lot of problems may be unrealistic. Some families with positive screening results for Krabbe disease may still continue on a diagnostic odyssey and uncertainty because a screening result does not always provide all the answers.

Strengthening Newborn Screening System

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

Dr. Calonge said that the optimization of health impacts from newborn screening across the nation would benefit from a cohesive approach that assures access to screening, diagnosis, and treatment regardless of where an infant is born. Currently, there are variations across states in the implementation of the RUSP that can create inequities. It is therefore important to explore the elements, enabling factors, and challenges that impact the implementation of new conditions added to the RUSP by state newborn screening programs. When the Committee submits a recommendation to add a new condition to the RUSP, the Secretary has discretion in accepting the recommendation or not, but an acceptance of the recommendation is not a mandate for states to implement the screening.

There is an "ecosystem" of newborn screening stakeholders, for which state and local public health is an overarching stakeholder for specific stakeholders such as newborn screening program directors, public health laboratory directors, state advisory committees, state public health leaders, state governors, state legislators, hospitals, providers, advocates, and families. Dr. Calonge pointed out that a state governor's office is an essential component because the governor's administration often has the ability to choose and/or prioritize whether screening for a specific condition is implemented or not. A newborn screening system includes elements of screening, confirmatory testing, and treatment that work together such that one element cannot be changed without impacting the other elements.

Dr. Calonge reviewed the roadmap for severe combined immunodeficiency (SCID) in its successful move from nomination to getting added to the RUSP. Enabling elements for SCID implementation included a high throughput assay from blood spots for screening, flow cytometry for diagnosis, funded pilot studies, an available effective treatment, decision support materials for clinicians and patients, and the ability to evaluate implementation at a regional level. Barriers to implementation included a lack of cost-benefit information, budget concerns, prior state commitments to implement other screening tests, the lack of widespread availability of experts within states, and the lack of an FDA-approved or cleared assay. The implementation of SCID screening, diagnosis, treatment, and long-term follow-up created additional benefits through the linking of different testing modalities and collaboration throughout the newborn screening community that supported its rapid implementation of spinal muscular atrophy (SMA).

Diagnosis and Treatment of RUSP Disorders
***Erica Wright, MS, CGC,* Senior Instructor, Certified Genetic Counselor Clinical Genetics and Metabolism Department of Pediatrics University of Colorado School of Medicine Children's Hospital Colorado**

Ms. Erica Wright is a genetic counselor and metabolic newborn screening follow-up coordinator for Colorado and Wyoming. The Colorado Department of Public Health and Environment contracts the follow-up of all abnormal newborn screening results to specialists. As a specialist, Ms. Wright is involved with both short- and long-term follow-up, enabling her to observe how families evolve throughout the process. Newborn screening programs are supported by several organizations that collaborate, communicate, and provide essential resources such as coaching, mentorship, guidance, and resiliency. Despite this support, newborn screening is becoming more difficult to implement.

Newly added disorders are becoming more challenging to implement because many require molecular analysis that can result in the identification of pseudodeficiencies, late-onset disease, and additional identified family members that need attention. These diagnostic tests are more complex, leading to delays and additional uncertainty. Treatments for these disorders can also be complex and costly, burdening both the medical system and families. Diagnostic processes differ from state to state, such as their capacity to conduct second tier testing. Ms. Wright talked about the process of implementing Pompe disease and mucopolysaccharidosis type I (MPS I) screenings in Colorado. The clinical side of the discussion lasted more than 12 months because of the careful consideration needed to create a process that was not burdensome to providers and

families and the need for their screening laboratory to shift into more of a diagnostic lab. They considered the turnaround time for diagnostic processes; the burden of collection and cost to hospitals and providers; and the burden on families such as insurance barriers, out-of-pocket costs, and travel distance to hospitals.

Ms. Wright added that the existence of an FDA-approved treatment does not ensure its availability to providers and families. There are limited specialists, metabolic clinics, and medical facilities with the capability of performing the treatments. Some disorders also have centers of excellence that can impact how insurance covers treatment. These limits can cause additional burden to patients and families through long wait times, inadequate insurance to cover the cost of treatment, and changes in family income as a result of the extensive time needed to care for the child. Regional clinics and telehealth have eased some of this burden, but there is a continued need for social workers, patient navigators, local public health nurses, and partnerships with the medical home.

Ms. Wright reiterated that state newborn screening programs differ in their funding, resources, and capacity, which affect diagnostic strategies and time to treat. There are also differences in diagnosis and treatment coverage across state Medicaid programs. With more complex disorders, there may not be a clear difference between short- and long-term follow-up but rather a follow-up continuum because of differences in symptom presentation and care needs. The definition, responsibilities, and expectations for this continuum can differ across state newborn screening programs. There are also state differences in the public health or clinical outcome metrics that are tracked. There is a need for an integrated real-time tracking system to ensure that patient populations are receiving the care they need.

Ms. Wright said that these barriers can be overcome and shared a story of a child with Pompe disease who lived in a rural community. Through the collaboration of a multidisciplinary team, the child was able to receive treatment through a local hospital and additional therapies when they were needed.

System Factors Impacting Implementation
***Scott M. Shone, PhD, HCLD(ABB),* Director North Carolina State Laboratory of Public Health**

Dr. Shone provided his personal perspective on the newborn screening system as a researcher, former program manager for a newborn screening lab, and public health lab director. He talked about a 2019 presentation from NewSTEPS to the Committee on the factors that impact the implementation of screening a new disorder. Since that presentation, NewSTEPS developed multiple publications, including the New Disorder Checklist that many states use to navigate the implementation of new disorder screening. Dr. Shone pointed out that every phase of the checklist requires multiple stakeholders, of which only the newborn screening program, parents, and advocates exist in every phase. The newborn screening program (i.e., lab and follow-up) is the only component over which newborn screening program directors and lab or follow-up managers have control. Other stakeholders, such as legislators, hospitals, providers, vendors, consultants, or procurement specialists, are outside of the newborn screening program but have an integral role in the successful implementation. The system of newborn screening exists within

the nexus of public health and medicine and has successfully navigated through challenges from both perspectives, such as timeliness, privacy, blood spot storage, and continuity of operations through public health crises. This "newborn screening exceptionalism" has moved the newborn screening program to where it is today, but cannot alone solve current systems issues.

There are several ongoing challenges in moving the newborn screening system forward. For instance, hiring and training new personnel, delays in the installation of new equipment, lab updates, and database management are issues that have been presented to the Committee in the last few years. There are also challenges common to any public health program, such as jurisdictional leaderships, federal regulations and management, public health mandates, funding, and supply chain issues. However, the one public health challenge that is unique to the newborn screening program is the RUSP. The RUSP is a recommendation, not a mandate. States that require the addition of disorders to their newborn screening program often have arbitrary timelines for implementation. For instance, the Committee recommended three disorders to be added to the RUSP between 2013 and 2015—Pompe disease, (MPS I, and X-linked adrenoleukodystrophy (X-ALD)—that were rated with high certainty of significant net benefit and high feasibility. By 2022, only a few states had implemented all three. In contrast, SMA, which was recommended by the Committee in 2018 and rated with moderate certainty of net benefit, is currently being implemented in all states.

Dr. Shone said that differences in the implementation of these programs are related to inherent differences that are not captured in the decision matrix. Early adopters of new disorders typically had funding and legislative requirements; later adopters typically waited based on lessons learned from other states and new funding opportunities. Funding, collaboration between states, and stakeholder engagement are important facilitators. Specifically, states that have the ability to hire new staff, obtain needed lab equipment and assays, and set short- and long-term follow-up guidelines are better equipped to implement screening for a new disorder.

Dr. Shone reiterated that the newborn screening system is complex and involves many stakeholders, many of which are outside of the newborn screening program purview. Moving forward, he said that there is a need to consider the legislative and regulatory processes and how they impact implementation timelines. He suggested that the Committee put into action the tasks needed to address the multiple systems issues that the newborn screening system faces today.

Committee Discussion

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

- Dr. Calonge provided the Committee with potential next steps for discussion. He suggested the Committee clarify the expectations of implementation timelines for screening for a new condition, given the complexity of systems issues. He said that there is an opportunity to collect and analyze data about the barriers and facilitators in implementation across different states, such as through an anonymous survey. He also suggested the Committee discuss the potential feasibility of developing an implementation toolkit for addressing specific barriers. Dr. Calonge added that there may be individuals outside of the Committee that may be interested in advocating for legislative pathways.

- A Committee member said that every disorder had intrinsic issues and nuances that need to be considered to create an effective newborn screening, follow-up, and treatment program. These nuances may differ between states and between clinical and public health perspectives. A survey would be valuable but if it is too general, it would not identify these nuances.
- A Committee member asked about the risks and benefits of different legislative approaches, specifically between individual disorder legislative mandates, legislative authority to add a RUSP condition, and legislative requirements to add a RUSP condition.
    - Dr. Calonge said that states with a direct legislatively mandated addition of a condition that was not subject to the Committee's evidence-based review or recommended by the Committee may generate evidence that the Committee could use to make a recommendation.
    - Dr. Shone said that legislation in 2018 streamlined the addition of conditions in North Carolina. It was not an instantaneous process, but it did provide benefits such as a constant source of funding. North Carolina recently passed a law requiring the addition of RUSP conditions within three years, but with no other caveats. He added that the challenge is not just within specific programs but with the entire system. Each condition has its own nuanced challenges and barriers and partnering with parents and advocates can help break down these barriers. He emphasized that there is a diversity of challenges that each state faces and it is incumbent on everyone in the newborn screening system to understand what role they can play in breaking those barriers down.
    - Ms. Wright said that funding and budget barriers are common across states and legislative action could assist with states that are struggling with mandates.
    - Dr. Calonge said that, as an example, Colorado has tax legislations that limit both what can be spent and raised, which is an added challenge.
    - The Committee member said that many people see the newborn screening program as the only tool for screening and diagnosis and there may be other tools, such as carrier or prenatal screening, that could enhance the newborn screening program. It is important to recognize that everyone in the community shares the same goal of early identification and treatment. Although there are different legislative approaches, it is useless without funding to support it.
    - Dr. Shone agreed that funding is critical but that it needs to be used across all the newborn screening stakeholders to improve their role in the system. He added that implementation legislation is valuable in that it provides an opportunity to partner with advocates, but that there are opportunities to change that could create profound impact.
- An organizational representative said that although it is important to have an emphasis on understanding states' experiences with their newborn screening system, there also needs to be an understanding of what it is like to be a parent who would have a different outcome for their child if they lived in a different state. It would be helpful to have those stakeholders present on their daily challenges. The organizational representative added that as disorders become more complex, communication and education also become more complex. It would therefore be beneficial to address investing in and strengthening communications. Additionally, it is important to recognize that there is a difference

between families and advocates, which are two groups that are often combined. Each has different perspectives and educational needs.

- An organizational representative commented on the need to address long-term follow-up to ensure that families have access to available treatment. The organizational representative asked Ms. Wright to expand on their transition from a screening lab to a diagnostic lab. Ms. Wright answered that their newborn screening results had been reported directly to the specialist who had the decision-making capacity to determine what confirmatory testing to utilize and what laboratory would conduct the molecular study and interpretation. With the shift, the health department used the dried blood spot to initiate molecular studies as a diagnostic algorithm. This shift meant that results were being reported back to the newborn screening program for interpretation. Now that they are thinking about next generation sequencing, they are exploring if the health department has the expertise and capacity to interpret those results or if the results would be sent to clinicians for interpretation. It is important that results are handled carefully and are well-explained to pediatricians and families, with the benefit of genetic counseling on the backend.
- An organizational representative pointed out that there is not a family or patient representative on the Committee. There seems to have been a consolidation of expertise in pediatric sub-specialties with less public health representation. It is important to have more diversity both in roles and geography to support the focus on equity in the newborn screening program. Newborn screening involves a complexity of different systems that does not end with diagnosis. There are dramatic changes to reproductive care and screening that are occurring across borders, changes in Medicaid coverage for formula and specialty care, and other components of access to care that should be addressed.

Dr. Michael Warren shared that HRSA forecasts a new grant for state newborn screening programs in fiscal year 2023 (Grants.gov Forecast) to award 20 states with up to $275,000 to improve and expand their newborn screening system, achieve timeliness, and examine equity and disparities in short- and long-term follow-up.

Dr. Calonge closed Day One of the meeting by reminding the Committee that their next steps were to identify the potential solutions for moving the newborn screening system forward. To that end, he charged thethe Workgroups (Education and Training, Follow-up and Treatment, and Laboratory Standards and Procedures) to convene to address three questions:

- What are the successes and challenges in implementing conditions added to the RUSP?
- What issues/factors contribute to the variability of implementation status of conditions added to the RUSP across states?
- What are potential solutions or resources that can address these issues/factors?

The Workgroup Chairs and Co-Chairs would summarize their Workgroup discussions on Day Two of the meeting.

DAY TWO: Wednesday, August 31, 2022

Welcome and Roll Call

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

Dr. Calonge reminded the Committee that there was a notice in the Federal Register soliciting nominations for new Committee members and that he and HRSA are actively working to bring on a family member representative and other representatives that would ensure diverse representation.

Dr. Calonge acknowledged that this Committee meeting would be the last for Dr. Max Muenke and thanked him for his contributions as an organizational representative for the American College of Medical Genetics & Genomics.

Education and Training Workgroup Update

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

Dr. Jane DeLuca reviewed the Education and Training Workgroup's discussion on the three questions that Dr. Calonge had provided. The Workgroup first addressed successes and challenges in education and training for conditions added to the RUSP. They noted that this question was difficult to answer without knowing the goals for education and training. There are many stakeholders, each of whom requires education on new conditions. However, there are also basic gaps in understanding that could be prioritized. For instance, the public generally does not understand the differences between screening and diagnosis and many families do not have a baseline understanding of genetics. Content is needed to help families better understand what is being screened and why it is important. People might rely on information from the internet, which might contain politicization and misinformation. Some families want to understand everything about newborn screening, while others only want the information they need to know. Families have a continuum of choice for prenatal screening but do not have an active choice in newborn screening which need to be addressed in education. The timing of sharing information, especially at the time of diagnosis and referral, should be considered. Despite these challenges, the Workgroup agreed that there were excellent education materials already available.

Dr. DeLuca reviewed the Workgroup's discussion on the issues that contribute to variability in the implementation of RUSP conditions across states. A condition can be added to the RUSP in multiple ways, such as through legislation, state advisory board authorization, or as a result of advocacy efforts. The public may not understand the processes involved in adding a condition and why one state may do so more quickly than others. Therefore, there is a need to help the public understand the RUSP process and variability in its implementation across states. There are ethical, legal, and social considerations involved in adding a condition, as well as resource issues. There are also challenges in imparting information about false positives and long-term follow-up. These are the issues that should be addressed in education, but the challenge is in bringing the different pieces together. There is also a lack of outcome measures to assess if

education tools are effective and the challenge of a diminishing clinical workforce. The Workgroup suggested that the Committee may not spend enough time discussing the effectiveness of education and training.

Dr. DeLuca addressed the final question about potential solutions for education and training. The Workgroup agreed that good training and mentorship programs do exist. States could expand their efforts toward reaching a standardized expectation based on these existing education programs. Increased sharing of educational materials might be needed, but there is also a need to measure if families are using the materials. The Workgroup talked about using technologies such as YouTube or TikTok to communicate messages. They also agreed that there were not enough materials available for diverse families that may not understand English. Materials for languages beyond Spanish are needed, as are materials that are culturally appropriate. There could be more of a focus on equity in achievable health outcomes across diverse populations and states. The Workgroup suggested that the Committee would benefit from broader public health perspectives.

Dr. DeLuca talked about the specific solutions that the Committee could address. For instance, the Committee could develop standards for screening education. It could also support public service announcements to help raise awareness and culturally appropriate materials to address inequalities across states. The Workgroup reflected on the name of the Committee, which is focused on heritable disorders and not newborn screening. Therefore, the Committee could expand the landscape beyond newborn screening to identify partnerships with federal agencies and communities in related areas. The Committee could determine the conditions that are better suited for screening across different time frames. Dr. DeLuca summarized the key takeaways, which were the need for goals and effectiveness measures for education, a standard for addressing variability across states, culturally sensitive materials, both basic genetic and broad education topics, and consideration for the timing of screening.

Discussion: Education and Training Workgroup Ideas
***Ned Calonge, MD, MPH*, Committee Chair**

- Dr. Calonge talked about three overarching themes from the Education and Training Workgroup summary. The first theme was about who to train and educate and the importance of separating out the different stakeholders with specific objectives and goals. For instance, there could be training on new techniques and systems for clinicians, laboratorians, and administrators. Education could be made available to obstetrical and pediatric providers on screening, how to have a dialogue with families, and next steps after a positive screen. The level of education that is provided to all families as compared to those with a positive screen also needs to be considered. The second theme was about the effectiveness of training and education. Dr. Calonge referenced the Back to Sleep initiative for sudden infant death syndrome (SIDS) and how the number of SIDS deaths was a direct outcome measure. The third theme was the need to communicate effectively with diverse populations. Dr. Calonge said that the CDC has an outstanding communications branch that ensures that messaging matches target audiences.
    - A Committee member spoke about targeted training at CDC and said that there has been a focus on training laboratorians but there will be a new team that is more focused on state and personnel engagement.

- An organizational representative from the Training and Education Workgroup said that there needs to be an understanding of what change is desired (or not) for any education campaign for the broad public. For instance, nearly all newborns are screened, which is a metric that should not be changed. It is also important to recognize that education without action will not be sustained.
- An organizational representative said that communication modalities have changed in recent years and that many state education efforts utilize their own communication methods with some degree of success. Going forward, it is important to recognize those newer communication modalities and how they reach families and health care providers. There can be a tremendous amount of time being invested in education that is restricted to older communication modalities.
- An organizational representative talked about how messaging and communication modalities from a decade ago are not effective today. The modalities by which people learn today are so much different and bring the risk of misinformation. There may be lessons learned from recent public health crises about how to get in front of misinformation with an authoritative voice.
- A Committee member from the Training and Education Workgroup reiterated that the cultural differences across and within states was a significant challenge. It is important to serve these families effectively in ways that do not increase their anxiety.
    - Dr. Calonge said that there is research on culturally tailored messaging and the Committee should apply that research to newborn screening messaging.

Follow-up and Treatment Workgroup Update

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

Dr. Kyle Brothers provided an overview of the Follow-up and Treatment Workgroup discussion. The Workgroup defined follow-up as both short- and long-term follow-up that encompasses diagnosis and treatment referral, ensures that the family is continuing to receive appropriate care, and evaluates whether the screening resulted in reduced morbidity and mortality. Dr. Brothers reviewed the Workgroup's discussion of successes and challenges in follow-up and treatment in implementation. They talked about the implementation of SMA, which may have been successful because treatment occurred in infancy with treatment outcomes that could occur in a short period of time, making long-term follow-up not as critical. SMA also had available guidance and resources that were useful to programs and providers. Conversely, the Workgroup noted challenges to the implementation of Krabbe disease, including concerns about access to treatment, Medicaid coverage and timeliness to treatment, and greater travel distances to providers with expertise. Additionally, long-term follow-up can last for decades, straining the ability to conduct follow-up.

Dr. Brothers reviewed the discussion about issues that contribute to variability across states. The Workgroup agreed that follow-up and treatment have less of an effect on implementation variability compared to factors related to funding, laboratory, and staffing. However, one related factor is the shortage of specific specialties. There may be widespread shortages of experts that could affect a state's confidence in its ability to implement a new RUSP condition.

Dr. Brothers then reviewed the potential solutions for follow-up and treatment. The Workgroup focused on actionable solutions within the purview of the Committee or the communities represented in the Workgroup. They suggested that a uniform follow-up plan as an adjunct to the RUSP could provide universal expectations for follow-up and treatment, with some disease-specific guidance. Workgroup members highlighted existing resources developed by the Committee and other organizations that would support the development of the uniform follow-up plan. The Workgroup also suggested that the Committee could officially recommend that relevant professional organizations and societies provide guidelines on both universal and disease-specific guidance.

Another Workgroup suggestion was requiring a "blueprint" for follow-up and treatment in RUSP nominations. Nominators understand how best to collect data and advocates are well-positioned to organize data collection and participation. Data collection efforts could include leveraging claims data, using tertiary care centers as regional data collection centers, adapting existing surveillance systems (e.g., Birth Defects Surveillance Programs), and working with Title V Children and Youth with Special Health Care Needs programs. The Workgroup also discussed state-level programs funded by CDC and HRSA, although they tend to be state level and might not scale at the national level. They also suggested that it was important to incentivize providers to participate in data collection. The Workgroup recognized that none of these data collection approaches would capture important variables, such as impact to families. Additionally, none of their potential solutions would address the challenge of long-term follow-up and insurance coverage into adulthood.

Discussion: Follow-up and Treatment Workgroup Ideas
***Ned Calonge, MD, MPH*, Committee Chair**

- A Committee member talked about the frustration of not having long-term follow-up data. It is one thing to respond to requests for minimal datasets, but there is no built-in process to provide additional data. Additionally, only the Cystic Fibrosis Foundation has been successful in gathering newborn screening and clinical follow-up data, which is due to their level of funding and the ability to incentivize data collection. No other advocacy group has access to the funding needed to replicate this.
- A Committee member talked about how the newborn screening program affects the entire population of newborn infants and their families. More effort needs to be invested into collecting follow-up data on individuals impacted by positive screens and high-risk screens with or without a diagnosis. It is challenging for the Committee to move forward with decisions without more data on those biological uncertainties, especially in lower prevalence conditions. It is an urgent need toward understanding the net benefit of the screening program.
- An organizational representative said that because it may be impossible for most advocacy group to support follow-up data collection, it may be more productive to encourage advocates and families to let legislators know about the importance of data collection. Supporting constituent individuals and advocacy groups could move the needle when mandates and recommendations do not.

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 Laboratory Standards and Procedures Workgroup discussion of the three questions. The Workgroup started by reviewing Dr. Shone's presentation and public health system impact (PHSI) assessments for the last several conditions added to the RUSP. One idea from their discussion about successes and challenges in newborn screening laboratories was that the PHSI assessment might not be taken into account during the Committee's decision-making. Each state has different legislative and administrative processes for getting authority to screen and getting more specific information around this through modifying the PHSI assessment can provide more insight into what is happening during the implementation of a new condition. Additionally, there are competing program initiatives and public health priorities that can delay implementation. There are also limitations in how much more area is available on a dried blood spot to obtain a sample for additional tests.

The Workgroup also talked about funding challenges associated with implementation. There is much appreciation for funding mechanisms sponsored by CDC, HRSA, and NIH. However, there are instances in which the same programs are successful with these grants and other states miss the opportunity because they may not have the staff, expertise, or other resources needed to be competitive. States also struggle with a lack of staff and space, limited access to and establishing relationships with specialists, and wait times for contract laboratories to receive the screening test. The Workgroup pointed out that screening tests that can be multiplexed with others and do not require additional space or instruments can shorten the time to implementation.

Dr. Kelm reviewed the Workgroup's discussion on variability in implementation across states. States may have different levels of expertise, resulting in variability in the ability to develop and validate tests. If a state wanted to add an analyte to an FDA-cleared test, the modification would become a laboratory developed test, which can be a complicated process. States also have their own criteria for adding a screening panel, despite the Committee's recommendation. Cost benefit consideration may be very important to a state but is not always included in the Committee's recommendation. A high number of false positives may require second-tier testing, which is an additional burden on states. States also have different ways of assessing the certainty of screening, often requiring a large pilot study to establish certainty. The Committee, however, may consider small studies, different pieces of smaller studies, or applications for large pilot studies in their recommendation.

Dr. Kelm then reviewed the Workgroup's discussion on potential solutions. Multiplexing, when possible, could be one solution but not always the optimal solution because the use of existing methodologies for a new test could lead to false negatives, false positives, and other issues. Other solutions include having infrastructure and expertise in place and the use of well-defined protocols and guidelines. Laboratories that do not have the same level of expertise to develop, troubleshoot, and validate tests can contact the CDC to have a technical team help with implementation. It is also helpful when a test kit is FDA-cleared. The Workgroup suggested that advocates who are experts, such as project managers already in the system or geneticists with publications, can help push for the addition of new conditions and support the implementation of

new tests. States that are not as competitive with grant proposals could benefit with support from a non-federal entity. There could be opportunities to develop and evaluate tests that use specimen types other than dried blood spot.

The Workgroup talked about the sensitivity of screening tests and what is considered acceptable to states and laboratories. They considered convening stakeholders to obtain input on the factors to consider for the sensitivity and accuracy of new tests beyond some of the traditional approaches for minimizing false negatives and positives. CDC could continue to develop tools for states that use newborn genetic screening protocols. Additionally, for states that have their own criteria to assess a condition and make a decision to not it to their panel, these states potentially can be categorized as such rather than "not screening". Finally, newborn screening programs continue share insights with each other and attend national trainings.

Discussion: Laboratory Standards and Procedures Workgroup Ideas
***Ned Calonge, MD, MPH*, Committee Chair**

- In the interest of time, Dr. Calonge asked Committee members to email their questions for this Workgroup. He thanked the presenters for their insights and ideas and hopes to move their suggestions into action.

Krabbe Disease Evidence-Based Review –Phase 1 Update

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

Dr. Alex Kemper presented the preliminary review of the Evidence-Based Review Group's evaluation of the Krabbe disease nomination. Krabbe disease is an autosomal recessive lysosomal storage disease caused by homozygous or compound heterozygous pathogenetic variants in the gene coding for glucocerebrosidase (GALC). The expected birth prevalence of Krabbe disease is approximately 1 per 100,000. The target for newborn screening is the infantile form of Krabbe disease, which onsets before 12 months of age and is associated with irritability, spasticity, blindness, seizures, failure to thrive, and aspiration pneumonia. Without treatment, death is expected before two years of age. There are also late infantile, juvenile, and adult forms of Krabbe disease.

A number of states have already implemented Krabbe disease newborn screening, and the Evidence-Based Review Group is in process of gathering primary data from these programs. Additionally, KrabbeConnect publishes case data that may also be helpful. Collectively, state programs have screened more than 6.7 million infants from screening years ranging from 2006 to 2021. Historically, first tier screening tests for Krabbe used GALC enzyme activity in dried blood spots, which resulted in a high number of false positives. The addition of a second tier test using psychosine in dried blood spot reduced the number of false positives and also helped to stratify expected phenotypes..However, this second tier test is not used in all of the state newborn screening programs. Dr. Kemper added that some have suggested psychosine be used as first tier testing, but it is a more challenging test to conduct and it cannot be multiplexed.

Diagnosis after a positive screening involves confirmation of low GALC activity. Elevated psychosine is a helpful, but not perfect, marker. Additional neurologic evaluations may also support diagnosis, including magnetic resonance imaging (MRI) nerve conduction,

electroencephalogram (EEG) auditory and visual evoked potentials, and cerebrospinal fluid protein. Molecular genetic testing is also supportive and especially helpful for stratifying risk.

Dr. Kemper reviewed an article outlining recommendations for classification and long-term follow-up. Those with dried blood spot levels of psychosine over 10 nmol/L are consistent with infantile form and should receive an immediate referral for diagnostic evaluation and treatment. Those with intermediate levels of psychosine should be seen within two to four weeks with a specialist or primary care provider and receive further testing. Those cases that are classified as high risk should have specialty visits every two to three months for two years, every six months until three years of age, annually until 12 years of age, and every two to five years until adulthood. Those classified as low risk should have specialty visits every six months for two years, annually until 12 years of age, and then two to five years until adulthood. Dr. Kemper said that the Evidence-Based Review Group is considering the sensitivity of psychosine because of a case report of an infantile form of Krabbe that did not have elevated psychosine.

The current treatment for Krabbe disease is hematopoietic stem cell transplantation, which is recommended by 30 days of age or younger and may be too late by 45 days of age. There are two open trials for gene therapy, the results of which are unlikely to be available at the time that the Committee votes on this nomination. Dr. Kemper reviewed the contextual questions that the Evidence-Based Review Group will consider, which include current diagnostic approaches for infantile onset, availability and evidence base of clinical practice guidelines, accessibility and uptake of care, and barriers and facilitators for newborn screening for Krabbe. In their systematic review, they will focus on analytic and clinical validity of screening strategies, impact of Krabbe disease screening compared to usual case detection on timing for diagnosis and treatment, impact on mortality and development, and potential negative consequences from screening for Krabbe disease. They are currently reviewing evidence from the past ten years and working with University of Michigan on modeling. They also will be partnering with the Association of Public Health Laboratories to initiate PHSI surveys in October.

Committee Discussion

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

- Dr. Calonge asked Dr. Kemper what he is most concerned about in the evidence review and where there may be evidence gaps. Dr. Kemper answered that they are looking for clarity on the screening experience, accuracy of testing, clarity on predicted phenotype, benefits of early intervention with transplant, and the impact and outcomes from intervention. One area that is not conducive to systematic review is availability and accessibility of transplants, especially because there is a very narrow window for treatment. They also hope to understand potential equity issues.
- A Committee member asked about the parsing of early and late infantile presentation and whether psychosine can separate early from later infantile cases. Dr. Kemper said that the Evidence-Based Review Group debated how to classify individuals. In their initial review, they decided to ask programs to stratify infants who would have been expected to have onset by 12 months of age so that they could focus on those with the most severe form who would benefit the most from newborn screening. They plan to look at the data again to capture information about stratification after 12 months of age. They can shift to include the first 36 months of life if the Committee is interested. Once they obtain

psychosine levels and outcomes, they will be able to clarify its sensitivity for classifying cases.

- A Committee member asked if Dr. Kemper anticipates available data on the potential for intervention for later onset disease or on the benefit of early intervention on later onset cases. Dr. Kemper said that it would be challenging to find comparable cases to really understand potential benefit. However, the experts suggest that infants with the most severe disease benefit most from very early intervention. He thinks about Krabbe disease as a spectrum of onset with several factors involved. It makes sense that early treatment would result in better outcomes for infants with slightly later onset. However, stem cell transplants carry their own risk and should not be taken lightly. It is also important to recognize that once an infant has profound involvement, they are not eligible for transplants.

Long-term Follow-up for Severe Combined Immunodeficiency and Other Newborn Screening Conditions

New York State Newborn Screening Long-Term Follow-up and Patient Registry for Inherited Metabolic Disorders
***Michele Caggana, ScD, FACMG,* Director, Newborn Screening Program Wadsworth Center New York State Department of Health**
***Kathy Chou, PhD,* Supervisor, External Systems Quality Unit Newborn Screening Program Wadsworth Center New York State Department of Health**

Dr. Michele Caggana said that the goals of the HRSA-funded Long-term Follow-Up (LTFU) for Severe Combined Immunodeficiency and Other Newborn Screening Conditions program were to ensure that newborns and children identified through newborn screening can achieve the best possible outcomes and to support collaboration with clinicians, public health agencies, and families to create a system of care. The New York LTFU program is intended to go beyond the classical newborn screening model, which typically concludes with confirmation of both the diagnosis and the delivery of care and treatment. The objectives of the LTFU program were to implement LTFU model protocols and data collection in at least five sites in New York by July 2022 (which they achieved); to demonstrate integration of LTFU data from clinical and public health systems; and to increase by 20 percent the number of infants, children, and families who received coordinated LTFU care by the end of the project in July 2023.

Dr. Caggana reviewed the New York newborn screening program, which was mandated by a Public Health Law in 1965 and currently screens for more than 50 conditions. Of the approximately 220,000 newborns screened annually, about 3 percent return with abnormal results. On average, approximately 1 in 300 infants born in New York will have one of the screened conditions. New York's short-term follow-up includes a referral to a primary care physician or specialist, who then contacts parents to arrange clinical evaluation, management, and treatment. The outcome of the clinical evaluation is sent back to the newborn screening program, which then uses the information for continual improvement to the program.

The LTFU project partners with ten inherited metabolic disorders specialty care centers across New York. The project maintains a registry of patients with one of the inherited metabolic disorders identified by the New York newborn screening program with consent from parents or

families. Patients will be enrolled in the study until age 18, at which point the patient may reconsent on their own. The research team started with a small study in 2012, then received institutional review board (IRB) approval in 2016 for a limited number of conditions with a small number of care centers. In 2021, they were awarded the HRSA LTFU cooperative agreement that allowed them to expand the number of conditions and provide contracts to all of their specialty care centers. In April 2022, IRB deemed the project to be non-research/quality improvement, which did not require IRB approval. The centers had to determine whether their institution would require IRB approval or defer to the non-research status. After this designation, the research team still obtained parental consent for transparency, but all references to research had to be removed.

In 2016, the research team developed a data sharing agreement with the Newborn Screening Translational Research Network (NBSTRN) to collect public health and disease-specific data using the NBSTRN REDCap database. The conditions included in the study were fatty acid oxidation disorders, Krabbe disease, Pompe disease, and X-ALD in 2016, with amino acid disorders, organic acid disorders, biotinidase deficiency, galactosemia, MPS I and GAMT deficiency added in April 2022. Participation from the specialty care centers is voluntary with no incentives. Previous to April 2022, the project received some state funding that provided the resources needed to onboard all ten sites but there was no full-time staff dedicated to the LTFU project. There were challenges aligning data elements and conducting data entry into REDCap, no resources to develop educational materials or translational services, and only 7 of the 11 eligible patients had been recruited. The additional funding in April 2022 allowed the team to expand the eligibility criteria, hire more staff (including a public health educator and data administrator), standardize data collection, update the database, conduct social media outreach to families, and develop educational resources for families. These improvements will ultimately provide de-identified aggregate data to providers to help refine care standards, allow knowledge discovery, and conduct quality improvement.

Dr. Kathy Chou provided an update on the program's progress since receiving the HRSA funding. To achieve the objective of expanding study eligibility to include all inherited metabolic disorders, the LTFU team created a Dataset Review Workgroup to update existing data elements in REDCap and to review and elicit disorder-specific data elements. To date, they have updated data elements for 12 disorders, standardized data collection for both general and disorder-specific data elements, and divided their online forms into initial and follow-up visits. They are also providing support for individual centers and updating the data input forms to be more user-friendly. Dr. Chou talked about progress with outreach to families. They have translated their consent forms into 13 languages, updated patient registry and family resource brochures, created a website for these resources, and launched a social media campaign to promote awareness of the program and the importance of newborn screening.

Dr. Chou reviewed some of the hurdles that the team encountered. While the shift in status from a research study to a quality improvement project did expedite adding disorders to the project, it also created a labor-intensive administrative burden for the clinical sites that needed to consult with their institution about determination requirements. Additionally, there were no existing LTFU datasets for inherited metabolic disorders and there was a need for more standardized LTFU data elements. The specialty centers often had staff shortages and the project was paused

during the COVID-19 pandemic. Since LTFU in New York is not mandated, their registry only has data for consented patients. Going forward, the team will continue to review and update disorder-specific data elements, train specialty center staff on the REDCap database, and begin data collection for the 31 patients they have consented to date.

The Connecticut Newborn Screening Network LTFU Program Update
***Debra Ellis, RN, BSN,* Program Coordinator Connecticut Newborn Screening Network Connecticut Children's**
***Katherine Raboin, MSN, RN,* Program Coordinator/Senior Analyst Connecticut Newborn Screening Network Connecticut Children's**

Ms. Debra Ellis talked about newborn screening in Connecticut. The Connecticut newborn screening program at the state laboratory and the Connecticut newborn screening network are combined to form a highly integrated newborn screening system. Of the approximately 35,000 births per year, approximately 400 are referred and more than 100 of those referrals will receive a diagnosis. The newborn screening network is responsible for connecting primary care providers and families to a specialty care team. The network also provides education and information to primary care providers, hospital-based providers, newborn intensive care units (NICUs), and families; access to genetic counselors; and telehealth visits. Prior to 2018, Connecticut did not have a centralized reporting system for newborn screens, resulting in potentially delayed care and loss to follow-up. The launch of the newborn screening network in 2018 led to the development of data registries, workflows, and educational resources. Additional funding in 2020 led to the creation of a family advisory group and expanded access to genetic counseling. In 2022, the network received the HRSA grant to support their LTFU program.

Ms. Ellis reviewed the goals of the Connecticut LTFU program, which were to improve family-centered care, increase the number of community and public partnerships and collaborations, improve quality chronic disease management through continuous monitoring, improve access to age-appropriate preventive care, create capacity for LTFU data and reporting, and strengthen readiness for transition from pediatric to adult care. The program engaged their family advisory group to help fine-tune the LTFU workflow and increase diversity in the family advisory group. They also hired a program evaluator to conduct needs assessment surveys, interviews, and focus groups. These have identified areas of improvement, such as the need for early and frequent education about the condition and treatment plans and family frustration about the lack of consistent knowledge between providers. Additionally, the Connecticut LTFU program aims to increase their community partnerships and collaborations to improve long-term follow-up through education and training, advocacy, care coordination and workflows, and technology such as mobile applications.

Ms. Katherine Raboin talked about the Connecticut LTFU's Epic Registry Dashboard, which documents metrics from pre-diagnosis to LTFU. The dashboard also collects metrics through program-specific dashboards. For instance, there is a registered nurse coordinator dashboard that tracks pre- and post-diagnosis patient care through the lens of a care coordinator. Specialty dashboards for hematology, genetics, endocrine, immunology, and neurology collect metrics relevant to their specific populations. Overall, the registry dashboard houses 24 registries and tracks more than 700 metrics that are updated in real-time. The Epic Registry Dashboard also

translates guidelines into electronic health records to monitor and address care gaps, such as routine procedures or immunizations. The dashboard highlights when a patient is overdue for care and aggregates patient data to show the percentage of the patient population that is up-to-date. Ms. Raboin demonstrated the different dashboards and reports that are available to the care team.

The additional funding provided by the HRSA grant allowed the team to hire a program evaluator, who conducted interviews with care teams to identify opportunities for improvement. The team used this feedback to optimize the dashboard build and workflows and to develop a continuous quality improvement framework. The team continues to meet with the care team on a quarterly basis to identify patients who are overdue for care or require increased care coordination. From August 2021 to March 2022, all specialty care team metrics have significantly improved, with increased number of visits, referrals, and up-to-date labs. An additional benefit of the dashboard is the ability to pull data from any external data from the state Health Information Exchange, allowing specialty care providers to view primary care metrics such as health visits, developmental screenings, and immunizations. The LTFU team has an existing incoming and outgoing interface with the Connecticut Department of Health, which they use to receive referral information and to send back aggregated LTFU data.

Ms. Raboin reviewed their transition readiness project, which supports the transition from pediatric to adult care using a staged transition process, a transition readiness screener and checklist, and transition tools built into the Epic Registry Dashboard. The team used their sickle cell cohort to pilot this project and hopes to go live with the Epic dashboard integration in mid-September 2022.

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

- A Committee member talked about how their state's version of the Epic Registry was not user friendly. Since many health care systems use it, there is an opportunity for Epic to assist states in which data is not as well-integrated.
- A Committee member added that many academics also use Epic and that there is an opportunity to use that as a catalyst for larger projects.
- An organizational representative asked what the team's plan was for sustainability and if the team had challenges parameterizing different versions of Epic. Ms. Raboin answered that the registries run in the background and just collect data that clinicians are already documenting. As long as a hospital or clinic is using the same common datasets, then the data can be pulled into the registry.
- An organizational representative asked if there was a plan to provide patients, families, and providers with the aggregated data. Ms. Raboin answered that the specialty care team sees aggregate data, but the primary care team does not. It is definitely an idea that could be explored. They are also considering how to connect with families about how they feel the patient is doing developmentally and to abstract that information into the dashboard.
- An organizational representative asked the New York team to talk about the analyses they conduct with their social media campaigns (e.g., reach or behavior change) and asked the Connecticut team to speak more about the frustrations that families experience with the lack of consistency in provider communications.

    - Ms. Ellis answered that the family advisory group expressed frustration over having to repeat the same information to multiple providers and the need for all providers to have access to the same information. They also felt that information shared between providers may not be accurate and that the primary care providers did not seem to even know their child very well. The team talked to the family advisory group about their aim to connect developmental information from pediatric visits and the hope that the LTFU program would help alleviate those frustrations.
    - Dr. Chou answered that their social media campaign is focused on awareness and education for the general public. They do make adjustments to messaging based on data they receive from the social media vendor.
- An organizational representative expressed concern about the sustainability of a program that is reliant on sequential grants and the inability to conduct an important part of a program until sufficient funding was available. The organizational representative also expressed concern over the common practice of using metrics that are readily available rather than using metrics that may not be as easy to access but that are more important and asked the panelists to share their thoughts on the sustainability of their programs from the perspective of independence from grant funding and balancing between easy to access data and important data.
    - Dr. Caggana answered that the New York program is using the funding to develop the infrastructure of the system, including the database, common data elements, and streamlined workflows. They are also trying to automate as much as possible. They plan to use these efforts to demonstrate the feasibility and worth of the project.
    - Ms. Raboin answered that they designed their registries to capture information that was important rather than easy to access, although this also led to some weakness in terms of sustainability. It is not a perfect system and not everything can be captured automatically. A computer will never replace the person who is inputting notes or reviewing charts. There will always be a need for people, thus there will always be a need for funding.

New Business

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

Dr. Calonge invited Committee members and organizational representatives to share new business or announcements.

Ms. Bonhomme said there have been a number of media articles about newborn screening and the use of blood spots. Genetic Alliance has been proactively reaching out to media about the science and technology and referring them to bioethicists and other experts to help explain the complexity of policies regarding consent and parental permission.

Dr. Calonge shared with the Committee that September is Newborn Screening and Sickle Cell Awareness Month.

Dr. Calonge thanked Committee members and said that the next Committee meeting will take place on November 3-4, 2022 and is planned to be in person.

Adjourn

Dr. Calonge adjourned the Committee meeting at 3:00 P.M. E.T.