Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Minutes of August 12-13, 2021

Virtual Meeting

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DAY ONE: Thursday, August 12, 2021

Welcome, Roll Call, Committee Business

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

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

Committee members in attendance were:

- Dr. Kamila Mistry (Agency for Healthcare Research & Quality)
- Dr. Mei Baker
- Dr. Kyle Brothers
- Dr. Jane DeLuca
- Dr. Carla Cuthbert
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Michel Warren/Ms. Joan Scott (Health Resources & Services Administration)
- Dr. Shawn McCandless
- Dr. Melissa Parisi (National Institute of Health)
- Ms. Annamarie Saarinen
- Dr. Scott Shone
- Dr. Cynthia Powell

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 and Genomics, Dr. Max Muenke
- Association of Maternal and Child Health Programs, Dr. Jed Miller
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health, Dr. Christopher Kus
- Association of Women's Health, Obstetric & Neonatal Nurses, Dr. Shakira Henderson
- Child Neurology Society, Dr. Jennifer Kwon
- Department of Defense, Dr. Jacob Hogue
- Genetic Alliance, Ms. Natasha Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Gerard Berry

Dr. Powell welcomed Dr. Gerard Berry, who will replace Dr. Georgianne Arnold as the organizational representative for the Society of Inherited Metabolic Disorders. Dr. Berry is a biochemical geneticist

and pediatric endocrinologist. He serves as the Harvey Levy Chair in Metabolism and Director of the Metabolism Program at Boston Children's Hospital, a professor of pediatrics at Harvard Medical School, and Director of the Harvard Medical School Biomedical Genetics Training Program. He is President of the Society for Inherited Metabolic Disorders.

Mucopolysaccharidosis Type II (MPS II) Evidence Review - Phase 1 Update

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

Dr. Alex Kemper presented on behalf of the Evidence-Based Review Group (ERG) on newborn screening for mucopolysaccharidosis type II (MPS II). MPS II was nominated in May 2021 and the ERG convened a technical expert panel (TEP) to gather additional information and advise on any unpublished data that would help them understand context and make an informed decision. This is the first interim presentation; another is scheduled for November 2021 and the final presentation will be made in February 2022.

MPS II is an X-linked lysosomal inborn error of metabolism caused by deficiency of the enzyme iduronate 2-sulfatase (IDS). This deficiency creates an accumulation of specific glycosaminoglycans (GAGs). There are over 500 mutations associated with the IDS gene, many of which are private mutations, creating a challenge in predicting a phenotype. The prevalence for this disorder ranges from 0.2 to 2.5 per 100,000 live births, varying across different states that are screening for MPS II.

There are different classifications of MPS II based on severity and clinical presentation. Severe disease typically has progressive multiorgan and joint damage, cognitive impairment and regression, and is diagnosed in early childhood with death occurring in the late teens to 20s. About two-thirds of all cases are considered severe. Attenuated disease typically involves a later diagnosis but can also show progressive multiorgan involvement. Individuals with attenuated disease may live into adulthood and experience later death, which may be associated with the lesser degree of central nervous system (CNS) comorbidity. Dr. Kemper reiterated that attenuated disease is not benign and that there is a wide spectrum of the disease. Pseudodeficiency is a classification not associated with morbidity or mortality and should be ruled out to avoid unnecessary treatment. Dr. Kemper pointed out that phenotype is not typically predictable at the time of diagnosis because of the many private mutations.

There are two approaches to screening MPS II, both of which measure enzyme activity. One approach is tandem mass spectrometry assay multiplexed with other non-MPS II markers. The other is using a microplate fluorometric assay that is not multiplexed. After a positive screen, the first step is to confirm enzyme activity to measure GAGs. This can also rule out pseudodeficiency and multiple sulfatase deficiency.

One treatment approach is enzyme replacement therapy through idursulfase delivered intravenously (IV), which was approved by the Food and Drug Administration (FDA) in 2006 and has become standard therapy. The TEP advised that enzyme replacement therapy should begin as soon as possible after diagnosis because once GAGs have developed the damage has been done. There is a risk of developing antibodies to the enzymes, for which they are currently reviewing the evidence to determine how this affects treatment effectiveness. Another treatment approach is hematopoietic stem cell replacement transplantation, which is not considered a major

therapy because of the risk of mortality and the lack of clear neurodevelopmental benefit. There are also some novel therapies in development.

Dr. Kemper highlighted information on the drug label for ELAPRASE (the brand name for the enzyme replacement therapy), which states that the drug did not show improvement in disease-related symptoms or long-term clinical results in patients 16 months to 5 years old but did reduce spleen size similarly to patients aged 5 and older. The label also states that it is not known if the drug is safe and effective in children under 16 months old. Although this language may cause concern about newborn screening, post-marketing studies have since provided much more clinical information since the drug was first FDA approved. Dr. Kemper said that it would be challenging to enroll participants for a trial to support new label language.

Dr. Kemper reviewed studies of the safety and effectiveness of enzyme replacement therapy. In one study, all of the participants were able to continue with the therapy, which is an important consideration. In another study comparing early and late treatment in siblings, researchers found that the sibling treated at four months of age had significantly better outcomes in facial appearance, joint stiffness, and severity of intellectual disability than the sibling who was treated at three years of age. Since the enzyme replacement therapy does not cross the blood-brain barrier, the difference in the developmental quotient was interesting but might be explained by increased stimulation in the absence of joint stiffness.

The ERG is looking at both published and unpublished data, some of which comes from the Hunter Outcome Survey of more than 1,000 individuals with MPS II. This survey describes natural history, treatment history, and patient- and parent-reported functional outcomes. Future data will also come from the ScreenPlus study, which includes screening for MPS II and will hopefully begin soon. There are also international studies and open-label, uncontrolled trials to consider.

Dr. Kemper reviewed Missouri's full population screening program that started in 2018. They used a benchtop fluorometric test as a first assay to separate positives from negatives. The cost per unit is about $5, although this number needs to be further evaluated and is only shared with the Committee to provide an idea of cost. The Missouri program did not find that a second-tier test was particularly helpful, but Dr. Kemper is working with them to develop an algorithm to understand each step in the testing. In 2020, they screened 86,000 newborns and found 20 cases of pseudodeficiency prior to referral and another 12 cases that were referred. Dr. Kemper also reviewed the Illinois program that began in 2017 using tandem mass spectrometry multiplexed with other lysosomal storage disorders. By the end of May 2021, they had nearly 560,000 specimens, 72 of which were positive and 23 of those due to pseudodeficiency. In both the Missouri and Illinois program, no positive females were identified.

The ERG conducted a literature search resulting in 4,000 articles. They are looking at natural history, epidemiology, clinical validity, multiple treatment outcomes, and safety and effectiveness for early treatment as compared to case detection. They will eventually move to an evaluation of the potential impact on the screened population and are considering modeling and outcome measures. They are also working with colleagues to assess readiness and feasibility, and they will compete a cost assessment of the two screening methods.

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

- A Committee member asked about the incubation time for the microfluidic method. Dr. Kemper answered that his understanding is that it is a few hours, which is an important consideration for cost and the implication for other newborn screening programs.
- A Committee member asked how variability was accounted for in the rate of progression. Dr. Kemper answered that many factors are involved in a neurodegenerative disorder, some of which are outside of CNS involvement but still impact neurodevelopment. For instance, challenges in movement will impact neurodevelopment. There will be no single metric. There are standard metrics, and they are cataloging everything as they learn.
- A Committee member asked if the Committee would have an update on the current status of gene therapy efforts at the final evidence review. Dr. Kemper answered he will provide an update of the different studies.
- A Committee member asked if the siblings in the study had the same genotype since it was stated that the phenotypes were expected to be similar, or if there was an uneven clinical presentation between siblings. Dr. Kemper answered that common wisdom would suggest they are the same, but that will need to be explored in the data.
- An organizational representative asked if it was easy to distinguish between the less severe form and early onset form in the post-newborn period and what impact that might have for families. Dr. Kemper answered that the disease is a very complicated spectrum disorder and that the terminology (i.e., attenuated, severe, neuronopathic, or non-neuronopathic) does not capture the profound impact on families. As they learned more about the disease, it became harder to classify subjects. Newborn screening and early treatment will change the trajectory of the disease. Enzyme replacement therapy will have a major impact, but the effect on CNS will not be the same and individuals classified as neuronopathic may always be classified as severe.
- An organizational representative asked if the outcome measures of newborn screening would include overall survival or other measures of success. Dr. Kemper said that most severe cases do have higher risk of mortality and there might be a difference in overall survival. There are other patient-centered measures that will be explored with the TEP.

Overview of the Committee's Review of the Evidence Review Process and Proposed Updates

***Alex R. Kemper, MD, MPH, MS,* Lead, Evidence-Based Review Group**
***Cynthia M. Powell, MD, MS, FACMG, FAAP,* Committee Chair**

Dr. Kemper provided an overview of the Committee's review of the evidence review process, which began in February 2019 when the ACHDNC convened an Expert Advisory Panel (EAP) to inform the Committee on approaches to strengthen the nomination, evidence-based review and decision-making process and develop transparent, consumer-friendly guidance. Dr. Kemper presented potential updates categorized by level of actionability: immediately actionable, needs further discussion, needs further research, and needs policy or system changes.

Updates categorized as needs further discussion, further research or needs policy or system change included assessing stakeholder values, making changes to the Public Health System

Impact (PHSI) assessment to consider or assess long-term follow-up plans and anticipated costs for conditions nominated for addition to the RUSP, developing more detailed guidance for deliberations resulting in B-rating on the decision matrix and the review of conditions currently on the RUSP.

Dr. Powell reviewed actionable next steps. In fiscal year 2022, the Committee plans to update the website with consumer-friendly guidance, frequently asked questions, and a revised nomination form that includes additional questions and clarifications on the requested information. In the evidence-based review process, the procedures for assessing both published and unpublished evidence are ready for implementation. The PHSI assessment has been revised and is ready to implement. A new Disorder Readiness Tool also has been developed and a revised process for reporting cost estimates in broad categories will be adopted in fiscal year 2022. Additional guidance is being drafted for the decision matrix process, which the Committee received for review.

Dr. Powell reviewed the major, ongoing issues including the need to revisit the decision matrix to improve communication of the purpose of the matrix and strengthen guidance on B-ratings. There were some key issues that were removed from consideration for feasibility. There is limitation in terms of conducting an in-depth review to address nomination package bias. Expanding the decision matrix to include conditional or provisional recommendations was not feasible. Consideration of multiple conditions was not deemed as actionable in the near future.

Committee Discussion

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

- An organizational representative asked if they were addressing how to include family perspectives. Dr. Kemper noted that in evidence-based reviews the ERG talks to some individuals with the condition and families of children who have the condition to include outcomes that are important to them. It will also be important to hear from families with children who have been tested through newborn screening but may or may not have the condition.
- A Committee member suggested that the need for long-term follow-up has been well established and should move forward with discrete, time-driven actions using lessons learned from the states on implementation. He also suggested that inequities in access to care are well-established and there is a need to be more forward with the issue, potentially collaborating with HRSA's Office of Health Equity. Additionally, the nomination process still drives advocacy groups and scientists into dried blood spot screening and there are opportunities for nominations that look beyond that system.
- A Committee member asked if there will be an opportunity for modification or feedback between this meeting and the November vote. Dr. Powell answered that there will be opportunities for public comment and Committee members will have an opportunity to review specific changes before discussing it at the November meeting.
- A Committee member asked what the need for and goal of the review is. Dr. Kemper answered that the evidence reviews had been conducted for quite some time and over that time it became clear that improvements were needed to increase efficiency and transparency. The Designated Federal Official added that the vote in November will not be an end to the

discussion, which should be ongoing. Dr. Powell suggested that it is always a good idea to review decision-making processes to improve them.

- An organizational representative asked if non-disease specific treatments that may provide benefit over the course of illness could be considered. Dr. Kemper answered that they do assess evidence for early versus later identification in terms of additional, non-disease specific supports.
- An organizational representative asked if there were markers of success for the consumer-friendly materials and commented that equity is important to consider in the nomination process. Dr. Kemper answered that they have a writer ensuring materials are written at the appropriate reading level and that he will obtain guidance from subject matter experts to ensure the materials are accessible.

Public Comment

A. Kim Tumminello

Ms. Kim Tumminello is a family nurse practitioner, the Founder and Director of Advocacy for the Association of Creatine Deficiencies, and the mother of two children diagnosed with guanidinoacetate methyltransferase (GAMT) deficiency. GAMT was first nominated to the RUSP in 2016, but it did not move forward because the criterium for at least one infant being positively identified during a newborn screen was not met. Ms. Tumminello understands the devastating consequences of delayed identification and treatment of GAMT, given that her eldest child first received treatment at 10 months old but her youngest child was identified and received treatment upon birth. While the cost of testing for GAMT is as low as 30 cents per baby, research from the Children's Hospital of Philadelphia (CHOP) suggests that a child with an intellectual disability or autism spectrum disorder costs more than $2 million. Accordingly, Ms. Tumminello believes that GAMT is an optimal disease for newborn screening, and she implored the Committee to move it forward.

B. Heidi Wallis

Ms. Heidi Wallis is the President of the Association for Creatine Deficiencies and works for the Utah Public Health Lab in the Newborn Screening Program. She is the mother of two children with GAMT deficiency and understands first-hand the long-term consequences of delayed treatment. GAMT cannot be easily detected by pediatricians because the condition lacks a hallmark dysmorphic feature or a common symptomatology; therefore, newborn screening or family history is necessary to ensure that children with GAMT receive immediate treatment. Ms. Wallis emphasized that GAMT deficiency is common (with estimates as high as 1 in 120,000 children), easy to screen (through GUAC analysis), and inexpensive (requiring no additional blood spot, instrument, or staff).

C. Nicola Longo

Dr. Nicola Longo is a medical and biochemical geneticist at the University of Utah. He drew comparisons between GAMT deficiency and phenylketonuria, conditions both characterized by normal presentation at birth followed by progressive developmental delays and movement disorders. Consequently, diagnosis often comes too late. GAMT-deficient newborns who receive early creatine therapy—a safe, inexpensive, accessible treatment—may develop typically through childhood and remain unaffected by symptoms of the condition. He strongly encouraged expansion of the newborn screening panel to include GAMT deficiency.

D. Marzia Pasquali
Dr. Marzia Pasquali is a clinical biochemical geneticist at the University of Utah, where her lab developed, validated, and implemented a newborn screening assay for GAMT deficiency. She discussed feasibility of GAMT screening from the laboratory perspective. GAMT screening is performed by measuring creatine and guanidinoacetate in blood spots using mass spectrometry, a technique already used in newborn screening laboratories. Therefore, GAMT screening can be easily integrated into any laboratory workflow without requiring additional samples, instrumentation, or personnel. Both derivatized or non-derivatized methods are effective for newborn GAMT screening, as are second-tier biochemical and molecular tests. Other validated tests can biochemically confirm or exclude GAMT deficiency after a newborn screens positive. Dr. Pasquali concluded that there are no technical barriers to implementation of GAMT deficiency newborn screening.

E. Becky Tribe
Ms. Becky Tribe is the mother of an eight-month-old child who screened positive for GAMT deficiency after Utah implemented statewide screening for the condition. Because her child received treatment at only a week old, he has so far achieved normal development and is meeting standard milestones. Ms. Tribe reiterated that newborn screening for GAMT deficiency is essential and that babies who receive diagnosis and treatment from birth can live healthy, productive lives.

F. Joanne Kurtzberg
Dr. Joanne Kurtzberg is the Jerome Harris Distinguished Professor of Pediatrics, a professor of pathology at the Duke University School of Medicine, and Director of the Marcus Center for Cellular Cures in the Carolinas Cord Blood Bank at Duke. During her career, she and her team have transplanted more than 360 infants and children with leukodystrophies, including 60 patients with Krabbe disease. She announced that in July 2021 they submitted a nomination package to add Krabbe disease to the RUSP. The condition was previously nominated in 2010 and the Committee voted not to recommend addition to the RUSP. In response, the Krabbe Disease Newborn Screening Taskforce at the Hunter's Hope Foundation have systematically addressed and filled gaps identified by the Committee during the evidence review.

Currently, nine states screen for Krabbe disease, and others are working to implement the screen. Multiple medical centers across the country can treat affected newborns with stem cell transplantation, and those who undergo transplant in the first few weeks of life typically lead happy, independent, long lives. Dr. Kurtzberg expressed her belief that Krabbe disease should be added to the RUSP using the effective and efficient screening approach outlined in the recently submitted nomination package.

F. Elisa Seeger
Ms. Elisa Seeger founded the ALD Alliance after losing her son Aidan to adrenoleukodystrophy (ALD) in 2012. She thanked the Committee for adding ALD in 2016 and offered several comments about the review process for new RUSP nomination packages. She cited the EveryLife Foundation for Rare Diseases' Community Congress as a powerful rare disease patient community that advocates for science-driven legislation and policy.

The Community Congress urged the Committee to consider the following recommendations for additional information on the condition nomination form. First, the assessment of the benefit of screening for new conditions should accept a degree of uncertainty regarding available data following treatment approval and should include other information sources such as community insight. They recommended the creation of a central database for long-term newborn screening data. The Community Congress also urged the Committee to update their decision matrix to account for variability in disease trajectory when considering the benefits of newborns screening.

G. Dean Suhr

Mr. Dean Suhr spoke on behalf of the Metachromatic Leukodystrophy (MLD) Foundation. He pointed out that the Committee's focus on thorough, evidence-based review is quite intensive, and in the meantime, newborns fail to receive potentially life-saving screening. He called for systemic changes to the Committee. These include maintenance of high standards while adopting an FDA-inspired approach to considering patient and community voices; redesign of Committee reviews to address the decades-long process from research to public health implementation; and a nomination process that begins with high-value baseline data, undergoes thorough Committee review, and then is jointly assessed for implementation.

Children who receive an early diagnosis of MLD can receive gene therapy, which was approved by the American Medical Association (AMA) last year and is accessible through a compassionate use program. So far, the MLD Foundation has provided screening to more than 100,000 babies in the U.S., two of whom were identified as having MLD. Unfortunately, unidentified children will die from the disease while the RUSP nomination process is underway. Mr. Suhr urged the Committee to design and test new paradigms that satisfy the high bar for evidence-based data while balancing the immediate needs of babies and their families. He briefly mentioned the RUSP Round Table, which will meet again in November 2021.

H. Liesl Broadridge

Ms. Liesl Broadridge is the policy fellow for the EveryLife Foundation for Rare Diseases. This year, the Foundation's newborn screening policy work has continued to focus on aligning federal RUSP recommendations with state implementation and to support stakeholders' preparation for RUSP nomination. This spring, the governors of Georgia, Ohio, and Arizona have signed legislation requiring states to screen newborn babies for any and all disorders on the RUSP. Additionally, the North Carolina House of Representatives passed similar legislation in May, which is pending Senate action.

With respect to stakeholder engagement and capacity building efforts, the Foundation will again partner with Expecting Health to host the third Annual Newborn Screening Boot Camp in fall 2021, which will provide resources and opportunities for cross-sector engagement with community stakeholders. The Foundation has also convened the Community Congress Newborn Screening Working Group to discuss revisions to the evidence review process and data requirements of studies conducted for RUSP nomination. The EveryLife Foundation therefore urges the Committee to create a suite of stakeholder-targeted education materials that identify changes to the evidence review process in the context of the newborn screening system. They

also encourage the Committee to establish a multi-stakeholder working group that includes representatives from the patient community.

Guanidinoacetate Methyltransferase (GAMT) Deficiency Nomination Summary

***Carla Cuthbert, PhD* on behalf of the Nomination & Prioritization Workgroup; Ex-Officio Committee Member - Centers for Disease Control and Prevention (CDC)**

Dr. Carla Cuthbert presented the findings of the Nomination and Prioritization Workgroup review of the nomination package for GAMT deficiency for inclusion on the RUSP.

GAMT is one of the enzymes involved in the synthetic pathway for the formation and uptake of creatine, which is important for tissue functioning, maintaining an energy supply, and neurotransmitter functioning in the CNS. Importantly, about half the creatine in the body is derived from this synthetic pathway and the other half is derived from dietary sources. Homozygous or compound heterozygous mutations in the GAMT gene can result in GAMT deficiency. The pathophysiology of GAMT deficiency, especially the biochemical phenotype, is a reduction of creatine and a marked increase in neurotoxic guanidinoacetate (GAA) in both plasma and urine. The onset of clinical presentation can occur between the first few months to the first few years of life and involves a number of clinical features such as cognitive impairment, developmental delay, speech delay, and hypotonia. Some children will also experience seizures (varying in severity), movement disorders, and developmental disabilities (such as autism spectrum or autoaggressive behavior). There are two treatment approaches for GAMT deficiency—restoring the creatine pool through high-dose creatine and S-adenosylmethionine supplementation or reducing GAA through increased ornithine supplementation and adding sodium benzoate to bind with and excrete accumulated glycine.

Dr. Cuthbert reviewed the key questions used to evaluate the suitability of the nomination package. These questions addressed if 1) the nominated condition was medically serious, 2) the case definition of the condition was well-described, 3) there were available prospective pilot data, 4) the screening tests had analytic validity, 5) the characteristics of the screening tests were reasonable to include, 6) there was an approved confirmatory diagnostic process, 7) there were defined treatment protocols, and 8) the treatment results showed clinical utility.

The Nomination and Prioritization Workgroup found that based upon the information provided in the nomination package GAMT deficiency is a medically serious condition. The second question was resolved because the clinical presentation of GAMT deficiency is well described and can help predict a phenotypic range of children identified from population-based screening. GAMT deficiency is a very rare condition, but with more widespread newborn screening, the full spectrum of phenotypic presentation will be more evident.

In response to the third key question, there have been ongoing, population-wide screening in two states and in two programs in other countries. These screening activities began several years ago and, during that time, two newborns were identified with the condition. She pointed out that the primary newborn screening assay could be multiplexed with the amino acid and acylcarnitine analysis and the second-tier test involved liquid chromatography to separate out any interference, which is another approach for detecting GAA and creatine.

The fifth key question addresses reasonable characteristics of the screening test, such as whether or not there is a low rate of false negatives. Across the established programs, there have been no known false negatives and second-tier tests are available to reduce false positives. The programs maintained close relationships with the metabolic programs within their state, therefore there was reasonable certainty they would be aware of any missed cases. One of the states had a high number of referrals, which prompted the Workgroup to question the underlying reasons for a high number of false positives. The program had found that there was interference in their 2019 testing and made modifications to that test to eliminate it. They validated their procedure and implemented it in 2020, which markedly reduced the number of false positives. There are also widely available CLIA or FDA-approved confirmatory tests, which addressed the sixth key question.

The Nomination and Prioritization Workgroup considered the availability of an FDA approved treatment. They found that the supplements were easily accessible and that most insurances cover the cost with proper preauthorization. Dr. Cuthbert pointed out that it is important that treatment is provided early in life to ensure normal or near-normal development, and then maintained throughout the child's life.

Dr. Cuthbert reiterated that intellectual disability can be prevented if infants are treated within the first month of life. Treatment after one month of age is still effective but may not totally reverse the intellectual disability. Consequently, these results do support clinical utility.

Dr. Cuthbert summarized the Workgroup's findings, which was that all but the fifth key question were answered affirmatively. The fifth key question was considered unclear. Based on this evaluation, the Nomination and Prioritization Workgroup recommends the Committee move forward with a full evidence-based review of GAMT deficiency.

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

- A Committee member asked about the third patient in the case series, who had a break in treatment and experienced poorer outcomes. Dr. Cuthbert said this highlights the importance of maintaining treatment in newborns.
- A Committee member wondered if there were guidelines for defining the "rareness" of a disorder in the context of the RUSP. Another Committee member said that rareness likely will not prevent disorders from being considered.
- Committee members agreed that the performance of the screening test becomes more important as the condition becomes more rare to minimize the false positive rate. The discussion should include not only the performance of the screening test but also the next steps in the diagnostic testing regimen, particularly for disorders with a high rate of false positives.
- An organizational representative added that the ERG has always accounted for the rarity of the condition in that they evaluate the performance of the test for positive and negative predictive value, sensitivity, and specificity. He pointed out that disease incidence may rise as more people are identified presymptomatically. From the professional perspective of another organizational representative, "rare" means that a practitioner may never or only

once see a case of the disease. She agreed that the true incidence of these disorders currently are unknown.
- Organizational representatives concurred that diagnostic yield for creatine deficiencies may increase if diagnosis were conducted by dried blood spot, which is already collected for other metabolic testing, rather than just by urine.
- A Committee member stressed that urine samples are useful for other creatine deficiency disorders in addition to GAMT.
- A Committee member argued for careful reevaluation of conditions included on the RUSP using the current level of evidence review. Some conditions historically included on the RUSP have not undergone the same amount of scrutiny as newly added conditions.
- To balance the benefits and drawbacks associated with screening for very rare diseases, a Committee member suggested developing a scoring system.

A Committee member moved for a vote to move GAMT forward for full evidence-based review. The motion was seconded, roll was called, and the motion passed unanimously (one Committee member was absent). The ERG has nine months to complete the review and vote on whether or not to recommend GAMT deficiency for addition to the RUSP.

Emerging Issues in Newborn Screening

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

Dr. McCandless reviewed emerging issues in newborn screening to provide context for Committee discussion. He urged members to consider the tradeoffs associated with a slower, more deliberate decision-making approach versus an expedited approval process. He also asked them to address the capacity of this Committee to conduct the necessary work as the number of nominations continues to increase. Last, Dr. McCandless pointed out that the RUSP nomination process may favor stakeholders who have more resources and limit stakeholders who have fewer. He encouraged Committee members to consider fairness and equity in a system that prioritizes large, well-funded organizations over smaller advocacy groups or patient communities.

Committee Discussion

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

- A Committee member agreed that resource availability is a significant limiting factor and expressed support for multiplexed review. He encouraged the Committee to consider ways to address health equity and underrepresented populations more broadly.
- A Committee member echoed support for multiplexed review. She also felt that the newborn screening paradigm may benefit from prioritization of genomic analysis before biochemical enzyme assay, given that most of the target conditions are genetic. In this approach, molecular analysis would occur first, and biochemical assay would occur second to supplement and verify results.
- Regarding practical approaches to multiplexing, a Committee member said that a family of conditions may share a similar clinical phenotype and group of biomarkers that could be evaluated together on a single platform. Testing should be linked to clinical phenotyping.

- An organizational representative expressed concerns about resource and workforce capacity to deliver treatment for the substantially higher number of conditions identified through multiplexing. Although every baby deserves high-quality care, systems may push back on multiplexing given funding constraints for expensive treatments. She encouraged the Committee to consider the role of newborn screening within the health care system more broadly.
- An organizational representative addressed a potential shortcut by which FDA-approved conditions could automatically be considered a treatable condition. She urged caution in consideration of the different types of FDA approval; for instance, accelerated approvals entail a meaningful change in as surrogate endpoint followed by post-approval studies to demonstrate effectiveness.
- A Committee member added that FDA approval does not necessarily confer readiness for newborn screening in light of the basic tenet that presymptomatic therapy is preferable to clinical identification. An organizational representative agreed, pointing out that FDA approval does not indicate presymptomatic effectiveness. She emphasized that the Committee should remain sensitive to individual variations and treatments of particular disorders, even those similar enough to be multiplexed.

DAY TWO: Friday, August 13, 2021

Welcome and Roll Call

Dr. Powell welcomed participants to Day 2 of the August 2021 ACHDNC meeting.

Dr. Powell then conducted the roll call. The Committee members in attendance were:

- Dr. Kamila Mistry (Agency for Healthcare Research & Quality)
- Dr. Mei Baker
- Dr. Kyle Brothers
- Dr. Jane DeLuca
- Dr. Carla Cuthbert
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Michel Warren (Health Resources & Services Administration)
- Dr. Shawn McCandless
- Dr. Melissa Parisi (National Institute of Health)
- Ms. Annamarie Saarinen
- Dr. Scott Shone
- Dr. Cynthia Powell

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 and Genomics, Dr. Max Muenke
- Association of Maternal and Child Health Programs, Dr. Jed Miller
- Association of Public Health Laboratories, Dr. Susan Tanksley

- Association of Women's Health, Obstetric & Neonatal Nurses, Dr. Shakira Henderson
- Child Neurology Society, Dr. Jennifer Kwon
- Department of Defense, Dr. Jacob Hogue
- Genetic Alliance, Ms. Natasha Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Gerard Berry

National Registries for Hemophilia and Childhood Cancer

Dr. Powell provided an overview of registries for conditions identified through newborn screening and their importance for demonstrating the impact of early identification across the life course and to improve screening and follow-up services.

Community Counts Bleeding Disorders Surveillance

***Vanessa R. Byams, DrPH, MPH*, Lead Health Scientist, Division of Blood Disorders, CDC**

Dr. Vanessa Byams presented on Community Counts, a CDC-funded public health monitoring program to surveil and share data on bleeding disorders.

CDC has long collaborated with the bleeding disorders community to monitor prevalence and complications of these conditions. In 1975, HRSA received a Congressional appropriation to develop a program to support an integrated regional network of Hemophilia Treatment Centers (HTCs). Seven years later, Congress funded CDC for provision of AIDS risk reduction services for people with hemophilia and others who use blood-based treatment products, and CDC partnered with the HTC network. In 1995, CDC established a Hemophilia Surveillance System, which found that patients receiving care at HTCs were 60 percent less likely to die and 40 percent less likely to be hospitalized for complications than those treated at other facilities. The Universal Data Collection (UDC) Surveillance System followed to monitor HIV and blood-born viral hepatitis in patients with hemophilia. The Community Counts initiative was established in 2011 and has expanded the focus of the previous two iterations of surveillance.

The purpose of Community Counts is to collect and share information about health indicators and complications that affect people with hemophilia and other bleeding disorders receiving care at more than 140 HTCs in the United States. Baseline data are collected at the initial visit and updated during annual subsequent visits. Community Counts also conducts specimen collection to screen for the presence of inhibitors, which can reduce treatment efficacy. The three main components of Community Counts are the HTC Population Profile, the Registry for Bleeding Disorder Surveillance, and Mortality Reporting.

The project is a collaborative effort funded through a cooperative agreement awarded to the American Thrombosis and Hemostasis Network (ATHN), a nonprofit organization whose mission is to use technology to advance care and research for people with bleeding disorders. CDC’s role is to provide resources, scientific and programmatic guidance, laboratory testing, and technical assistance to ATHN and HTCs.

Dr. Byam described the strengths of this system. For one, the longstanding collaboration among HTCs, ATHN, and CDC has supported the impressive scope and longevity of the surveillance program, which has facilitated longitudinal data collection and specimen integration for trends and outcomes analyses. Additionally, participation at HTCs is high, and the system remains flexible to respond to emerging health priorities and new treatment products. Challenges include constant fluctuations in the treatment landscape. Additionally, there remains a need to fully harmonize the original registry data forms with the new electronic data infrastructure, although the project has made significant progress on these efforts in recent years. Delays related to informatics system dysfunction impeded early data dissemination efforts, the project has since released a Community Counts Data Visualization Tool that interactively displays deidentified patient data.

Strategies Promoting Success: Hemophilia Treatment Center Perspectives

***Judith R. Baker, DrPH, MHSA*, Public Health Director, Center for Inherited Blood Disorders; Regional Administrator - Western States/Region IX Hemophilia Network; Director, Public Health-Pacific Sickle Cell Regional Collaborative; Director, Public Health-Networking California for Sickle Cell**

Dr. Judith Baker discussed key factors that promote registry funding and sustainability for heritable disorders, particularly hemophilia and sickle cell disease. She described a longstanding regional model of care that began with 26 Centers of Excellence in the late 1970s and has since expanded to more than 140 Centers. The model centers the patient, who is surrounded by a core team of a hematologist, nurse coordinator, nurse practitioner, physician assistant, social worker, and physical therapist. In recent years, the core team has expanded to include data managers and clinical research associates to implement and manage the Registry. The services they provide include diagnosis, treatment, prevention, education, counseling, outreach, surveillance, pharmacy services, and care coordination across clinical and community settings.

She described the value of a regional model. Clinical experts in rare genetic disease are scarce and isolated, therefore regionalization is a critical solution to building a sustainable infrastructure and sharing expertise nationwide. The U.S. HTC Network (USHTCN) has established regional core centers in each of the eight HRSA regions, run by regional leadership who are responsible for oversight, technical assistance, onboarding, tactical response to emerging needs, and capacity building. The HRSA National Hemophilia Program Grant emphasizes access to these regional networks of coordinated comprehensive care, with a focus on evaluation, quality improvement, and communication.

She described several other registries under the USHTCN, including the Hemostasis and Thrombosis Dataset (HTDS), the US HTC Network Patient Satisfaction Survey, and the Regional Comprehensive Care Data Set. These primarily are funded through reinvested income from the 340B program. Dr. Baker highlighted the Guam hemophilia program as an exemplar of the value of regional care models for supporting HTCs across distance, insurance status, and health care availability.

She stressed that insurance status limits patient access to HTCs, thereby skewing registries and data collection towards insured patients. Dr. Baker also reviewed a model developed by Mary

Haines that aims to explain mechanisms and causal pathways of successful networks and registries. In the context of this model, characteristics of success include eternal support, perceived leadership, internal management, and well-designed quality improvement activities. Last, she presented Damschroder's Consolidated Framework for Implementation Research.

She briefly reviewed related efforts to address sickle cell disease, another heritable blood disorder within the purview of the Committee. The HRSA Sickle Cell Treatment Demonstration Project worked with five regions across the country, representing 13 states, to improve coordination and service delivery for individuals living with sickle cell disease. In 2018, they created a State Action Plan for California that named surveillance registries as a key priority alongside clinical care.

To conclude, Dr. Baker highlighted the importance of capacity and sustainability, workforce diversity, and regionalization of registries. Critically, registries should be embedded within the entire public health framework for rare disorders to ensure successful implementation and long-term sustainability of these essential programs.

The National Childhood Cancer Registry: Challenges and Solutions

***Lynne Penberthy, MD, MPH*, Director, Surveillance, Epidemiology, and End Results; Program Associate Director, Surveillance and Research Program Division of Cancer Control and Population Sciences/National Cancer Institute**

Dr. Lynne Penberthy discussed the National Childhood Cancer Registry (NCCR), the purpose of which is to leverage and link disparate data sources to create an infrastructure to support research on childhood cancer. The core data are derived from cancer registries and have expanded to include relevant clinical information such as treatment, genomic characterization of tumors, trajectory of care, and social determinants of health. These are integrated within the Childhood Cancer Data Initiative (CCDI), a federated data system sponsored by the National Cancer Institute.

The NCCR leverages existing data sources to capture information on all pediatric and young adult cancers in the U.S. Reporting to the registry is HIPAA exempt, and all states mandate that health care providers report cancer-related information on diagnosis, treatment, and outcomes to the state or general regional registry. The current participating registries represent about 77 percent of all U.S. childhood cancer cases from 23 states.

Dr. Penberthy described critical components of the NCCR. Routine linkages will be performed centrally via an honest broker with external data sources, and the first will capture complete abstracts on each cancer case and text documentation from 1995 to present. NCCR also links with the National Death Index, State Vital Records, and LexisNexis. They also intend to capture financial toxicity to understand the economic impact of cancer on patients and their families.

Other critical linkages are the Virtual Pooled Registry and Planned Central Linkages, which includes pharmacy data from CVS, Walgreens, Rite Aid, and United HealthCare. Claims data linkages enable the NCCR to capture detailed treatment and comorbidity, and they plan to expand this capacity by proposing linkage with a large subset of Medicaid data. NCCR links with Ambra Health and AIM to obtain radiology reports and images, as well as genomic data and

biomarkers from Foundation Medicine and Caris Life Sciences. NCCR also captures birth records, which can provide important insight into early childhood factors (e.g., maternal smoking) that may be associated with cancer. Dr. Penberthy reviewed several data analyses that characterize the tremendous value of these linkages.

She explained the NCCR workflow. Each participating registry has its own virtual server within an enclave hosted by an information management contractor, ensuring that the central component of the NCCR receives only deidentified data for access by researchers and individuals. The NCCR data platform is specialized to support cohort discovery, simple linkages, privacy, and complex structures.

Dr. Penberthy then reviewed considerations for data access and release. The mission of the National Cancer Institute is to allow open access to cancer surveillance data across all registries in the program within the constraints of the NIH data-sharing policy framework. Of utmost importance is protection of patient confidentiality and minimization of risks for inappropriate data use. Important considerations include high risk for patient reidentification given the rarity of these tumors. To mitigate this risk, the NCCR has developed a tiered system for data release with the potential requirement for Institutional Review Board (IRB) review, as well as a data release system linked to the central authentication and authorization process at NIH. They also have hired an external consultant to formally assess and mitigate risk.

Dr. Penberthy emphasized the importance of partnerships between registries, state legislatures, and health departments. Registries can work directly with legislators to create or modify reporting requirements that meet the evolving needs of health surveillance systems.

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

- A Committee member wondered about the cost to establish similar systems for newborn screening disorders and the potential value of existing infrastructures to expand to other disorders. He also wanted to know about the timeline for establishment of USHTCN and ATHN.
    - Dr. Byams responded that the USHTCN and ATHN predate the federal funding for bleeding disorder surveillance. Prior to 2011, CDC funded regions directly on behalf of HTCs; now, CDC funds ATHN, who then funds the regions that fund the HTCs. Accordingly, ATHN is responsible for coordinating programs at HTCs as well as data-capture infrastructure used for electronic data collection. She agreed that their infrastructure could be adapted to collect data for other disorders, although costs are difficult to estimate. At this time, CDC funds $4.3 million per year to ATHN for Community Counts.
    - Dr. Penberthy commented that the NCCR has linked to existing claims data to capture the tremendous amount of information encoded therein. She highlighted a project in collaboration with the National Heart, Lung, and Blood Institute, which has identified all patients with sickle cell disease who are insured through Medicare and Medicaid. They link data at the patient level, including patient-identifying information. Data may include ICD-10 codes, CPT codes, and HCPCS codes, which are specific to generic drugs and other types of treatment.

- A Committee member asked about the role of biobanks in the NCCR. Dr. Penberthy explained that that the larger Surveillance, Epidemiology, and End Results (SEER) Program includes a virtual SEER-linked Virtual Biorepository Project. This is a large pilot study to enable registries to establish a virtual biobank. Other registries are conducting similar efforts, including the Residual Tissue Repository.
- An organizational member asked panelists to comment on state health information exchanges (HIEs) given that they represent a point of convergence for public and private payors.
    - Dr. Penberthy said that her organization has experienced challenges to incorporating health information exchanges. They are working with Care Quality to encourage some of these organizations to share common data elements in a structured format rather than work with individual HIEs.
    - Dr. Baker said that the Networking California for Sickle Cell Care has created a data thinktank, the purpose of which is to harmonize opportunities for data work across clinics, surveillance systems, and HIEs. Their team includes an HIE consultant who provides extensive support. In the future, however, they hope to progress beyond reliance on data managers and clinical research associates in favor of immediate transfer of information across systems. Her team also connects with community information exchanges (CIEs) to collaborate on social determinants of health.

Newborn Screening Workforce: Laboratory and Follow-up

Scott M. Shone, PhD, HCLD(ABB), **Committee Member Director North Carolina State Laboratory of Public Health**

Dr. Shone began by reviewing the Association of Public Health Laboratories (APHL)'s role in developing the public health workforce. APHL recently completed review and revisions to its 2021-2023 Strategic Map, a key component of which is to build and support a resilient, emerging public health laboratory workforce, especially in the setting of the COVID-19 pandemic.

With regards to newborn screening workforce development more specifically, for the last decade APHL has sponsored Fellowship Programs including the Ronald H. Laessig Memorial Newborn Screening Fellowship in 2011 and the Newborn Screening Bioinformatics and Data Analytics Fellowship in 2019. Dr. Shone also highlighted two Fellows who have gone on to serve in newborn screening leadership roles in Wisconsin and New Jersey.

Dr. Shone described key successes in APHL's newborn screening workforce development efforts. Annual training workshops have included a Molecular Training Workshop for laboratorians and a Tandem Mass Spectrometry series for both laboratorians and follow-up staff. Mentorship programs include the newborn screening Follow-up Learning Exchange (FLEX) program, which encourages peer-to-peer connection of follow-up staff to address opportunities and challenges, and informal lab-to-lab collaboration.

In recognition of growing and significant emerging challenges with respect to newborn screening, APHL established the Newborn Screening Workforce Taskforce in late 2019. Focus areas include recruitment and retention, succession planning, and COVID-19 response for laboratory and follow-up staff. Dr. Shone identified several challenges in recruitment and retention for the newborn screening workforce and the public health workforce more generally. For example, recruitment suffers from noncompetitive salaries, hiring freezes, and nonspecific

training paths for laboratorians and follow-up staff. Retention is limited by personal liability, lack of career paths and promotion opportunities, and insufficient job openings. Unfortunately, these challenges pose risks to the newborn screening process.

Dr. Shone discussed opportunities to address some of these ongoing challenges. For one, APHL recently received a supplemental reward from CDC whereby $27 million may be allocated towards public health laboratory workforce development with an emphasis on fellowship and training programs. Going forward, Dr. Shone encouraged the development of public health workforce incentives for hiring and retention, messaging on the importance of the newborn screening workforce, a coordinated training approach across HHS divisions and screening stakeholders, and dedicated staff for future growth. He recommended a comprehensive survey of current staffing in newborn screening programs and the development of guidelines for minimum staffing consideration, and routine assessment of newborn screening program workforce and expertise.

Workforce Issues in Early Hearing Detection and Intervention

***Marcia Fort, AuD, CCC-A*, Unit Manager, Genetics and Newborn Screening Division of Public Health, Children and Youth, North Carolina Department of Health and Human Services**

Dr. Marcia Fort presented on workforce issues in early hearing detection and intervention. The original scope of the Early Hearing Detection and Intervention (EHDI) Program was newborn hearing screening, diagnostic audiology evaluation, referral to early intervention, and annual aggregate data reporting. Now, two decades later, the scope has expanded significantly to include family engagement, mentoring, late-onset hearing loss, early childhood hearing screening, a comprehensive electronic data system, individualized data reporting, and other important activities.

Funding for EHDI programs is limited, and sustainability is a concern. The Directors of Speech and Hearing Programs in State Health and Welfare Agencies (DSHPSHWA) conducted a sustainability survey in 2019, finding that 75 percent of respondents had some legislation governing EHDI, but only 14 percent of these included funding or budget notes. They also found that 30 percent of responding states had some contribution from the State General Fund, only 27 percent had funds from NBS fees, and only about half had access to Title V funds.

Other workforce challenges include incongruent policies and regulations and a shortage of qualified professionals. Additionally, EHDI has little authority to enforce procedures and policies across birthing facilities. Benchmarks (such as follow-up by 6 months of age) are dependent on other professionals, who often feel that a failed hearing screen is not an urgent issue. These challenges cause significant stress among EHDI program staff, leading to high turnover and loss of institutional knowledge. Since February 2019, 21 states and territories have experienced turnover of their EHDI Coordinator, and two have turned over the EHDI Coordinator three times. Turnover also occurs in hospital screening staff and other key personnel, impacting the capacity of programs to conduct newborn screening and to mentor new staff.

Dr. Fort discussed potential solutions to these problems. Foremost, improvements in sustainable funding would enable EHDI to carry out this important work and form new collaborations and partnerships that would support EHDI efforts and may offer new funding opportunities. Efforts may also benefit from an improved sense of urgency among supporting professionals and staff regarding follow-up after a failed hearing screen.

Newborn Screening and Follow-up of Children with Endocrine Disorders

***David B. Allen, MD*, Professor, Division Chief, and Fellowship Program Director, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health**

Dr. David Allen reviewed current successes and challenges in newborn screening and follow-up of children with endocrine disorders. Wisconsin screens for two endocrine disorders: congenital adrenal hyperplasia (CAH) and congenital hypothyroidism (CH).

About 1 in 2,000 live births are identified with CH, which is the most common preventable cause of cognitive disability. Like most states, Wisconsin uses a thyroid stimulating hormone (TSH) approach to detect the disorder. Wisconsin's program pioneered the development of age-specific cut-offs for TSH criteria, which substantially improved the false positive rate. Dr. Allen emphasized that follow-up for CH is very adaptable to telehealth platforms.

Fewer children are identified with CAH, representing about 1 in 10,000-15,000 live births. The screening relies on 17-hydroxyprogesterone, the metabolite that accumulates before the 21-OHD block. Because this is influenced by gestational age and birth weight, development of cutoffs has reduced the high false positive rate. Treatment involves cortisol and mineralocorticoid replacement, growth monitoring, stress-dose response management, and in puberty complex psychosexual and medical management.

Dr. Allen explained that specialty care for children with CH and CAH suffers from a shortage and maldistribution of pediatric endocrinologists. In Wisconsin, families must drive an average of 29 miles to receive pediatric subspecialty care in endocrinology, and 10 states have less than one pediatric endocrinologist per 100,000 children. In fact, the pediatric endocrinology workforce is dwindling: the total cohort of pediatric endocrinologist fellows decreased from 254 in 2012 to 243 in 2018, and 41 of 108 positions remain unfilled. Additionally, minorities and young professionals are underrepresented in the pediatric endocrinology workforce.
Several factors threaten the pediatric endocrinology workforce pipeline. First, there is a lack of early subspecialty exposure and mentorship given that endocrinology is not a required medical school rotation and rotations for pediatric residents in endocrinology typically don't occur until the third year of residency, after their career decisions have already been made. Other challenges include financial concerns. Health care providers with substantial student debt recognize that pediatric endocrinology is a relatively low-paying field. Many medical professionals also perceive low quality of life and limited boundaries between personal and professional life among pediatric endocrinologists, discouraging them from pursuing a career in this area.

To increase the size and diversity of the pediatric endocrinology workforce, there is a need to increase early positive exposure to the field. This may include outpatient subspecialty exposure in core rotations, accreditation support for early residency exposure to nonprocedural subspecialties, and professional society medical student recruitment initiatives. Other methods

involve efforts to decrease financial barriers to becoming a pediatric endocrinologist. For example, expanding loan forgiveness for work in underserved areas and lower-paid specialties, funding a targeted loan repayment program for non-procedural specialties, and implement shared-care models that value non-procedural pediatric endocrinology expertise. He also recommended re-evaluating the two-year training model and modifying the current three-year training if deemed appropriate, and addressing perceived lifestyle detractors, such as work-life balance.

Genetic Metabolic Dietitians

Rani H. Singh, PhD, RD, LD, **Professor, Emory University Department of Human Genetics and Pediatrics**

Dr. Rani Singh presented on the important role that genetic metabolic dieticians play in newborn screening and long-term follow-up. Genetic Metabolic Dieticians International (GMDI) was founded in 2005 to foster specialized skills for registered dietician nutritionists (RDNs) in the expanding field of metabolic disorders, many of which require complex nutritional management. Since then, GMDI has accrued nearly 500 members internationally and has supported training and professional assistance, networking, research, and advocacy and collaboration. Dr. Singh highlighted the development of the Project Extension for Community Health Outcomes (ECHO) for genetic nutrition training, the Guidelines Project to identify and publish best practices, and collaboration on advisory boards with relevant organizations.

A trained RDN workforce is necessary to support lifelong diet intervention, which requires ongoing care coordination, evidence-based interventions, quality improvement, and continuous knowledge generation. The RDN workforce should receive specialized training in genetic metabolic disorders, potentially facilitated by national networks, communication tools, and resources for harmonized efforts. RDNs have a valuable opportunity to take a leadership role in precision nutrition for individual patients' specific metabolic and dietary needs.

Dr. Singh described the diverse roles and responsibilities of genetic RDNs, who work in clinical and public health settings, sit on state newborn screening advisory boards, conduct research in clinical trials and patient registries, partner with industry on investigator-initiated protocols, serve in academia, and work in government. A GMDI survey revealed that 56 percent of GMDI RDNs work in university medical centers, 20 percent in public hospitals and medical facilities, 12 percent in private facilities, and 20 percent in industry. Most receive funding from hospitals (e.g., fee for service or salaried), state health departments, newborn screening contracts, or fees for multidisciplinary team visits.

Dr. Singh discussed challenges in the genetic RDN workforce. Dieticians specializing in genetic metabolic disorders require a unique skillset and intensive training to work with this complex population. However, at this time there are no requirements or recognized training protocols for genetic RDNs, indicating an urgent need to standardize the field. Dr. Singh pointed out that many dieticians are overburdened by care coordination activities, underpaid, and overworked. GMDI found that, on average, there is one dietician per 133 patients who need complex management. Additionally, there is a tremendous disparity between earnings and responsibilities; the starting salary for a post-master scholarship is around $55,000, and the average dietician spends more than five hours per week just on prior authorizations and letters of support to

insurance companies. The workforce also suffers from uneven geographic distribution and limited diversity.

To overcome these problems, Dr. Singh emphasized the importance of supports for nutrition services and medical nutrition therapy for individuals with genetic metabolic disorders. The workforce would benefit from enhanced diversity and form efforts to leverage telehealth management approaches that have emerged during the COVID-19 pandemic. She also suggested that newborn screening quality indicators should include access to genetic metabolic RDNs and medical foods.

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

- A Committee member asked Dr. Singh to comment on paths forward toward a unified infrastructure for driving initiatives in newborn screening. Dr. Singh emphasized the need to leverage emerging technologies to develop systems, partnerships, and registries that would support long-term follow-up. She clarified that there is no formal training program for metabolic dietitians. GMDI recently initiated the first 12-week academic Project ECHO train-the-trainer program, which has been successful so far, but no other programs exist.
- A Committee member asked Dr. Allen about efforts on the part of the Association of Medical School Pediatric Department Chairs (AMSPDC) Workforce Initiative to equalize compensation for nonprocedural medical specialties. Dr. Allen said that AMSPDC acknowledges the importance of alleviating student debt burdens through reduced tuition and targeted loan forgiveness such that students' specialty choices are less driven by finances. He also recommended developing programs to assure students that nonprocedural specialties are a valid, safe career choice.
- An organizational representative requested that Dr. Shone address the interface between lab work and follow-up. Dr. Shone emphasized that streamlined collaboration between lab and follow-up work are critical for the health of newborns and their families. He noted that several models have fostered success in these partnerships in a variety of settings, whether the lab and follow-up are co-located or dislocated organizationally and/or physically. Organizational site visits are an important way to identify opportunities for better communication and collaboration. Dr. Shone added that the partnerships must be bidirectional and include a feedback mechanism for continuous improvement.
- An organizational representative expressed strong support for inter-institutional and inter-agency collaborations. He hoped that these partnerships would dismantle existing siloes and promote new opportunities for health care providers involved in newborn screening, especially genetic metabolic RDNs. He cited a workforce study that focused on clinical and laboratory geneticists but excluded dietitians and other health care professionals whose work is essential in this field. Future work will address this problem by expanding to include relevant health workers.
- An organizational representative cited her work as co-Chair of the APHL Workforce Work Group, where she and her colleagues have struggled to determine how to promote interest in public health labs professions. She expressed concern about the development of a minimal staffing guideline for newborn screening because some groups may use this to justify minimal resource allocation.

- A Committee member thanked RDNs for their invaluable participation in newborns screening and follow-up teams.

New Business

***Cynthia M. Powell, MD, MS, FACMG, FAAP*, Committee Chair**
Dr. Shone reminded the Committee that September is Newborn Screening Awareness Month and Public Health Laboratory Awareness Month. Dr. Annamarie Saarinen added that it is the tenth anniversary of the addition of critical congenital heart disease (CCHD) screening to the RUSP.

Adjourn

Dr. Powell thanked the attendees for their participation and reminded them that the next meeting will occur virtually November 9-10, 2021. The meeting was adjourned at 2:00 pm.