Advisory Committee on Heritable Disorders in Newborns and Children

DRAFT Meeting Minutes of May 12-13, 2022
Virtual Meeting

These minutes will be formally considered by the Committee at its next meeting.

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DAY ONE: Thursday, May 12, 2022

Welcome, Roll Call, Committee Business

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

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

Committee members in attendance were:

- Dr. Kyle Brothers
- 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. Shawn McCandless
- Dr. Chanika Phornphutkul
- Dr. Melissa Parisi (National Institutes of Health)
- Dr. Cynthia Powell (Chairperson)
- Dr. Scott Shone
- 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
- Association of Women's Health, Obstetrics, & Neonatal Nurses, Ms. Katie Swinyer
- Child Neurology Society, Dr. Margie Ream
- Association of Public Health Laboratories (APHL), Dr. Susan Tanksley
- Department of Defense, Dr. Jacob Hogue
- Genetic Alliance, Ms. Marianna Raia
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Gerard Berry

Dr. Powell honored the passing of two important leaders in the newborn screening community. Dr. Harry Hannon made a profound impact on the public health newborn screening system through his 41 years of services at the CDC and his expert guidance for laboratory standards and quality assurance practices. Dr. Hannon was a recipient for several distinguished and lifetime achievement awards. His contributions were commemorated in 2008 through the creation of the Harry Hannon Laboratory Improvement Award in Newborn Screening—an honor awarded by

the Association of Public Health Laboratories to an individual who has made significant contributions to the field. Dr. Carla Cuthbert talked about Dr. Hannon's vision, insight, and contributions to the CDC Newborn Screening and Molecular Biology Branch.

Dr. Kwaku Ohene-Frempong was a leading pediatric sickle cell physician as the director emeritus at Children's Hospital of Philadelphia and as professor emeritus at the University of Pennsylvania. Notably, Dr. Ohene-Frempong pioneered a newborn screening and follow-up program in Ghana, where one in 50 babies has sickle cell disease, founded the Sickle Cell Foundation of Ghana, and was a founding member of the Global Sickle Cell Disease Network.

Dr. Powell acknowledged that this will be the last Committee meeting for Dr. Scott Shone and herself. She thanked Dr. Shone for his outstanding service, his valuable contributions to the Committee discussions, and the lasting impact these contributions have had on newborns and their families across the nation. Dr. Powell also welcomed Dr. Margie Ream, who will replace Dr. Jennifer Kwon as the organizational representative for the Child Neurology Society. Dr. Ream is an associate professor and child neurologist at the Nationwide Children's Hospital Child Neurology Program with extensive expertise in fetal physiology, neurology, leukodystrophy, and other rare genetic diseases.

At the February 2022 meeting, the Committee voted to recommend adding Mucopolysaccharidosis Type II (MPS II) to the Recommended Uniform Screening Panel (RUSP). Dr. Powell sent a letter of recommendation to the Secretary on behalf of the Committee and the Secretary's decision will be posted on the ACHDNC website when it is available. The Nomination and Prioritization Workgroup is continuing their review of the nomination package for congenital cytomegalovirus (cCMV) that was submitted by the National CMV Foundation in October 2021.

The Federal Register notices calling for nominations for new voting members and organizational representatives have been closed. The nominations for voting members are currently under review to ensure a Committee that meets the requirements of the Newborn Screening Saves Lives Act and is balanced across different points of view, including members of the public having lived experience.

Dr. Powell provided an update on the Committee's discussion at the February 2022 meeting on the Committee's capacity for reviewing multiple condition nominations each year and a process for prioritizing nominating conditions for review. A workgroup to develop prioritization criteria and processes is currently in the contracting phase and is expected to begin work in 2022.

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

Updates on Homocystinuria NBS Status: Panel Presentation

***Marzia Pasquali, PhD, FACMG,* Professor of Pathology, University of Utah; Section Chief & Medical Director, Biochemical Genetics, ARUP Laboratories**
***Dietrich Matern, MD, PhD, FACMG*, Professor of Laboratory Medicine, Medical Genetics, and Pediatrics; Co-Director, Biochemical Genetics Laboratory, Mayo Clinic**

***Kostas Petritis, PhD,* Laboratory Chief, Biochemical Mass Spectrometry Laboratory, Newborn Screening and Molecular Biology Branch, CDC**

Dr. Marzia Pasquali provided an overview of homocystinurias (HCUs), which is a group of amino acid metabolism disorders characterized by elevated homocysteine and, often, homocystine. HCUs can occur when the process to methylate homocysteine to methionine is impaired through one of three metabolic pathways. Primary biochemical markers necessary for the diagnosis of HCU include methionine, total homocysteine, free homocycstine, and methylmalonic acid.

Classic HCU is characterized by cystathionine β-synthase deficiency resulting in an accumulation of methionine and markedly elevated homocysteine. The clinical presentation includes manifestations to the eyes (lens dislocation and/or severe myopia), skeletal system (long limbs, scoliosis, osteoporosis, pectus excavatum), vascular system (thromboembolism), and central nervous system (developmental or intellectual disabilities).

Early diagnosis and treatment through diet and supplementation can prevent early mortality and morbidity. Screening is typically conducted through tandem mass spectrometry of the blood spot, but the sensitivity of screening depends on the choice of markers and cut-off values. Premature birth, low birth weight, enzyme deficiencies, and other conditions can elevate methionine, but biochemical and molecular second-tier tests can help reduce false negatives and positives through the identification of specific markers for metabolic conditions.

Dr. Pasquali summarized that newborn screening for classic HCU is available and effective. She provided recommendations for improving newborn screening, including revised cutoff thresholds, use of a more sensitive and/or a combination of markers, post-analytic tools, and the implementation of second-tier tests.

Dr. Dietrich Matern reviewed both proposed and currently available solutions for HCU newborn screening. Although methionine is easy to measure, it is not very sensitive or specific. Studies have shown that newborns with HCU have been missed when methionine was used as a primary marker. Additionally, total parenteral nutrition (TPN) solutions can cause false positives. One proposed solution has been to use a ratio of methionine to phenylalanine. However, this solution is not sufficiently sensitive or specific and can still result in false positives with the use of TPN. Molecular testing of the cystathionine β-synthase gene is another proposed solution. However, only a small portion of the variants are of known significance which can lead to uncertain or conflicting interpretations. Measuring total homocysteine instead of methionine is another potential solution that is both sensitive and specific but this technology may not be ready for wider implementation.

One currently available solution is a second-tier test of total homocysteine using liquid chromatography-tandem mass spectrometry (LC-MS-MS). Second-tier testing is sensitive and can be multiplexed with other markers and since HCU is not a time critical condition, the second-tier test can be regionalized.

Dr. Matern and his team published their experience with the second-tier test, which is a cost effective approach to reduce false positives that requires no additional patient contact and helps to reduce anxiety in families. Based on the data between 2005 and 2011 in Minnesota and 2012 cost data, extrapolating to the U.S. numbers, it is estimated that the second –tier testing can save about $71 million annually by reducing the number of false positives and follow-up. .

Dr. Matern summarized that the challenges of poor sensitivity and specificity of using methionine marker for HCU screening can be resolved by the currently available solution of using the second-tier testing that includes total homocysteine, which is sensitive, efficient, accessible, and cost effective.

Dr. Kostas Petritis provided on overview of advances in HCU newborn screening. Currently, second-tier testing is fragmented often with one assay for one disease, requiring high maintenance while not needing to run the assays very often, and thus not frequently done in-house by state labs. Dr. Petritis discussed a method of multiplexing 19 second-tier screening biomarkers including homocysteine that was developed and will soon be published. Another proof of concept work that is currently ongoing involves combining first- and second-tier screening analytes and using separation before mass spectrometry, where fast electrophoretic separations are used.

Dr. Petritis also presented on development of an assay to multiplex total homocysteine detection into primary flow injection analysis-tandem mass spectrometry (FIA-MS/MS) including the process of troubleshooting of reducing agent selection and derivatization methodology and the results of running the assay with newborn screening specimens. Dr. Petritis summarized that total homocysteine was a more clinically relevant screening biomarker than methionine and multiplexing it into primary FIA-MS/MS screening could streamline the use of total homocysteine as a screening marker for HCU.

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

- A Committee member pointed out that the challenge in newborn screening for classic HCU is similar to the challenge the Committee faced with tyrosinemia type I a few years ago, in which the screening methods were not sensitive enough and required a change. Remethylation defects, particularly in methylmalonic acidemia, continues to be a very serious health care issue that is well-documented in the literature and is important for the Committee to address. Using low methionine as a primary marker without the use of additional makers will result in continued infant death because the diagnosis will not be made or will be made too late.
- A Committee member expressed appreciation that the presenters highlighted the challenges associated with a lack of uniform newborn screening systems across the country and of adding new screening tests without the potential for harm created by false positives. It is critical to improve newborn screening methods through laboratory practices and research in order to reduce the burden of false positives. The Committee member asked about the potential for second-tier screening to also reduce false negatives. Dr. Pasquali answered that newborn screening can result in a lot of noise. Often the

solution for decreasing the noise is to increase decision limits and this can increase the number of false negatives. Second-tier testing rules out nearly all of those false negatives.

- A Committee member asked what role the CDC Newborn Screening Quality Assurance Program (NSQAP) could play in improving the quality of HCU screening.
    - Dr. Petritis answered that the CDC NSQAP does understand the limits of newborn screening for HCU and is currently in process of introducing a new secondary screening program that will include second-tier testing for total homocysteine. They have an annual workshop to train the different screening methods and the two methods that he presented can be included in these trainings.
    - Dr. Carla Cuthbert added that CDC does partner with APHL for technology transfer but that some of those efforts had been suspended because of the COVID-19 pandemic. CDC also provides funding opportunities, not just for new conditions, but also to improve existing conditions. While it would be ideal to get a dramatic change and improvement across all states; these transitions and improvements take some time.
    - The Committee member talked about the importance of advocating for longer storage of dried blood spots to use as primary data for research to optimize newborn screening methods.
    - Dr. Matern added that CDC does a great job in helping laboratories become well versed in technology. One of the frustrations is that second-tier testing is not part of the program and CDC could focus more on interpretive skills of metabolic profiles for multiple conditions rather than a single profile.
- A Committee member referenced the Committee's recommendation for succinylacetone as a marker for tyrosinemia type I that helped newborn screening programs overcome barriers such as supply procurement. The Committee member asked if this approach would be a good pathway to improve innovation for HCU screening. Dr. Matern said that a strong endorsement from the Committee that is based on published research, as was the case for succinylacetone, could make a difference.

Public Comments

Danae' Bartke

Ms. Danae' Bartke is the Executive Director of HCU Network America. She and her brother were both diagnosed with classic HCU. She was asymptomatic and had a late diagnosis at age 10 after brother was diagnosed when he experienced a retinal detachment. Her brother had missed major developmental milestones and continues to experience repercussions from HCU. After struggling to adhere to the prescribed diet, Ms. Bartke developed a blood clot and is lucky to still be here to advocate for people with HCU. The literature suggests that at least 50 percent of people with HCU are missed using the current screening approaches. The cut-off values range from lab to lab and analyses of medical claims data and genetic databases tend to look only at specific defects. These approaches may miss many people who suffer later in life with increased risk of premature stroke from blood clots and other issues. HCU Network America identified 24 people in the United States who were diagnosed within the past 32 years but were missed by newborn screening that was in place at the time of their birth. A late diagnosis usually results in irreversible damage and the only prevention is early diagnosis and treatment. The best long-term approach for detecting all cases of HCU is to screen for total homocysteine. HCU Network America is thrilled with the progress made from CDC's research and the solutions that were

presented today that can be implemented. Since the HCU Network America's first presentation to the Committee in 2018, they have been meeting with state newborn screening labs to discuss revised screening approaches. A few states have already begun lower methionine cut-off values and second-tier testing but others do not have the resources to make these changes. They urge the Committee to prioritize this effort and suggest they endorse the two-tier screening approach as a priority at the state level and to establish a first-tier screen for total homocysteine.

Terri Klein
Ms. Terri Klein is the President of the National MPS Society, one of the nominators for the recent approval of the addition of MPS II to the RUSP, and mother to a daughter with MPS II. Although her daughter was not given much hope for a long and productive life, today she is a scientist working on the clinical trial design for rare diseases. Ms. Klein said that science and discovery for rare diseases, such as MPS II/Hunter syndrome, provides individuals and families with a way forward. The only obstacle has been the way that newborn screening is conducted. First- and second-tier testing would benefit the community and change the outlook of newborns with MPS II/Hunter syndrome. The National MPS Society is prepared to support and educate every family that will be screened and has worked diligently to ensure that social workers and advocates have the information to guide and support families. The education, equitable access to treatment, and outreach to diverse populations including underserved communities are critical to their mission. They were grateful for the Committee's vote to recommend the addition of MPS II to the RUSP and anxiously await the Secretary's acceptance.

Dylan Simon
Mr. Dylan Simon is the Director of Public Policy at the EveryLife Foundation for Rare Diseases, which is a nonprofit, nonpartisan organization dedicated to empowering the rare disease community to advocate for impactful, science-driven legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments, and cures. The Community Congress Newborn Screening Working Group applauded the Committee's recommendation to add MPS II to the RUSP, which, when implemented, will provide approximately 38 newborns born annually in the United States with access to early diagnosis and treatment. However, they felt that the Committee's discussion of the nomination sometimes strayed from the examination of the quality of evidence and its impact on public health and instead focused on challenges of the current health care system. They encouraged the Committee to ensure that such challenges not become a barrier to adding new conditions to the RUSP. They also appreciated the Committee's preparation for an anticipated increase in nominations and expressed the importance of including a voice from the patient community in the review process. Therefore, as the Committee selects new members, they requested that all 15 member positions be filled, increase transparency during the onboarding process, and to ensure that the patient voice is represented in the process. They also requested that the Committee include two clinical representatives from the Evidence-based Review Group be available to answer questions during the Committee's final deliberation. They encouraged the Committee to focus on expanding capacity to review nominations rather than prioritization processes and to provide increased transparency on the details of pending nominations, including the schedules for review, discussion, and voting. Finally, they requested that discussions about challenges associated with newborn screening be addressed outside of individual RUSP nomination review processes.

Dean Suhr
Mr. Dean Suhr is the President and co-founder of MLD Foundation and parent to children with metachromatic leukodystrophy (MLD). He spoke on the nomination to include EveryLife Foundation as an organizational representative on the Committee. The EveryLife Foundation meets the requirements of an organizational representative and is already informing the Committee with recommendations from their Community Congress Newborn Screening Working Group, with representatives from several organizations and advocates who inform recommendations, programs, and activities in support of newborn screening. They are working to expand the Newborn Screening Saves Lives Reauthorization Act, which would not only support reauthorization, but also provide an increased budget to improve the Committee's operational capacity and impact. EveryLife Foundation is knowledgeable about RUSP alignment legislation and other regulatory and legislative processes involved in newborn screening. They are focused on helping the community become more informed, empowered, and impactful and advocating for novel research, innovative policies, and increased appropriations. The Committee would benefit from EveryLife Foundation's experience and potential for impact. Mr. Suhr therefore recommended that the Committee consider EveryLife Foundation an ideal organizational representative.

Kim Stevens
Ms. Kim Stevens is the President of Project Alive and co-Chair of EveryLife Foundation's Newborn Screening and Diagnostics Community Congress Working Group. They urged the Committee to include a patient advocacy representative as one of the two new Committee members that is open for new appointment. A qualified patient advocacy representative can provide expertise on rare disease and insight on the impact that newborn screening can have on the rare disease community. Patient representatives provide lived experience to the nomination review process, which not only brings an essential perspective to Committee discussions, but also signals to the community the importance of including their voice. The inclusion of a patient advocate promotes trust, builds diverse perspectives into the RUSP review process, and can alleviate fear and misunderstanding about newborn screening challenges. Patient advocacy organizations are vital to the newborn screening system and must have input on Committee decisions. They can serve as a bridge between the patient advocacy community and the Committee, which may foster buy-in and support. Ms. Stevens encouraged the Committee and HRSA to consider adding a patient advocacy representative to the Committee and to consider the standards set forth by the National Health Council for the membership of patient organizations.

Kim Tuminello
Ms. Kim Tuminello is the Director of Advocacy for the Association of Creatine Deficiencies (ACD) and mother of two children with guanidinoacetate methyltransferase (GAMT) deficiency—one who was diagnosed at 10 months of age and the other who was diagnosed in utero and received treatment since birth. She thanked the Evidence-based Review Group for their in-depth review of GAMT deficiency. GAMT deficiency is easily detectable, has an almost non-existent false positive rate, and can be treated with effective supplementation that can be ordered online. She thanked the New York and Utah newborn screening programs for their efforts and looked forward to the Committee's vote on the nomination.

Heidi Wallis

Ms. Heidi Wallis is the Executive Director of the ACD and parent to children with GAMT deficiency. She introduced the Committee to her children, one of whom was diagnosed at age five and the other at birth. She thanked the Committee and the Evidence-based Review Work Group for their review of the GAMT deficiency nomination and expressed her excitement for their vote.

Newborn Screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency: A Systematic Review of the Evidence (Part 1)

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

Dr. Alex Kemper provided an overview of GAMT deficiency, which is a disorder of creatine biosynthesis associated with elevated guanidinoacetate (GUAC) and low plasma creatine and caused by an autosomal recessive mutation in the *GAMT* gene. Diagnosis can be made soon after birth through tandem mass spectrometry screening or through magnetic resonance (MR) spectroscopy. Molecular analysis of DNA can be used to support diagnosis when screening results are uncertain. The prevalence of GAMT deficiency is estimated to be 0.4 per 100,000 live births (or one in 250,000); however, the rarity of the disorder and variance across different geographic regions can lead to heterogeneity in prevalence estimates.

Untreated, GAMT deficiency results in progressive neurological impairments that are typically not apparent until after three month of age. These impairments can include significant intellectual disability, limited speech development, recurrent seizures, behavioral problems, weakness, and movement disorders. Although GAMT deficiency is not directly related to an increased risk of mortality, some of its comorbidities (e.g., seizures) can be. Studies show that the age of clinical identification can range from two to 29 years of age.

Dr. Kemper reviewed GAMT deficiency screening programs in Utah and New York. The Utah newborn screening program began screening for GAMT deficiency in June 2015 using laboratory developed tests. Between 2015 and 2019, they used a first-tier screen with FIA-MS/MS derivatized assay and a second-tier test of LC-MS-MS. They screened 195,425 newborns with this method, resulting in two positive second-tier tests and no diagnosed cases. In 2019, they brought their newborn screening program into their laboratory using only a first-tier non-derivatized FIA-MS/MS. Since adopting this approach, they have screened 125,888 newborns, resulting in two positive first-tier screens and one diagnosed case. Between 2015 and 2021, the Utah program referred 0.93 per 100,000 newborns screened and diagnosed GAMT deficiency in 0.31 per 100,000.

The New York newborn screening program began screening for GAMT deficiency in October 2018 using laboratory developed tests. Initially, they used a first-tier screening using FIA-MS/MS and a second-tier test using high-performance liquid chromatography and discontinued the second-tier test in September 2021. New York provides GAMT molecular sequencing as part of their referral process. In 2021, they screened 211,232 newborns, resulting in 82 positive screens, five referrals, and 77 requests for a repeat test that resulted in one additional referral. Of the six total referred, one was diagnosed with GAMT deficiency and another with arginase

deficiency. In 2021, New York referred 2.8 per 100,000 newborns screened and diagnosed GAMT deficiency in 0.47 per 100,000. Between October 2019 and April 2022, New York screened 759,246 newborns, resulting in 24 referrals (3.2 per 100,000) and one diagnosis (0.13 per 100,000).

Dr. Kemper reviewed other GAMT deficiency newborn screening activities. The Michigan newborn screening program approved screening for GAMT deficiency in late 2018 and is currently validating their screening approach before full implementation. British Columbia, Canada began GAMT deficiency screening in 2012 using a three-tier process. Of the 428,140 newborns screened, they found 1,228 with a positive first-tier assay, 28 with a positive second-tier assay, and three with a positive third-tier assay. Of these, no cases of GAMT deficiency were diagnosed. GAMT deficiency screening was recently approved in Ontario, Canada and they plan to implement screening this summer. Victoria, Australia began screening for GAMT deficiency in 2002 using FIA-MS/MS. Each year, they screen approximately 80,000 newborns, resulting in an average of 20 second-tier tests, 3 repeat samples, and 0.3 referrals. Of the 1.4 million newborns screened over the life of the program, they have found one likely case of GAMT deficiency.

Dr. Kemper provided summary data of the GAMT deficiency screening programs. In the United States between 2015 and 2022, 1.08 million newborns were screened, resulting in two diagnoses of GAMT deficiency (0.19 per 100,000). Across all screening programs between 2002 and 2022, 2.9 million newborns were screened, resulting in three diagnoses of GAMT deficiency (0.1 per 100,000).

Dr. Kemper reviewed treatment approaches for GAMT deficiency. Standard treatment is based on expert consensus and consists of creatine, ornithine, and sodium benzoate; a protein-restricted diet; and serum monitoring. A gene therapy using an adeno-associated virus vector to normalize GUAC is currently in development. He reviewed studies comparing outcomes from treatment administered before six months of age to treatment administered to their older siblings at a later age. The reports did not use standardized evaluations, but those with earlier intervention generally showed normal developmental outcomes and those treated later in life showed varying levels of developmental disability, speech and motor delays, and seizures.

Dr. Kemper then reviewed the estimated costs associated with newborn screening for GAMT deficiency. Cost data was collected from interviews with New York and Utah newborn screening programs and was estimated to be substantially less than $1 per infant. This cost estimate was based on the use of a laboratory developed test in programs that already have technical capacity and ability to validate the test.

Dr. Lisa Prosser reviewed the projected population-level outcomes of GAMT deficiency screening as compared to usual case detection in the absence of screening. Their modeling approach was based on an annual newborn cohort of 3.6 newborns in the United States and considered screening outcomes and cases of diagnosed GAMT deficiency. Only short-term outcomes were projected due to insufficient evidence to model long-term outcomes. The model was based on a systematic approach to decision-making using projected ranges of outcomes to determine the alternative with the most health benefit.

Data from the Utah and New York screening programs were combined and modeled. The projected probabilities are: 2.6 (range: 1.7-3.8) per 100,000 for a positive screen, 0.2 (0.02-0.6) per 100,000 for a diagnosis, 2.1 (1.6-2.4) per 100,000 for a false negative, and 0.0 (0.0-0.3) per 100,000 for loss to follow-up after a positive screen. Based on evidence review, the projected probability for confirmed GAMT deficiency by clinical identification ranged from 0.05 to 0.5 per 100,000.

The number of positive screens is projected to be 93 (62-135) per year. GAMT deficiency identified by screening is projected to be 7 (1-22) as compared to a range of 2 to 18 through clinical identification. The projected number of false positives was 77 (59-88) and lost to follow-up was 0 (0-12). Dr. Prosser summarized that an estimated seven cases of GAMT deficiency would be identified annually through national newborn screening. As there was insufficient evidence to compare estimate cases detected in absence of newborn screening, there was also insufficient evidence to quantitatively estimate the potential benefit of screening.

Newborn Screening for GAMT Deficiency: A Systematic Review of the Evidence (Part 2)

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

Mr. Jelili Ojodu reviewed the results of the public health impact assessment of GAMT deficiency newborn screening. The objective of the assessment was to determine the readiness and feasibility of implementing GAMT deficiency screening. To conduct the assessment, APHL developed a fact sheet and webinar to provide states with information about the GAMT deficiency screening. They also distributed a survey to 53 states, territories, and Washington, D.C. and conducted interviews with the three newborn screening programs that are screening or planning to screen for GAMT deficiency and two programs that are not currently screening.

Mr. Ojodu reviewed the results of the survey. Of the 53 surveys, 35 responded (66 percent) and four were excluded. New York and Utah already have a screening program in place. Michigan has a mandate to screen in place and is in process of developing an assay. Connecticut is exploring a program and is in process of developing an assay. Among the remaining 31 states included in the survey analysis, the majority indicated that the major challenges to implementation included the availability of a validated screening test, administrative issues, and increased fees. The majority considered the identification of specialists and the availability of treatment as not a challenge.

Of the states that conducted in-state laboratory testing, approximately half indicated that not having a method to screen for GAMT was a major concern. The majority also indicated that they did not currently have laboratory information management systems (LIMS) in place but could implement it within a year. Of the states that outsourced their laboratory testing, an overwhelming majority indicated that they currently had staff, specialists, treatment centers, and access to diagnostic services. The majority of these states also indicated that screening tests,

follow-up protocols, and adequate LIMS capacity were not currently in place but could be obtained within one year.

Approximately half of the states suggested that they did not consider second-tier testing to be necessary. Of the remaining states that considered second-tier testing important, approximately 30 percent indicated that they would not be ready to do so within one year, 20 percent would contract the second-tier test, and three percent would be ready within one year. The estimated cost to conduct screening was considered a minor barrier to implementation and competing program activities was considered a major barrier. The majority of states considered the cost-benefit, the level of advocacy for screening, expected clinical outcomes, and the ability to multiplex screening to be facilitators to implementation. Approximately half the states indicated that it would take 25 to 36 months to implement the GAMT deficiency screening program.

Mr. Ojodu reviewed lessons learned from interviews with states currently screening for GAMT deficiency. These programs highlighted the ability to multiplex GAMT deficiency with other disorders, little additional staff time, and the elimination of the second-tier test as advantages. They also indicated that the lack of an FDA-approved test kit and the need to make LIMS adjustments as challenges. Additionally, the Michigan program described their challenges in validating a GAMT deficiency assay with the other disorders and with a high number of false positives. These issues may be resolved with extensive cleaning or an update of their MS/MS equipment. The interviews with the two states that did not have a GAMT deficiency screening program in place indicated concern about competing program priorities, funding, staff, laboratory space and LIMS updates.

Mr. Ojodu emphasized that the variation across different state newborn screening programs limits the generalizability of results from the public health impact assessment. He summarized that approximately half of the newborn screening programs indicated readiness to implement GAMT deficiency screening within two to three years. This readiness varied considerably, with 35 percent indicating readiness to implement within two years and 20 percent will need longer than three years. The validation of GAMT deficiency screening may be a challenge and an FDA-approved test kit may facilitate implementation. The ability to multiplex and eliminate second-tier tests can also help facilitate implementation.

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

- A Committee member commented on the category for "other" outcomes in which positive screens could not be confirmed and asked if there were other conditions that contributed to this outcome.
    - Dr. Kemper answered that the technical expert panel said that arginase deficiency was the only condition they were aware of that could have this result. This category also included newborns who were referred but died prior to diagnostic evaluation.
    - Another Committee member added that arginine deficiency is currently on the secondary screening list and the addition of GUAC screening could improve its timely diagnosis. GAMT deficiency is one of three creatine deficiency disorders that are not currently screened. GUAC also has the potential to be a marker for

arginine:glycine amidinotransferase (AGAT) deficiency, which would also benefit from early identification and treatment.

- A Committee member said that treatments included in other evidence reviews had been endorsed by a national specialty group but that the treatment for GAMT deficiency was not because it was classified as a dietary supplement. The Committee member asked about the partnership to produce a higher quality supplement and the potential for supply chain issues that may impact a treatment classified as a dietary supplement differently than one that is classified as a pharmacologic.
    - Dr. Kemper said that although there was no specific endorsement for treatment, there were a number of published articles and a book chapter that defined treatment recommendations and that this seemed to indicate consensus among those who treat this rare disorder. The ACD was wise to recognize the need for treatment criteria and contract with a laboratory to make it easily available from a compounding pharmacist. There seemed to be no supply chain issues during their review.
    - The Committee member asked if there was a potential for more equitable access to this treatment than higher priced therapies. Dr. Kemper answered that the cost of treatment was not within the purview of the Evidence-based Review Group. The cost of this treatment is certainly lower than others but insurance coverage should also be considered. The cost of medical foods and supplements may be a challenge. The use of creatine as a supplement for strength-building is different than its use for a medical condition.
    - Another Committee member added that the FDA defines dietary supplements as an unadulterated component of food. It is clear that GAMT deficiency treatment is not a dietary supplement but rather small molecules that modulate the output of a biochemical pathway in an individual with a severe genetic disorder. There needs to be an effort to carefully define these molecules and to move away from the dichotomy of pharmaceutical versus dietary supplement.
    - Another Committee member talked about an effort by a separate advisory committee to advocate for the classification of medical foods as treatment for disease. The Committee should carefully distinguish between the two and insist on coverage similar to pharmaceutical treatment. The Committee member added that there are reliable suppliers for these supplements but the lack of FDA oversight in their production means that there is no way to know if supplies are coming from the same production.
    - Dr. Powell added that there has been legislation introduced for medical food coverage that was not passed. Cost to families is an important consideration because these foods can be extremely expensive for some.
- A Committee member expressed concern about Michigan's challenges. Modifying an FDA-cleared test kit makes it a laboratory developed test. New York and Utah have found a way forward but not every program can make upgrades to increase the sensitivity of their tests. Dr. Kemper said that the evidence review did not include what testing kit manufacturers have planned. If the Committee recommends the addition of GAMT deficiency to the RUSP, manufacturers will have incentive to develop and make available testing kits but it is unclear what the timeline could be.

Committee Report: Newborn Screening for GAMT Deficiency

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

Before introducing Dr. Jane DeLuca and Dr. Shawn McCandless, Dr. Powell presented an overview of the decision matrix and reminded organizational representatives that, unless otherwise directed, the deliberations of this presentation were for Committee members only.

Dr. McCandless provided a brief review of GAMT deficiency and its prevalence, symptomatology, screening methods, confirmatory diagnosis methods, and treatment. He reviewed potential challenges to the implementation of GAMT deficiency screening and the lack of formal published treatment guidelines. He talked about the benefit of early treatment as evidenced by sibling studies.

The potential harms of GAMT deficiency screening are primarily related to individuals who do not have GAMT deficiency and include the potential for a false positive screening, indeterminate results, loss to follow-up, and an added cost for confirmatory testing. However, these potential harms are rare or of low concern.

Dr. DeLuca described the balance between benefit and harm and the net benefit. Though limited, there was some evidence showing a benefit of pre-symptomatic therapy, extremely low risk of harm from treating individuals who would not benefit from treatment, and a relatively low risk of potential harm from an indeterminate status on families. Therefore, Dr. McCandless and Dr. Deluca assigned GAMT deficiency with a Category B for moderate certainty of significant net benefit. This designation was made based on the available evidence and constraining factors such as the number of studies and quality of evidence.

GAMT deficiency screening tests are available and appropriate for high-throughput testing. States may have challenges adding this screening within one to three years due to challenges in method development and a validation of an assay. However, screening costs are the same or less than other recent screening additions and the resources needed for follow-up are considered adequate. Therefore, Dr. McCandless and Dr. Deluca assigned GAMT deficiency with a Category 2 for developmental readiness, indicating moderate feasibility for implementation.

Dr. DeLuca summarized that newborn screening for GAMT deficiency meets criteria for Category B2. Their recommendation was that GAMT deficiency should be added to the RUSP as a core condition.

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

- A Committee member agreed with the classification for moderate evidence of benefit. Although the evidence is not strong, which is expected for a rare disease, sibling studies do provide compelling evidence. The Committee member believed that it was reasonable to add the condition to the RUSP.
- A Committee member talked about the legislative challenges of implementing screening state-wide and a hope that commercial vendors will invest in developing commercial

screening kits. Dr. McCandless responded that newborn screening decisions that affect population health should not be handled by legislative and administrative staff. It is reasonable to conduct a thoughtful review process towards a recommendation to add a condition to screen for but there needs to be recognition that a legislative body may not be scientifically equipped to set a deadline for its implementation. There should be an opportunity for the Committee to educate legislators about the newborn screening program to reduce the risk of worsening the situation.

- A Committee member said that the survey results about state readiness to implement this screening was similar to survey results from other disorders the Committee has reviewed. Mr. Ojudu agreed that there was nothing specifically different from these survey results as compared to other surveys. There is a disconnect between what the programs suggest can happen and the reality of what would happen. For instance, the last four approved conditions were examples of how long it can take for a screen to be added. APHL is trying to better understand the correlation between what is said via the surveys and what happens after a condition is added to the RUSP.
- A Committee member said that technological shifts can affect how long it takes to implement one screen over another. Specifically, the ability to multiplex or remove a second-tier test can shift timelines. The underlying issue is that the evidence review will identify a net benefit for early identification and treatment and programs will work hard to implement it. GAMT deficiency may be more like severe combined immunodeficiency (SCID) rather than spinal muscular atrophy (SMA).
    - Dr. Cuthbert responded that, as the Committee recommends to add a new condition to the RUSP, if there was not an FDA-approved test, the program would have to find another way to implement it. This was why some states had different responses about implementation. Some conditions have one biomarker, but GAMT deficiency requires looking at multiple biomarkers. Michigan went through an iterative process to address these added levels of complexity. These are the challenges inherently involved in adding different biomarkers.
    - Another Committee member added that it becomes difficult to continue adding tests to multiplexes and there would be a point in which more cannot be added. It would be good for a researcher to model this to provide the Committee with guidelines about what might be expected.
- A Committee member said that the magnitude of the effect of screening on affected individuals was very large, possibly more so than for phenylketonuria (PKU). But there was not a lot of data and there may be variability in response to treatment or partial treatment. Therefore, it may be valuable for the Committee to continue to fine-tune the decision matrix to capture the inadequacy of data in its inability to capture the nuance of benefit to affected individuals of treatment and the magnitude of that benefit.

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

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

DAY TWO: Friday, May 13, 2022

Committee Business

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

On behalf of HRSA and the Department of Health and Human Services, Dr. Michael Warren thanked Dr. Powell for her leadership and service to the Committee and to the field of newborn screening. Dr. Powell has served on the Committee since November 2017 and as Committee Chair since May 2019. Under her leadership, the Committee reviewed and strengthened their evidence-based review and decision-making processes and supported the development of consumer-friendly resources to explain these processes. She led the Committee's focus on the newborn screening workforce challenges and opportunities, health equity, and the capacity and prioritization for reviewing nominated conditions.

Dr. Powell announced that Dr. Ned Calonge will be the incoming Committee Chair. Dr. Calonge is an Associate Professor of Family Medicine at the University of Colorado and Associate Professor of Epidemiology at the Colorado School of Public Health. He has chaired groups including the Community Preventive Services Task Force for CDC, the Board on Population Health and Public Health Practice for the National Academy of Medicines, Health, and Medicine, and other evidence-based review groups.

Dr. Powell announced that May 23-27, 2022 was Public Health Genetics Week, hosted by the HRSA-funded National Coordinating Center for the Regional Genetics Network. May 26 is scheduled to focus on the newborn screening system.

Public Comments

Niki Armstrong
Ms. Niki Armstrong is the Newborn Screening Program Manager for the Parent Project Muscular Dystrophy (PPMD). She provided an update on the efforts in newborn screening for Duchenne muscular dystrophy (DMD), which included a plan to submit a nomination to the Committee later this year. For more than ten years, PPMD has supported the development of the infrastructure needed to implement newborn screening for DMD. They completed a two-year DMD newborn screening pilot in New York that included more than 36,000 newborns and identified four males with Duchenne or Becker and one carrier female. This incidence was consistent with the incidence of one in 5,000 found in Duchenne research. At least one state was considering adding DMD to their newborn screening panel and there are two other pilot programs in progress. The lessons learned from these efforts would be compiled in their nomination package. PPMD remained focused on removing the diagnostic odyssey for DMD so that no family will wait two years or longer for a diagnosis. They aimed to have newborns identified during newborn screening so that they can receive early follow-up, therapies, and benefit. She extended her gratitude to the families, experts, and partners who have helped PPMD.

Jacque Waggoner

Ms. Jacque Waggoner is the CEO of Hunter's Hope Foundation, which was co-founded by her daughter Jill and son-in-law Jim Kelly in 1997 after their son Hunter was diagnosed with Krabbe disease. Ms. Waggoner quit her job to help with her grandson's care and therefore has lived experience with the devastation of this disease. Hunter was seemingly healthy at birth but his health soon declined. He was misdiagnosed as his health continued to decline and was eventually diagnosed with Krabbe leukodystrophy. Despite the expectation that he would not live past a year old, Hunter exemplified courage and continued to live for eight-and-a-half years. Since the Committee voted against including Krabbe in the RUSP, 136 children (that they know of) have been diagnosed with Krabbe in the United States. Through Hunter's Hope Foundation, they continue to advocate for Krabbe newborn screening, partnering with families and experts to help fill the gaps identified by the Committee in their first review of the nomination. Ms. Waggoner said that there was an astounding difference between a clinically diagnosed child with Krabbe and a child diagnosed through newborn screening and subsequently received a transplant. Without treatment, children will suffer a painful death; with treatment, children can live their best life possible.

Natasha Spencer
Ms. Natasha Spencer is a parent to her son, Keenan, who was diagnosed with Krabbe in 2011. Because he was not diagnosed through newborn screening, he missed the opportunity to intervene with a stem cell transplant. Keenan experienced rapid neurological deterioration and painful muscle spasms during the first two years of his life. As the white matter in his brain deteriorated, he lost muscle tone and the ability to move voluntarily, including the ability to swallow and vocalize. His pupils stopped dilating and his respiration reduced from 20 to 30 breaths per minute to four to eight breaths per minute. Ms. Spencer experienced an intense regimen of daily treatment and feeding, weekly therapies, and extensive advocacy. Keenan died in 2018. Ms. Spencer reflected on the normal trajectory of a child who gains more independence as they meet developmental milestones in contrast to the reduction of independence that Keenan experienced as he deteriorated into the disease. His brain tissue was stored in the Neurodevelopment in Rare Disorders Repository to help advance knowledge of Krabbe disease through research.

Karlita Blackwell
Ms. Karlita Blackwell is mother to a son, Ezra, who was diagnosed with Krabbe leukodystrophy in 2016 through a newborn screening program. Though they were devastated with the diagnosis, they were also given a glimpse of hope through treatment with a stem cell transplant. It has been five years since Ezra received treatment and Ms. Blackwell considers what might have happened had her son not been screened early. He would not have been excited to start kindergarten, eat his favorite foods, or ride his bicycle. He would have missed the ability to live a gratifying life. Ms. Blackwell talked about the families who missed the opportunity for treatment and the same precious moments with their children. Her hope is for change to ensure that no other family misses these moments and that no other child is resigned to an early and painful death.

Joanne Kurtsberg
Dr. Joanne Kurtzberg is the Director of the Marcus Center for Cellular Cures and of the Pediatric Blood and Marrow Transplant Program at Duke University, where they have transplanted nearly 400 children with leukodystrophy including 60 children with Krabbe disease. Krabbe disease is a

medically-serious life-threatening disease that most commonly affects young infants in their first year of life. The estimated incidence is approximately one in 100,000 births. Without treatment, infants develop feeding problems, spasticity, extreme irritability, seizures, blindness, and profound developmental delay and will die within the first few years of life. Hematopoietic stem cell transplantation can significantly extend and improve quality of life if performed within the pre-symptomatic stage. Newborn screening for Krabbe disease was initially piloted in New York and has since advanced with second-tier tests using psychosine to definitively identify infants within a matter of days. Most families do not know their newborn is at risk of Krabbe disease and often learn about the disease after their child is sick and symptomatic. While treatment is not a cure, research has shown it to be highly effective and can transform lives—prolonging life by decades and improving quality of life. Newborns should be identified early to give their families the opportunity to choose treatment. Newborn screening is the only option for early identification and treatment. Other innovative therapies are in early clinical trial and are expected to be available within the next few years. Dr. Kurtzberg strongly encouraged the Committee to vote to move Krabbe disease into full evidence review.

Dr. Dieter Matern

Dr. Dieter Matern is a medical geneticist at the Mayo Clinic and Division Chair of Laboratory Genetics in the Department of Laboratory Medicine and Pathology in Minnesota. Krabbe disease was nominated in 2008, underwent an evidence review, and was voted to not be added to the RUSP in 2010. Dr. Matern agreed with the Committee's 2010 decision and in 2015 voted against the addition of Krabbe disease to the Minnesota newborn screening program as a member of the Advisory Committee on Heritable and Congenital Disorders. New York began a screening program for Krabbe disease in 2006 using a sensitive but not very specific screen. After eight years, New York has reported a predictive value of only 1.4 percent for infantile Krabbe disease. Dr. Matern firmly believed that the false positive rate must be kept as low as possible and an approach based on enzyme activity as a second-tier test does not meet this requirement. However, from a laboratory testing perspective, Krabbe disease can be identified by dried blood spot with elevated psychosine as a marker to adjudicate clinically-relevant activity. The Mayo Clinic adopted psychosine as a marker in 2015. Soon after, Kentucky added Krabbe disease to its newborn screening program and asked the Mayo Clinic to perform their laboratory screening using the New York screening model but also adding psychosine. Since February 2018, they have screened approximately 350 newborns and identified two with Krabbe disease. Both cases received a bone marrow transplant within their first month of life and are doing well. Dr. Matern said that it was clear that the transplant was life-saving and the disease would not have been identified without the psychosine marker. The nomination was not only to add Krabbe disease to the RUSP but also to recommend a screening approach based on measurement of galactosylceramide as a primary test and psychosine as a second-tier test. Additionally, the recommendation was to screen for infantile and late infantile Krabbe disease as a core condition and the later onset forms as secondary targets. Dr. Matern concluded with his support of the nomination of Krabbe disease to the RUSP. He said that the gaps in knowledge have been closed as much as possible and relevant follow-up and monitoring guidelines have been developed and published.

Krabbe Nomination Summary

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

Dr. Powell briefly reviewed the nomination review process and the history of the first nomination of Krabbe disease in 2010 and presented the findings of the Nomination and Prioritization Workgroup review of the nomination package for Krabbe disease for inclusion on the RUSP.

Krabbe disease is an autosomal recessive lysosomal storage disease. It is caused by homozygous or compound heterozygous pathogenic variants in the gene coding for the enzyme glucocerebrosidase (GALC). The intended target for newborn screening of Krabbe disease is the infantile form, which is the most severe form of the disease that results in symptoms such as irritability, feeding issues, failure to thrive, seizures, aspiration pneumonias, and the loss of vision, fine and gross motor skills, and communication skills. Symptom onset occurs within two to 12 months of life and most children will die by two years of age. Other forms of Krabbe disease include late infantile, juvenile, and adult onset.

The Nomination and Prioritization Workgroup used three key questions to guide their decision to move forward with full evidence review. The first key question was whether prospective pilot data from population-based assessment was available for Krabbe disease and the Nomination and Prioritization Workgroup determined that there was. There are eight programs across nine states that screened for Krabbe disease, resulting in nearly six million newborn screens. Of these, 15 were identified with infantile form and two with late infantile form, representing an estimated incidence of one per 338,418.

The second key question was whether the screening test for Krabbe disease has established analytic validation and the Nomination and Prioritization Workgroup determined that it does. There is an FDA-approved test kit for Krabbe disease that screens for six lysosomal storage disorders using MS/MS. First-tier screening measures GALC activity, which has low specificity and will detect carriers and pseudodeficiencies. New York used Collaborative Laboratory Integrated Reports (CLIR), which decreased the need for repeat GALC analysis and second-tier testing. However, the Nomination and Prioritization Workgroup had some concern about the availability of CLIR for all state newborn screening programs. In addition, there is a need to refer positive screens to a testing laboratory for a second-tier psychosine measurement that costs approximately $100 per sample. This cost is reasonable but there is a concern about the availability of psychosine testing. Some states also use molecular gene sequencing as a second- or third-tier test to detect severe pathogenic variants, as well as pseudodeficiency alleles to help reduce the number of positive screens. A recent study from the Illinois program showed that second-tier testing for psychosine helped identify infantile Krabbe disease, probable late infantile Krabbe disease, and pseudodeficiencies.

The third key question was whether there was a widely-available, CLIA- and/or FDA-approved confirmatory diagnostic process and the Nomination and Prioritization Workgroup determined that there was. The Illinois study showed that positive predictive value increased from 2.8 percent using GALC measurement to 40 percent using second-tier psychosine testing and to 100 percent using molecular genetic sequencing.

The Nomination and Prioritization Workgroup determined that the condition was medical serious but were concerned that the case definition and spectrum of the disorder were still unclear. Although psychosine testing helps identify positive cases, some genotype-phenotype correlation with alleles is known to be associated with the infantile form but some infantile cases can be difficult to differentiate from late infantile form. The Nomination and Prioritization Workgroup asked the nominators to provide additional information for all known individuals with Krabbe disease from published and unpublished sources and reviewed a study that was published during the nomination package review. Based on the available information, the Nomination and Prioritization Workgroup determined that the screening tests were reasonable and appropriate for newborn screening, with no known false negatives reported and a reasonable second-tier approach using psychosine.

The Nomination and Prioritization Workgroup also determined that those most likely to benefit from treatment were identifiable through second-tier and confirmatory testing. There are a number of patients who had slightly elevated psychosine with variant of uncertain significance alleles and are currently being followed to determine whether they are carriers or have a later onset disease. Importantly, studies showed that treatment within the first 30 days of life results in the best outcomes. The Nomination and Prioritization Workgroup considered the availability of defined treatment protocols to be unclear, with only nine of 100 pediatric centers in the United States conducting transplants for lysosomal storage diseases and not all of them have experience with Krabbe disease. The centers with Krabbe disease experience are willing to help those that do not; however, there may be logistical challenges involved with out-of-state transplants.

A study showed that transplantation within six weeks of life resulted in improved developmental outcomes, including significantly improved language and cognitive skills and some continued motor challenges. Although the study described the children as doing well, more specific data on developmental outcomes was still needed, specifically on motor skills, longer-term follow-up, and treatment within 30 days of life.

Based on this, the Nomination and Prioritization Workgroup recommended that the nomination for the addition of Krabbe disease to the RUSP move forward for a full evidence-based review and public health impact analysis.

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

- A Committee member said that the decreased number of false positives that was shown in this nomination as compared to the previous nomination was helpful for moving the nomination forward.

A Committee member moved for a vote to accept the recommendation for a full evidence-based review of the Krabbe disease nomination. The motion was seconded, roll was called, and the motion passed unanimously.

Dr. Powell thanked the Committee for their thoughtful consideration and will assign Krabbe disease to the Evidence-based Review Group. The Committee has nine months to complete the

evidence-based review and vote on whether or not to recommend Krabbe disease for addition to the RUSP.

Updates on Newborn Screening Family Education Program

***Natasha Bonhomme,* Founder, Expecting Health*;* Chief Strategy Officer, Genetic Alliance**
***Marianna Raia, MS, CGC,* Associate Director of Programs, Expecting Health**

Ms. Natasha Bonhomme introduced the Newborn Screening Family Education Program, a HRSA-funded initiative, and the program's vision, purpose, and objectives. The program focuses on the education, engagement, and training of families and recognizes that multiple approaches at multiple levels are required to ensure that families learn and can apply this knowledge into their child's health care.

The program has consistently met their goals. They have trained 234 families, developed formal partnerships with 25 organizations to disseminate information, cultivated 12 community ambassadors across 10 states, and reached more than 3,000 medically-underserved individuals. Ms. Bonhomme talked about some of the specific activities that the program conducts and highlighted their prenatal education initiatives and social media outreach campaigns. She emphasized the need for multiple strategies to achieve success and the need to meet families where they are through community partnerships and innovative online and in-person approaches.

Ms. Marianna Raia talked about the importance of prenatal education as a critical time period for families to learn about newborn screening. They have found that receiving prenatal information about newborn screening from a health care provider increased parent satisfaction and trust. Additionally, parents stated that they want to receive this information prior to labor and delivery rather than learning about newborn screening after the screen has already been conducted. The American College of Obstetrics and Gynecology (ACOG) recommended and provided guidance on prenatal education on newborn screening. Despite this, prenatal newborn screening education is not commonly practiced among prenatal health care providers because providers were often very busy and families were already overwhelmed with information.

The Newborn Screening Family Education Program initiated a pilot program to increase awareness about the importance and process of newborn screening during prenatal period, particularly for medically-underserved populations. They also aimed to assess the accuracy of knowledge about how, when, and why newborn screening occurs and the information that was provided when a family received an out-of-range result. In the development of the pilot, they collaborated with communities to ensure that their materials were culturally- and linguistically-relevant and leveraged trusted relationships with health care providers. They developed practical and relatable materials and incorporated them into existing workflows to reduce the burden of new information during an already overwhelming time.

Ms. Raia talked about the specific steps of the pilot program. They partnered with community-based prenatal groups that were already working with expecting mothers. They administered a brief pre-test assessment and then provided an education booklet on the importance of newborn screening, the potential results that they might receive, and a list of resources. After the mothers

read the booklet, they were given a post-test assessment to evaluate the effectiveness of the information.

Their first pilot was conducted in a high-risk obstetrics clinic in Texas that served a primarily Spanish-speaking population. Their second pilot was conducted in a community health clinic in Indiana that served primarily Amish and Mennonite families. Because these communities were so different, the pilot was implemented using tools that were most familiar to the populations. For instance, they used digital information and assessments in Texas but provided paper versions through midwives during home or birthing center visits in Indiana. They plan to conduct a third pilot for a tribal community in Oklahoma and work towards creating a model for wider dissemination across other prenatal care centers.

Ms. Raia shared initial positive results from their pilots where participants reported significantly increased awareness, knowledge, and confidence in finding more information or talking to their doctors.

Some of learned lessons included that integrating information into workflows and the flexibility to create culturally-relevant and relatable materials and processes were important to their success. Other prenatal groups and state newborn screening programs had reached out with interest in implementing an education program. In the future, they would like to conduct longitudinal studies to demonstrate the long-term impact of their education materials.

Ms. Raia reviewed the Newborn Screening Family Education Program social media campaign that they initiated to expand their reach to younger adults. Their phase one approach aimed to determine how to reach a target audience (i.e., age, gender, medically underserved communities) within a 30-day campaign. They completed phase one in August 2021, which resulted in reaching 67 percent (approximately 2 million individuals) of individuals who met the target audience criteria. A six-month long phase two launched in March 2022, aimed to determine how best to reach individuals with an expressed interest in pregnancy or are currently expecting and to share their informational booklet.

Ms. Raia summarized that innovative strategies can be used to reach families and that using trusted partners was a key component to success. They are currently partnering with midwife and doula groups and university programs and hope to share their results with the Committee in the future.

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

- A Committee member asked how they defined newborn screening in their informational booklet and if the booklet would be available outside of their program in the future. The Committee member also asked whether they experienced any challenges working with prenatal providers. Ms. Raia answered that their definition of newborn screening was general because it is a national effort. The booklet defined the screening period as between 24 and 48 hours after delivery and included a guide for results and additional resources. The booklet is available to anyone via both digital and paper forms. She said their pilot did not require the provider to provide the additional education but rather to

stress the importance of the information. Providers were open to leveraging clinical staff and midwives to provide education and individuals themselves read the materials. Therefore, there was not much burden placed on providers.

- A Committee member said that transitioning this effort into a real world experience would require consideration for how it would be paid for and who would be conducting it. Genetic counselors already had very tight schedules. The results of the pilot are encouraging and the next step may be to make the link available and conduct a real world study to determine these practical issues. The Committee member was familiar with the Plain populations, who may already be knowledgeable about newborn screening because of the potential cost they may have to bear. The Committee member asked how they see moving this program into the real world setting.
    - Ms. Bonhomme said that they are always thinking about sustainability. Public health initiatives such as these often fall under federal and state agencies. Sometimes private companies will fill an educational gap. There was an opportunity to follow other models of public health education support and validation, particularly from federal agencies such as CDC or HRSA's Maternal and Child Health Bureau. Education should not be tagged onto a newborn screening program but rather integrated into the system.
    - Ms. Raia added that they were excited to partner with state programs that have expressed interest. The next step may be to implement at the state-level.
    - The Committee member suggested that they share any lessons they learn from these state partnerships.
- A Committee member said that the advocacy community talked about having to go from state to state to make changes to their newborn screening programs and asked if the education component would also have to be conducted at the local and state levels rather than at a national level, such as through ACOG.
    - Ms. Raia suggested that it would take both a national approach to determine what information should be shared and a local approach to disseminate information.
    - Ms. Bonhomme added that it would take investment at each level. Not every step needed to be replicated. For instance, new content does not necessarily have to be created and successful programs can be modeled for others. The question is of investment. Each state is different and their program is at the beginning stage of learning how to partner with states and how to share models.
    - The Committee member said that it was important to stress both the materials and the process (i.e., identifying champions or defining roles) that should be modeled using lessons learned from other public health activities.
    - Ms. Bonhomme said they conducted an extensive needs assessment in their first year to determine how to present the materials. She agreed that it was important to focus not only on the "what" but also the "how."
- A Committee member asked if they conducted the pre- and post-test assessments under an informed consent process and if they experienced any barriers to gaining buy-in from practitioners to conduct the assessments. Ms. Raia answered that their initial pilot site is part of the University of Texas health care system. They did undergo an institutional review board process and it was submitted and approved as a quality improvement project. They did not, by design, collect specific demographic information to reduce those barriers. When they replicated the process in other locations, it was integrated into

the clinic as quality improvement and therefore did not need to go through the consent process.

- A Committee member asked if their social media campaign attempted to address some of the challenges that can arise from groups that aim to message the potential negatives of newborn screening or if their focus was only on positive messaging and their educational information.
    - Ms. Raia answered that their 30-day social media campaign included simple advertisements to generate interest and nothing else. There were no negative messages. It was too early to tell if this will become an issue in their six-month effort but to date there have not been any issues.
    - Ms. Bonhomme added that the best way to combat negative information in social media is by flooding the market with more of their messages. As they consider the sustainability of the program, they understood that there may be other campaigns that will spend millions of dollars to flood the market with their messages. They hoped to know more at the end of their six-month campaign.
- An organizational representative talked about the effort in their state on prenatal education of newborn screening had not been very successful in reaching target audiences and hoped that this program will be generalizable. The organizational representative suggested looking into whether families retain the information they learn at the end of six months.
- An organizational representative asked whether they had plans to reach out to the prenatal special interest group at the National Society of Genetic Counselors (NSGC) to facilitate the time constraints they may face in providing these services. They may be able to help facilitate a freestanding education program. The organizational representative also asked if they received any resistance from the lay midwives in the Plain population and suggested working with the Plain Community Health Consortium to help expand their program. Ms. Raia answered that they had shared a toolkit of all of their resources with NSGC. They had not experienced resistance from midwives but that may be because they worked with a champion within the community who was already connected to the midwives. This spoke to the importance of working with trusted partners who have relationships with the community. The midwives had reached out for additional information.
- An organizational representative said that obstetrical care is very structured and programmatic. A key for this program to be implemented may be through ACOG and the American Academy of Family Providers (AAFP). Because there are certain things that must happen at certain visits, it would be helpful to provide a flowchart of their workflow to show that it could be incorporated into their current processes without adding to what the provider already has to do or any other automated function such as a link to information. Additionally, changes could be made by including it in training programs because younger doctors who take the training will incorporate the information into their practices. Innovation is spread through early adopters.
- An organizational representative talked about the Plain community and their effort to provide prenatal and preconception information to this population. The Plain Insight Panel conducts carrier testing for a number of common variants. There had been significant interest for variant testing from the Plain community that was possibly ahead of other populations.

- Dr. Powell talked about the value of adding a new condition and the challenge of not having a group of diversified members of the public who were aware of and knowledgeable about newborn screening. She asked if they had encountered individuals who might be available to advise the Committee on their experience during evidence review of new conditions.
    - Ms. Bonhomme answered that members of their Ambassador program represented a widely diverse population of individuals interested in newborn screening for different reasons. Many are thinking in terms of systems level changes and are more connected to what the public thinks. They may also be interested in specific conditions but what is special about their Ambassador program is that they consider the entire system, from what happens during screening to clinical care and follow-up.
    - Ms. Raia added that some of their Ambassadors often join the Committee meetings as viewers.
    - Ms. Bonhomme said that it was important to remember that the public cannot be placed into one bucket because they individually have different concerns and motivations. Just as there is no one clinician to speak to all aspects of newborn screening, there is no one member of the public to represent all of public input. It required looking across trends and perspectives.

New Business

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

Dr. Powell thanked Committee members and said that the next Committee meeting will take place on August 30 and 31, 2022 and is planned to be in person.

Adjourn

Dr. Powell adjourned the Committee meeting at 12:40 P.M. E.T.