# Advisory Committee on Heritable Disorders in Newborns and Children

# Meeting Minutes of November 9-10, 2021

# Virtual Meeting

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**March of Dimes**
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## DAY ONE: Tuesday, November 9, 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 (ACHDNC) meeting and conducted the roll call.

Committee members in attendance were:

- Dr. Kamila Mistry
- Dr. Mei Baker
- Dr. Jeffrey Brosco
- Dr. Kyle Brothers
- Dr. Jane DeLuca
- Dr. Carla Cuthbert
- Dr. Kellie Kelm
- Dr. Shawn McCandless
- Dr. Melissa Parisi
- Dr. Cynthia Powell
- Ms. Annamarie Saarinen
- Dr. Scott Shone
- Dr. Michael Warren (Day 1 morning); Ms. Joan Scott (Day 1 afternoon); Debi Sarkar (Day 2)

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 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. Margie Ream
- 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. Georgianne Arnold

Dr. Powell acknowledged that this will be the last Committee meeting for Committee members Dr. Mei Baker, Dr. Jeffrey Brosco, and Ms. Annmarie Saarinen. She thanked them for their

outstanding service, their valuable contributions to Committee discussions, and the lasting impact these contributions have had on newborns and their families across the nation.

In July 2021, HRSA received a nomination package for Krabbe disease, a lysosomal storage disorder. The Committee first received a nomination for Krabbe disease in 2007 and in 2009 voted to not recommend addition to the Recommended Uniform Screening Panel (RUSP). The Nomination and Prioritization Workgroup is reviewing the nomination package. In October 2021, the National Cytomegalovirus (CMV) Foundation submitted a nomination package for congenital CMV (cCMV). HRSA reviewed their original nomination package in March 2019 and requested additional information missing from the package. Currently, HRSA is reviewing the resubmitted nomination package.

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

## Mucopolysaccharidosis Type II Evidence-Based Review – Phase 2 Update

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

On behalf of the Evidence-Based Review Group (ERG), Dr. Alex Kemper provided the second interim update on the nomination for Mucopolysaccharidosis Type II (MPS II) for newborn screening. He provided an overview of MPS II, which is an X-linked lysosomal inborn error of metabolism caused by deficiency of the enzyme iduronate 2-sulfatase (IDS) creating an accumulation of specific glycosaminoglycans (GAGs). There are over 500 mutations associated with the IDS gene and the prevalence for this disorder ranges from 0.2 to 2.5 per 100,000 live births.

MPS II can be classified as severe or attenuated based on the degree of severity, involvement of organs or joints, and cognitive impairment. Some who screen positive will have pseudodeficiency. The phenotype is not typically predictable at the time of diagnosis because of the many private mutations. Screening is based on tandem mass spectrometry or microplate fluorometric assay. Targeted treatment is available through enzyme replacement therapy (Idursulfase), which is standard treatment, and hematopoietic stem cell transplantation.

Dr. Kemper reviewed the articles and sources of data used for the evidence review. He highlighted the Hunter Outcome Survey, pointing out that there was a relatively large number of individuals included in the survey and that enzyme replacement therapy was shown to be effective. The outcomes of the Hunter Outcome Survey also showed that there is an effect from age of onset and types of symptoms associated with the disease. He reviewed common treatment outcomes found across the reviewed studies, including respiratory failure, cardiac involvement, liver and spleen volumes, development, ability to ambulate and endurance, physical features, and urinary GAG levels. Dr. Kemper said that the studies show that enzyme replacement therapy lowers the risk of death over time.

He then discussed a three-year follow-up case study of twins and their older sibling. The older sibling had MPS II and was not treated early with enzyme replacement therapy, but their diagnosis led to the early identification of MPS II in one of the twins (the other was negative).

The twin with MPS II was treated with enzyme replacement therapy at three months of age. During the follow-up assessments, the twin with MPS II showed normal ranges of movement, cardiac valves, and facial appearance. Both twins had IQs in the normal range, while their older sibling had a reported IQ of 24 and a wide range of other findings consistent with MPS II. The case study illustrated the effectiveness of early intervention. In a later study of the twins at age nine, there was still no evidence of disease in the twin with MPS II, who was still receiving enzyme replacement therapy, with the exception of minor restriction of hip movement.

Dr. Kemper provided an overview of a Hunter Outcomes Study on the long-term effects of enzyme replacement therapy. The study followed males with MPS II categorized by when enzyme replacement therapy was initiated—ranging from under 18 months to five years old—and for whom therapy was continued for at least five years after. The study assessed a wide range of outcomes in children older than five years of age with no reported cognitive impairment. Dr. Kemper reviewed the results of the six-minute walk test, which showed that the mean walking distance in participants who received enzyme replacement therapy before 18 months of age was 33 meters more than those who started therapy after 18 months of age. Despite the importance of these types of analyses, the results should be interpreted with some caution because of study limitations including the lack of statistical significance in the age of therapy initiation, overlapping confidence intervals, and a limited ability to conduct statistical inference analyses.

He reviewed other literature showing GAG as reliable markers to rule out pseudodeficiency and clinical trials of novel therapies, such as pabinafusp alfa, ETV:IDS (DNL310), and RGX-121, which are currently underway.

Dr. Kemper talked about newborn screening for MPS II in Illinois and Missouri. In Illinois between December 2017 and May 2021, they found 63 positive screens from approximately 473,000 screened newborns. The referral rate was approximately 13 of 100,000 live births and MPS II was identified in 1.7 of 100,000 live births. In Missouri between November 2018 and June 2021, they found 28 positive screens from approximately 200,000 newborns. The referral rate was 14 of 100,000 live births and MPS II was identified in 1.5 of 100,000 live births.

Dr. Lisa Prosser provided an update on the decision-analytic model of MPS II newborn screening as compared to clinical detection. These comparisons can be used to estimate the proportion of newborns likely to fall into each of the screening and diagnostic categories and provide the Committee with context in the projected number of screening outcomes. Given the scarcity of data on newborn screening, these projections would provide an estimated range of positive screens and newborns identified with MPS II if newborn screening were implemented at the national level.

The ERG has determined that there is insufficient evidence to model longer term outcomes and the effectiveness of early detection, diagnosis, and treatment because of the heterogeneity of outcome measures across different systems and the absence of key markers of progression of the disease. In lieu of providing these population-level long-term outcomes via the model, they will conduct an additional systematic review of the health outcomes and outcome measures from

clinical trials. These clinical trials and other sibling studies will provide the team with the ability to infer the effectiveness of early diagnosis and intervention.

Dr. Kemper provided an update of the Public Health System Impact (PHSI) survey representing more than 40 newborn screening programs. The Association of Public Health Laboratories (APHL) has completed newborn screening program interviews in Illinois and Missouri, is in progress with interviews in New York, and is interviewing other states that are considering adding MPS II to their panel. He also reviewed the cost assessment outcomes, including startup and operating costs, which is estimated to range from $1-6 per newborn screened.

The next steps for the ERG are to complete the evidence synthesis focusing on the treatment impact related to earlier identification, modeling screening outcomes based on the available evidence, and completing the PHSI survey assessment and cost evaluation.

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

- A Committee member reflected on the paucity of data needed to model the effectiveness of treatment attributable to early detection and intervention and asked if the reason was because the condition is ultra-rare or because there is not much literature published on the outcomes needed for the model. Dr. Kemper answered that it is both the rarity of the condition and the fact that not many children have been treated based on newborn screening. It is known that enzyme replacement therapy is effective and that there does seem to be a benefit to earlier intervention. The challenging question is whether early treatment initiated as a result of newborn screening leads to better outcomes. Without a large sample size of children identified through newborn screening, there tends to be a reliance on case series and sibling studies, which cannot really be used in quantitative modeling. Committee members will therefore need to decide how to weigh the data from sibling studies and case series.
- A Committee member asked Dr. Kemper how the Committee should evaluate the results of the six-minute walk test and the quantitative outcome of those with early treatment walking 33 meters more than those who started treatment later.
    - Dr. Kemper answered that the study had only been published in October 2021 and he intends to talk further with the investigators to better understand how their findings may affect families in terms of sustained improvement to quality of life.
    - Dr. Prosser added that it is important to differentiate between the evidence of effectiveness from sibling studies and the ability to quantitatively characterize and model those findings at a population level.
    - Dr. Kemper reminded the Committee that the six-minute walk study was restricted to individuals without reported cognitive impairment and that enzyme replacement therapy has a limited effect on the central nervous system (CNS).
- A Committee member asked about the eight reports of variants of unknown significance in the Illinois data and what that category means in the context of both newborn screening and in a model for identifying adverse effects.
    - Dr. Kemper said that the challenge in looking at newborn screening outcomes is that there is a laboratory perspective and the follow-up program perspective. From the laboratory perspective, information is being entered into a system that was developed for other conditions and may not entirely fit this condition; therefore, the laboratory system

classifies these cases as variants of unknown significance. The individuals responsible for follow-up care need time to gather information about how to classify those individuals.
    - Dr. Prosser added that these cases would fall under probable MPS II in the model, which would be detailed in footnotes and definitions. Modeled projections would be based on evidence from the literature and not directly from the outcomes captured from the laboratories.
- A Committee member asked for clarification about how the category of variants of unknown significance is considered a benefit or harm when often the unknown significance category is considered benign. Dr. Kemper agreed and said that this is a vestige of how the laboratory records information. Variants of unknown significance indicated that they are not sure and follow-up is needed.
- A Committee member asked if the false positives include pseudodeficiency or if false positive is another term for pseudodeficiency.
- Dr. Prosser answered that the two categories are combined, but they can be separated out if that is useful for the Committee.
- Another Committee member agreed that it would be helpful to separate out the false positives from pseudodeficiencies.
- A Committee member asked about the cost estimate and if the range is due to laboratory and type of technology used. Dr. Kemper answered that the range is related to the type of technology used and the degree to which one has to purchase reagents. Different programs will have access to different resources.
- A Committee member suggested that understanding the outcomes that are important to families should be understood in order for the Committee to make good decisions about whether nor not to recommend MPS II for addition to the RUSP. He also asked if outcomes were available from the five children who were identified through newborn screening. Dr. Kemper agreed and said that they learned from families that an intervention for toileting would make a profound difference on their daily lives but they have not yet been able to find data for that measure. He also cautioned against putting too much weight on the 33-meter difference in the six-minute walk study because of the population restrictions and other limitations.
- A Committee member commented on the twin study with the older female sibling with MPS II and asked if the authors of the study provided a reason for why the female would have such a severe case. Dr. Kemper answered that they had not provided further information other than the sibling was female.
- An organizational representative asked what states are using to determine their affected rate, suggesting that this data is also missing in the literature. Dr. Kemper said that the studies he reviewed used dried blood spots from affected individuals, individuals with pseudodeficiencies, and unaffected individuals. The data are compelling that measuring the GAG clearly separated out affected from unaffected.
- An organizational representative asked if there is data that stratifies race across screen positives and pseudodeficiencies to determine if there is a population difference in who is seen in the clinics. This would be important for the discussion of newborn screening and equity. Dr. Kemper said that is an important issue to consider and they would have to go back to the data to determine that.

- An organizational representative suggested that it would be helpful to harmonize the laboratory data with long-term outcomes that impact families. Dr. Kemper agreed that it is an important issue.
- An organizational representative asked if the variants of unknown significance did have detected GAGs and if this was the reason that these cases were not classified as pseudodeficiency. She also asked if the severity was an attenuated or severe form. Dr. Kemper answered that they do not have information of where these cases were expected to be attenuated or severe. The challenge of getting this data comes back to the issue of unifying the data collection systems.
- An organization representative commented that the six-minute walk test has been a traditional measure for enzyme replacement therapy for other lysosomal storage diseases. She added that laboratory and follow-up terminology are not the only data that need to be integrated, but also the clinical terminology.
- An organizational representative asked if the twin study aimed to compare the clinical features of the twin brothers with their older sister. Dr. Kemper confirmed that this was the aim.
- An organizational representative asked about the survival table of the Hunter Outcome Survey and if the methodology for assessing cognitive impairment was binary or if parents were able to talk further about severity. Dr. Kemper said that cognitive impairment in this study was dichotomous based on parent report.

## Overview of Immediately Actionable Committee Process Updates

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

Dr. Powell explained that in February 2019 the Committee began an initiative to review, update, and strengthen Committee processes for nomination, evidence-based review and decision-making for conditions nominated for inclusion on the RUSP. The Committee has gathered information on and discussed proposed updates and received public comment. At the August 2021 Committee meeting, she and Dr. Kemper presented an overview of the proposed updates, which were categorized as immediately actionable or requiring further discussion, research, or policy change. The four main focus areas of the proposed updates were: 1) nomination, 2) evidence-based review, 3) decision matrix, and 4) review of conditions on the RUSP. The Committee discussion at this meeting focused on the immediately actionable proposed updates.

### *Nomination Form Updates*

The revised nomination form would include new information requests and clarifications to existing questions. Dr. Powell reviewed the proposed changes which included:

- **Condition Information and Treatment**: The proposed enzyme (if applicable), United States (U.S.) incidence estimates and citation, relevance of timing in screening to onset of clinical manifestations, and the U.S. distribution and prevalence of known phenotypes.
- **Treatment**: Medical and clinical requirements including standards of care, clinical indications and contraindications, and availability of follow-up treatment.
- **Validation of the Laboratory Test**: Timing requirements in screening or specimen collection, the platforms and procedures of screening, as well as the FDA approval status of second tier tests, modality of specimen samples for tier two tests, if the condition is considered time-critical, and incidental findings in screening.

- **Confirmatory Testing and Short-Term Follow-Up/Diagnosis:** The sample specimen needed; the sensitivity and specificity of validation; year and reference of FDA clearance or approval; how, when, and by whom the diagnosis is confirmed.
- **Prospective, Population-Based Screening:** Pilot study information, description and algorithm of screening methods, confirmatory testing and number of positives and referrals, key outcomes of interest and evidence basis, long-term follow-up plans including contact information, state status in screening mandates, and the patient databases or registries for the condition.
- **List of References:** No limits to the number of references included.

### *Evidence-Based Review Updates*

The proposed updates for the evidence review process include:

- Expanding current procedures for assessing gray literature and incorporate standard procedures used in GRADE for collecting expert-derived evidence to supplement unpublished evidence.
- Consider and review registry and other unpublished sources of data as unpublished evidence.
- Report cost estimates in general terms in the PHSI cost assessment.

### *Decision Matrix Updates*

No immediately actionable changes have been proposed for the decision matrix. However, additional guidance was drafted to support Committee members in utilizing the decision matrix, including more detailed information about net benefit and descriptions for each criterion.

**Committee Discussion**

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

- A Committee member asked about the addition of the enzyme and if the disorders that do not have an enzyme problem should add "not applicable" in this section. Dr. Powell confirmed that would be an acceptable response.
- A Committee member asked how conditions such as cytomegalovirus (CMV) or congenital hearing loss would be listed as a proposed condition with such specific information being requested. Dr. Powell answered that, depending on the condition, not all areas will need to be completed. A Committee member suggested using "critical biomarker" or "critical measurement."
- An organizational representative wondered if the new content about including U.S. distribution and prevalence is intended to mean the distribution of phenotypes relative to each other or to the distribution of ethnicity and geography. Dr. Kemper answered that the intention was to understand the epidemiology of the condition in the U.S.
- A Committee member asked if they were voting to modify what is already in the briefing book as opposed to leaving it as-is. Dr. Powell said that if there are just a few minor revisions, the Committee can vote on the full proposal with those revisions. If there are more major revisions needed then the vote will probably need to be delayed.
- A Committee member from the U.S. Food and Drug Administration (FDA) said that she can help ensure that the wording for FDA clearance or authorization is accurate.

Ms. Morrison suggested that the revisions are relatively minor and can be summarized so that Committee Members can vote on the nomination form. The Committee moved for a vote to approve the immediately actionable updates to the nomination, evidence-based review, and decision-making process with minor modifications. The motion was seconded, roll was called, and the motion was passed unanimously. Changes to the nomination form will not go into effect until January 2022. In early 2022, a series of consumer-friendly education materials explaining the nomination, evidence-based review and decision-making processes will be made available on the Committee website.

## Review of the Committee's Evidence-Based Review and Decision-Making Processes: Recap of Key Issues Identified for Future Consideration

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

Dr. Powell provided a brief summary of the recommendations requiring further discussion, research, or policy change. There was a recommendation to establish a plan to conduct regular review of conditions on the RUSP including the frequency, prioritization process, nomination or selection processes, other considerations and criteria for reviewing conditions, and the goals of outcomes for this review.

Another recommendation was to assess the long-term follow-up of newborn screening including evaluating its impact, identifying short- and long-term treatment and clinical outcomes, determining the cost of implementation, assessing the impact on the health care system and providers, and considerations for equity and long-term access.

Other recommendations included establishing a priority list of ongoing research and development issues, revisiting the decision matrix (specifically guidance for B-ratings), and assessing stakeholder values and preferences.

## Public Comment

**Zhanzhi (Mike) Hu**

Mr. Mike Hu is the co-founder of Project Guardian, a nonprofit organization dedicated to newborn screening, and father to three boys. His two older sons were diagnosed with MPS II in 2011. His younger son has shown better outcomes as a result of a pre-symptomatic diagnosis and treatment. He acknowledged that screening a healthy population is challenging because of the need for high specificity and sensitivity. Although it is important to consider the family, social, and economic implications of false positive screenings, it is also important to not ignore the devastating consequences of not screening. Knowing the progressive nature of this condition, it is difficult to argue against early identification and treatment. Research suggests that the family impact of a false positive screening may be minimal and transient and can be managed through awareness and education. No screening test is perfect and lower sensitivity should not be an automatic exclusion.

**Niki Armstrong**

Ms. Niki Armstrong is the Newborn Screening Program Manager for the Parent Project Muscular Dystrophy (PPMD). She provided an update on the Duchenne Newborn Screening Pilot in New York, which has screened more than 36,000 newborns for Duchenne. Of these, 42 newborns were referred for genetic testing because of a positive screen for increased risk, four of

whom were males with Duchenne or Becker and one of whom was a female carrier. Their incidence is consistent with the expected incidence of 1/5000 males. The pilot was conducted with support from PPMD and tools, resources, and expertise from the Newborn Screening Translational Research Network (NBSTRN) and the New York State Department of Health. They are currently compiling the RUSP nomination package for future consideration by the Committee. During this process, they are continuing data collection, analyses, and publication and the families of newborns with Duchenne/Becker are receiving clinical support and follow-up. They will continue to track outcomes from early screening and intervention.

**Dylan Simon**
Mr. Dylan Simon is the Newborn Screening and Diagnostics Policy Manager for the EveryLife Foundation for Rare Diseases, which is focused on ensuring babies receive lifesaving treatment through early diagnosis from newborn screening. They work to empower rare disease advocates to successfully navigate the newborn screening ecosystem through the facilitation of their annual Newborn Screening Bootcamp program. This is a three-week event designed to educate newborn screening stakeholders. Their last virtual event had more than 230 participants attending at least one week. This expertise added valuable insight on the newborn screening system and the process of adding a condition to a state newborn screening panel. Mr. Simon noted that the revisions to the evidence review process and data requirements will impact stakeholders and the type of data required to develop a RUSP nomination package. EveryLife suggested that the Committee establish a working group that includes representatives from the patient community to inform the development of educational materials on the updated requirements.

## HRSA Newborn Screening Portfolio Evaluation: Current and Future Needs of the Newborn Screening System

***Melissa Raspa, PhD,*** **Senior Scientist and Director, Genomics, Ethics and Translational Research Program, RTI International**
Dr. Melissa Raspa reviewed the HRSA newborn screening portfolio evaluation conducted by RTI. The purpose of the evaluation was to better understand the needs of the newborn screening system, its stakeholders, the unique role of HRSA in addressing those needs, and the unmet needs that would inform future programs. RTI shaped their evaluation around the six goals of the HRSA newborn screening system as described in the Newborn Screening Saves Lives Authorization Act of 2014.

The first, and overarching, goal is to enhance, improve, or expand the ability of states to provide screening and counseling. The second goal focuses on the provision of education, training, and technical assistance; the third focuses on follow-up care and treatment; the fourth focuses on the timeliness of newborn screening; and the fifth focuses on education with families and other consumers. The sixth goal represents the ultimate aim of the HRSA newborn screening system, which is to improve health equity and morbidity and mortality outcomes for all families through the provision of quality services.

The evaluation focused on six of HRSA's current or former newborn screening programs. Dr. Raspa reviewed four of the guiding evaluation questions that were most relevant to the Committee. The first guiding question aimed to determine the extent to which the portfolio has contributed to achieving HRSA's overall goals for newborn screening. The remaining three

evaluation questions aimed to identify the current, unmet, and expected future needs of the newborn screening system. RTI used primary data from stakeholder interviews and focus groups, which were transcribed, analyzed, and aligned findings across the six HRSA goals. They also used secondary data from grantee-reported materials, published literature on the newborn screening system, and an environmental scan of newborn screening system websites and partner organizations. They then synthesized the data from both primary and secondary sources.

Dr. Raspa reviewed the findings as aligned with the six HRSA goals. Under the first goal, they found that HRSA's portfolio has made progress over the last decade toward creating a more efficient and proficient system through an expansion of states' ability to expand their newborn screening panels. Despite this progress, there are still opportunities for improvement. For instance, additional federal guidance is needed to improve the "patchwork" newborn screening system. There are also challenges around the states readiness to implement screening for new conditions. Enhanced data interoperability is needed to increase efficiency and accuracy across the system. Some potential solutions to address these needs include collaboration across federal agencies, increased federal guidance, expanded newborn screening workforce, evaluations of the newborn screening system and the RUSP evidence review process, and increased investment for new equipment and staff support.

Under the second goal, they found that HRSA has provided strong support for training and technical assistance, particularly around timeliness, adding new conditions, and the NewSTEPs data repository. However, they found there is not a widespread focus on educating health care providers. Additional training and technical assistance is needed for state lab and follow-up staff, especially in under-resourced states, and for health care providers to better understand new conditions and how to communicate with families. Some potential solutions include increasing the education and training provided to different stakeholders and revising training and technical assistance models, such as providing support for "early adopter" states to mentor others.

Under the third goal, they found that HRSA funded programs play a key role in strengthening short-term follow-up, but there is a need for a national long-term follow-up system with clear definitions, goals, and guidance. There is also a need to address inconsistencies across states, specifically on primary care provider knowledge about newborn screening and how families are contacted and receive follow-up support. One potential solution is to develop a long-term follow-up system to improve collaboration, create a Center of Excellence, and track health outcomes. Other solutions include improving the coordination of treatment and support through condition-specific guidance, connecting families with patient advocates, and developing a clearinghouse of family and clinical resources.

Under the fourth goal, they found that HRSA investments have made significant improvements to newborn screening timeliness. These successes can be maintained through ongoing education, quality improvement, and funding; improving timeliness beyond diagnosis and into treatment; increasing focus on the most time-sensitive conditions; and providing education and training to providers across the states. Specific potential solutions include a focus on reducing the time between diagnosis and treatment through the development of timeline metrics, supporting automated data entry in the NewSTEPs repository, education and training for providers on the

importance of timeliness for certain conditions, and continued state funding to continually improve timeliness of specimen collection, transport, and screening indicators.

Under the fifth goal, they found that HRSA programs are perceived as high-quality and accurate but lack visibility across all stakeholders. HRSA could focus on dissemination of educational materials for parents in the prenatal period, improved consistency of educational materials across states, and development of high-quality online educational materials—including materials tailored for specific consumer groups. Some potential solutions include the development of specific educational materials for diverse stakeholders, identification and implementation of effective education dissemination strategies, creation of education and support for families after a diagnosis of a new condition, and partnerships with new patient advocacy groups to include their perspectives in the development of new educational materials.

Finally, under the sixth goal, they found that HRSA investments make continual improvements in health equity and outcomes, especially for underserved populations. There are still some gaps that need to be addressed, including closing the gap in equity related to cost of care, access to care, and social supports. There is also a need to ensure that systemic racism and implicit biases are addressed and that states have adequate training and support to reduce existing disparities. Potential solutions include providing training on systemic racism and implicit bias to all newborn screening staff and clinical providers; using a long-term follow-up system to track outcomes of positive screens; developing a system to provide more support and coordination to connect families with genetic services; improving support for non-English speaking families; and developing metrics to measure program effectiveness.

Dr. Raspa summarized by reviewing broad recommendations for policy, infrastructure, and practice recommendations. Policy recommendations included creating a strategic plan for newborn screening, conducting an evaluation of state newborn screening programs to identify areas of improvement, and providing state-level funding through the Title V Maternal and Child Health Bureau (MCHB) Block Grant program to implement new conditions and reduce variability between states. Infrastructure recommendations included creating a long-term follow-up registry to track health outcomes (without duplicating existing efforts) and continuing a focus on interoperability between the states. Practice recommendations included a continued focus on technical assistance and support for timeliness across states, including a model of tiered support depending on program size, performance and need. They also recommended wraparound support for new RUSP conditions including education and connecting families to services and supports.

**Committee Discussion**

- A Committee member reminded the Committee that Title V MCHB Block Grant funds are awarded at the discretion of the states based on their identified need and their broad maternal and child health priorities.
- An organizational representative provided insight about how family physicians approach education for a situation that they encounter relatively infrequently. There are a lot of continuing medical education (CME) programs, many of which are mandated CME hours. It is important to understand a lot of the education that most practicing family physicians seek is at the point of care. Therefore, there is a need to embed education into the places that

family physicians actually seek information. The challenge is how to have information on these conditions pop-up in resources such as UpToDate or Medscape.

- An organizational representative asked if two issues –early education for families and connecting families to patient advocacy organizations – was seen by stakeholders as two different types of experiences or under one umbrella. Dr. Raspa answered that pregnant mothers in particular were not as focused on early screening because they had not yet experienced it. Connecting families with resources was relevant for those families that had experienced a positive screen.
- An organizational representative asked if stakeholders talked about funding for education. Dr. Raspa answered that the stakeholders were very clear about the need to continue support and funding in all areas, even though education was not specifically highlighted in the presentation.
- An organizational representative commented that systemic racism and implicit bias does not always "creep in" to the system but is rather already "baked in" to the system and that it is important to frame this challenge accurately.
- An organizational representative expressed appreciation for the highlights on the improvements in timeliness and the importance of early education for families as the Committee has worked on both of these topics extensively.
- An organizational representative said that the American Academy of Pediatrics does support newborn screening and continually publishes articles on it. At the state-level, some states have invested significant resources in provider outreach and education but hear divergent preferences for communication and education approaches. There is no easy answer for outreach and education. The Committee will have to consider diverse methods of outreach and education, including reevaluating printed materials and how to reach people where they are.

## DAY TWO: Wednesday, November 10, 2021

*Guanidinoacetate Methyltransferase (GAMT) Deficiency Evidence-Based Review – Phase 1 Update*

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

Guanidinoacetate methyltransferase (GAMT) deficiency is a cerebral creatine deficiency caused by a mutation in the GAMT gene that is associated with elevated plasma, elevated urine guanidinoacetate (GAA), and low serum creatine. Untreated, GAMT deficiency can lead to global developmental delays, seizures, muscle weakness, and movement disorders. At the August Committee meeting, the Committee voted to move GAMT forward for a full evidence review. The ERG first met with technical experts in October 2021, including representatives from the Utah newborn screening program, and reviewed 339 articles. Dr. Alex Kemper presented a phase one evidence review update for GAMT on behalf of the Evidence-Based Review Group.

While diagnosis of GAMT deficiency is based on biochemical confirmation of low creatine and elevated GAA, molecular analysis can also support biochemical confirmation. Treatment is typically creatine, ornithine, and benzoate supplementation and dietary restriction of arginine, which is generally recommended to begin at approximately two to four weeks of age with serum level monitoring to ensure effectiveness. Screening is based on dried blood spots using tandem mass spectrometry for GAA and creatine. In the U.S., New York began screening GAMT in

2018, resulting in approximately 537,000 screened, 23 referred, and one diagnosis. Utah began screening in 2015, with approximately 274,000 screened, three referred, and one diagnosed. Utah is a two-screen state, using a first-tier ultra-performance liquid chromatography (UPLC) tandem mass spectrometry and, if positive, a confirmatory test of urine and serum GAA and creatine. The cost of screening is less than $1 per child and relatively few numbers of children move on to confirmatory testing.

The next steps of the review process include review of the gray literature, the Association for Creatine Deficiencies registry, novel therapies such as gene therapies and GAA inhibitors, and a technical review with the New York newborn screening program. In early January 2022, they will conduct the PHSI Assessment and population health modeling. Dr. Kemper said that there will be limited quantitative data available for predicting long-term health outcomes, but the Committee will be able to base their recommendations on the numbers of individuals identified and treatment effects.

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

- A Committee member asked if there was an explanation for the substantial difference in referral rates between New York and Utah and also commented on the cost of screening, which only describes the cost of the reagents used. Dr. Kemper said that they will learn more about the differences in referral rates after they speak to the New York representatives. In terms of the cost of screening, they will be able to provide more details in future updates but their current understanding is that the labor costs for referrals did not create additional expense. This was based on one state and the numbers per baby was somewhat inflated because it was based on a two-screen state.
- An organizational representative and member of the ERG added that Utah's cost for GAMT testing was based on bringing the capability in-house and the cost was essentially based on the reagents even with confirmatory testing averaged in. They may find cost differences in New York when they conduct a deeper dive into that program.
- An organizational representative and member of the ERG said that the evidence review will help provide a blueprint of expected follow-up and treatment as well as the capacity for a system to absorb the expected costs.
- A Committee member asked about the difference between screening with and without the second-tier test and if there is a difference in yield and potential miss rate. Dr. Kemper answered that the primary marker is GAA and if that is elevated, they can look at creatine. If the creatine is also abnormal, then they can refer to diagnostic testing with serum and urine. But if the markers are only modestly elevated or not elevated at all, Utah can use a second-tier screening that occurs a few weeks after birth. They will know more about yield and potential miss rates after they talk to the New York newborn screening program.
- A Committee member thought there were other GAMT screening programs globally and asked if those data were available to present. Dr. Kemper said that there is international data available. Although the ERG has access to those published reports, they have not yet had a conversation with those programs. Generally, they look within the U.S. first and then review international programs.

The next ERG update will take place at the February 2022 Committee meeting.

### *Workgroup Updates*

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

Dr. Powell asked all three Workgroups to assess the potential ways in which the Committee could support current and future needs of the newborn screening workforce, including considerations for:

- The availability of follow-up experts for reviewing a new condition nominated to RUSP
- How information can be collected
- How to call attention to identified shortages in follow-up experts

### Education and Training Workgroup Update

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

Dr. Powell asked the Education and Training Workgroup to also consider:

- The major gaps in the newborn screening workforce education
- Recommendations on resources or opportunities to address workforce shortages
- How those resources could be expanded to further strengthen newborn screening

Dr. Jane DeLuca spoke on behalf of the Education and Training Workgroup. The Workgroup framed the discussion by defining the newborn screening workforce as everyone in the newborn screening system including the laboratory workforce and public health practitioners involved in short-and long-term follow-up. They discussed major gaps in workforce education categorizing them in phases of newborn screening (i.e. pre-analytical, provider-clinical, and short- and long-term care). The Workgroup had previously developed a Newborn Screening Educational Planning Guide, which identified newborn screening educational needs by stakeholder category but did not apply formal education ideas or resources for those stakeholders to improve their knowledge.

Newborn screening education often begins at the workplace, within laboratories, from on-the-job training, and through internet sources such as NewSTEPs. The Workgroup discussed formal education programs, such as the Lysosomal Storage Disease fellowship or the North American Metabolic Academy (NAMA) program and suggested that other professional organizations could also be charged with providing training. The Workgroup also discussed the different levels of education needed for the wide array of workforce roles, recognizing that there is limited time to provide complex education. Rather than relying on training that skim across information, there needs to be opportunities for the workforce to develop in-depth knowledge about their roles in the field.

Additionally, the workforce is shrinking and there are few training opportunities for fellows. Therefore, a greater number of fellowships and incentives (i.e., greater pay, paid leave) may be needed to attract candidates. The level of stress on this workforce is considerable, and public health personnel who may continue to work through the pandemic may leave in the future because of the increased pressure. APHL has a workforce development project to consider these challenges. There are also workforce shortages across laboratory workers and data managers, studies of which have recently been published. Of paramount concern is how the workforce can manage implementing newly added RUSP conditions amid many competing priorities.

The Workgroup considered how to improve educational materials for families and providers. They suggested that family communication guides can be improved by considering how information is conveyed and assessing for impact and effectiveness. Additionally, there is a need to ensure that families have access to factual, and not outdated or inaccurate, information. These improvements would help build trust between families and providers, as well as with health systems and government agencies. Conversely, poor communication and knowledge deficits can lead to direct harm to families. The communication process is difficult and with screening for more complex disorders, the messages are more complex than before.

The Workgroup recommended increasing the workforce by targeting young people who potentially have a passion for newborn screening (such as has been done with attracting students to the field of genetics), developing a specialty in newborn screening, cultivating patient navigators (such as midwives or doulas) who can help build trust with families, and helping professionals pivot to newborn screening roles. The Workgroup also recommended packaging education into "small doses" within formats that are commonly used today (i.e., podcasts or videos in waiting rooms), identifying champions for screening (i.e., midwives, doulas, obstetricians, or birthing groups), and other "just-in-time" approaches. They also recommended offering competitive prizes for completing newborn screening education.

The Workgroup suggested that the Committee consider the availability of follow-up experts when reviewing a new nominated condition by engaging with professional groups, encouraging states to increase newborn screening resources, addressing inequities across states, and using successful states as models for others. Dr. DeLuca said that these are important issues that will need novel, and potentially regional, approaches. The Workgroup is also considering developing a white paper to outline the educational needs and challenges of the workforce.

### Follow-Up and Treatment Workgroup Update

***Jeffrey P. Brosco, MD, PhD,* Chair, Follow-Up and Treatment Workgroup**

Dr. Powell asked the Follow-Up and Treatment Workgroup to also consider:

- The key workforce-related challenges impacting access to short- and long-term follow-up
- Examples of workforce innovations that support short- and long-term follow-up care

Dr. Brosco spoke on behalf of the Follow-Up and Treatment Workgroup. The Workgroup identified the key challenges, which were that the workforce did not have enough clinical specialists (i.e., dieticians, genetic counselors, social workers, physicians), the addition of new conditions to screening programs further burdens the already diminished workforce, and treatment protocols, especially for new conditions, are often difficult to access. Burnout is therefore not uncommon across the workforce. These challenges, however, are built upon assumptions for current models of care. For instance, there may not be enough pediatric endocrinologists available, but that is based on an assumption that every child with hypothyroidism must receive care from an endocrinologist when, in fact, pediatricians across the rest of the world routinely manage such complicated issues. The model of care that most of the urban areas in the U.S. uses is not necessarily the only model to work with.

Telehealth and consultation models are alternatives that successfully provide direct patient care but may have challenges such as changes in telehealth payment models, medical-legal issues

with consultation models, and state licensure that limits access to specialists. There are also challenges within the health care payment mechanisms, with some of the screening workforce shortage attributable to lower pay. Value-based, bundled payment models may help distribute payment across the care team and provide support for the necessary training and screening needed across the health care system. The challenge with value-based payment models for child health is that newborn screening conditions are rare.

In terms of considering the availability of follow-up clinical experts in the review of new conditions, the Workgroup had mixed opinions. Some suggested that if there are no available clinicians, it would be wrong to screen for a condition that cannot be treated. Others suggested that if a treatment exists, then there should somehow be a way to provide it. The Workgroup felt it would be better to view the answer to the question as a continuum based on variations in access to treatment, geography, insurance, race, ethnicity, and other factors. There should be a component that measures clinical impact to determine how clinician availability impacts the results of adding the new condition and if there is a reasonable path to sufficient capacity to treat all identified children.

The Workgroup discussed clinical information collection, suggesting that the nomination package could ask for the identification of the clinicians involved (i.e., primary care versus specialist) in diagnosis and treatment and the proposed plan for reaching all identified children. During evidence review, there could be consideration for the pathway to implementation, such as ensuring clinicians are ready to receive children with a presumptive positive finding. There should also be consideration for how to process referrals for presumed positives and the workload needed to address those. Finally, Dr. Brosco emphasized the need for the Committee to address the needs of children with rare conditions as they consider value-based care.

### Laboratory Standards and Procedures Workgroup Update

***Kellie B. Kelm, PhD,* Chair, Laboratory Standards and Procedures Workgroup**

Dr. Powell asked the Laboratory Standards and Procedures Workgroup to also consider:

- What resources used at the state or national levels could address laboratory workforce challenges
- How those resources could further strengthen the newborn screening laboratory workforce

Dr. Kellie Kelm spoke on behalf of the Laboratory Standards and Procedures Workgroup. APHL had a Workforce Workgroup that is currently addressing this issue, aiming to identify newborn screening laboratory workforce programs and their critical components and to develop a position statement. The fellowship programs were highlighted as particularly successful. There are also a limited number of grants that laboratory staff can apply for but there is an administrative burden in applying for and using them.

The Workgroup discussed challenges in pay, with all public health laboratories experiencing difficulty recruiting and maintaining their workforce when they are not as lucrative as other industries. They suggested that incentives such as paid training, loan repayment programs, mentorship, and telework may help people stay in newborn screening. Some states requiring certification or licensure will provide limited-time exemptions for those who work in a public

health laboratory, and one solution may be to extend the time for these exemptions to incentivize people to stay within public health.

The Workgroup also talked about cooperative agreements between the federal government and public health laboratories, such as the Public Health Emergency Preparedness program and the Epidemiology and Laboratory Capacity program. These types of cooperative agreements can provide funding for additional staff, infrastructure, and governance structure to ensure that the program is able to meet their goals. This type of funding, structure, and governance can not only increase the newborn screening workforce, but also help tackle the longstanding challenges within the newborn screening system and reduce disparities across states.

In terms of availability of follow-up experts for new conditions, the Workgroup indicated that context is important (e.g., rare condition, number of specialists needed, distribution of specialists across states). It is also important to consider if there have been robust pilot studies, if there is a good test with positive predictive value, and the potential burden on the system. There could be a survey for states to identify their capacity for the hours needed per child and per specialist. Some states that are considering adding a condition will have already done this homework, but in states that have not, the amount of information needed to answer those questions may be a significant burden. It is already known that twice the number of geneticists are needed for the current workload than are in place and states may be further behind in terms of a lack of specialists for a certain condition. Dr. Kelm said that despite these challenges, states do find a way to add a condition, even if that means going out-of-state for a specialist or finding extra resources.

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

- A Committee member asked about barriers to a regional approach. Dr. Powell commented that it would be important that a regional approach ensures equity across states.
- A Committee member commented on the growing divide between states and programs, much of which is a result of adding disorders but there are also other factors. There has been some success in public health preparedness from the support of federal investment in capacity and infrastructure, notably in the long-term response to the COVID-19 pandemic.
- A Committee member suggested that a federation system in combination with state-retained autonomy to regionalize or federalize access to technology and expertise would be very cost effective and timely for the screening system nationwide.
- A Committee member commented on the workforce gaps with physicians and clinicians being overworked. Without an organized health care system, the number of physicians is driven by different market and pseudo-market factors. He encouraged the Committee to focus on the needs of the public health system and create clear expectations and guidelines for what an excellent newborn screening program should look like.
- An organizational representative suggested the Committee should consider sharing clear, accessible language about challenges facing the newborn screening workforce. There is an opportunity to communicate the concerns about the current and potential future issues in the workforce with all stakeholders who are invested in newborn screening.
- An organizational representative said that regionalization has already occurred in some areas, but newborn screening is still a state-based issue. One way to improve these challenges is to leverage centers of excellence for bioinformatics or second tier testing. Infrastructure is a

mechanism that would help states compete towards becoming a center of excellence for a certain projects.

- A Committee member said that it would be useful to look into the literature addressing telehealth and how it was used from initial contact to long-term follow-up before telehealth dissipates. Dr. Powell agreed that telehealth worked very well but some states are losing capacity due to changes in insurance coverage.

### *Newborn Screening Pilot Programs*

#### ScreenPlus: New York

***Melissa Wasserstein, MD*, Chief, Division of Pediatric Genetic Medicine, Professor of Pediatrics and Genetics, The Children's Hospital at Montefiore, The University Hospital for Albert Einstein College of Medicine**

Dr. Melissa Wasserstein reviewed ScreenPlus, which is a comprehensive, flexible multi-disorder pilot newborn screening program. The pilot is currently running at nine hospitals, most of which are in New York. These hospitals must meet specific criteria including having a high birth rate, being located in ethnically diverse communities, and having newborn screening referral sites. They aim to recruit 175,000 babies over five years with a consent rate of 73 percent. They will obtain informed consent after a one-on-one conversation with a study coordinator. Once parents agree to participate, they complete a REDCap form for the baby and link parents with a brochure and copy of consent.

Their panel currently includes 14 disorders and is fluid so that disorders can be removed or added at any time during the recruitment period. The criteria for a disorder to be included in ScreenPlus include having a dried blood spot screening assay that can be multiplexed, is high throughput, is reasonably priced, and has had positive baseline validation studies. The disorders should also have significant morbidity and mortality if untreated and a pediatric phenotype to ensure that a number of children will be identified. Finally, the disorder should also have an FDA-approved treatment or a promising treatment in clinical trial.

All disorders included in ScreenPlus use at least two tiers of screening to enhance accuracy and potentially reduce false positives. Ideally in the future these data could be used to help predict phenotypic severity. As the disorders included are new to newborn screening, it is critical to capture longitudinal follow-up data. Confirmatory testing results may be unclear until the child does or does not express a phenotype. There is also a need to determine if there is a benefit for early detection. Dr. Wasserstein provided an example of these guidelines applied for metachromatic leukodystrophy. Data are shared with all of the pilot hospitals to help ensure that data collection is uniform.

ScreenPlus has a unique cost-sharing infrastructure with National Institutes of Health (NIH), industry sponsors, and patient advocacy groups. This cooperative approach helps streamline costs and maximize efficiency. Dr. Wasserstein reviewed the organizational and financial infrastructure of the pilot to illustrate how sponsor funding is dispersed to pilot hospitals, laboratories, suppliers, and the different institutes involved.

Parents are also asked to participate in the Ethical, Legal, and Social Implications (ELSI) survey, which assesses how well they understand the consent process and information about the pilot,

and also collects sociodemographic factors. One month after results of the screening are provided, parents of babies with a negative screen are given a series of surveys on their opinions about screening, genome sequencing, and the informed consent process. Between six months and two years after results are provided, they conduct a qualitative interview with parents with babies who received an uncertain or positive screen to learn how the results are impacting them and ways the newborn screening community can strengthen available supports. The overall goal of the ELSI study is to learn from parents to improve their understanding of how the newborn screening process meets family needs and the optimal ways to expand screening in the future.

Early results show a consent rate of between 60-80 percent and they have been using information from the ELSI surveys to revise their materials. Not surprisingly, parents indicated that the most important source of information was the one-on-one discussion with study coordinators. They are in process of initiating all pilot sites within the next quarter. Because parents are being discharged earlier than usual because of the COVID-19 pandemic protocols, they have had to develop passive consent models. They also seek feedback from a community advisory board to ensure that their study materials are appropriate and comprehensive.

### Early Check: North Carolina

***Don Bailey, PhD,*** **Distinguished Fellow, Genomics, Bioinformatics and Translational Research Center, RTI International**

Early Check is supported through an Innovation Award from the National Center for Advancing Translational Science and additional support from other federal and nonprofit sources. It is a research study based in North Carolina to evaluate methods of offering free, voluntary screening to 120,000 parents a year for conditions not currently on the RUSP. Data from the study is used to inform policy and is a long-term research resource for which new conditions may be added. Recruitment and consent is conducted virtually through multi-phase public outreach and consent includes the use of dried blood spots that have already been collected. A negative result is followed with information provided to parents through a patient portal; a positive result is followed with an immediate call by a genetic counselor and then a referral for confirmatory testing and diagnosis. The team then conducts follow-up assessments and provides support and information about interventions.

RTI partners with multiple institutes and laboratories across the state. They systematically assess parent preferences and needs towards the development of practical materials and processes, and they use a sophisticated system for tracking and evaluating every component of the study from consent to follow-up. They have published articles on their methodologies and formative work, such as their use of social media to assess the words and images that resonate most with their target population.

One important component of their study is the use of virtual technologies for recruitment, consent, counseling, assessment, and intervention, which allowed them to continue their study during the COVID-19 pandemic. They do recognize that virtual recruitment is not as effective as in-person recruitment, although it is more cost-effective. Currently, their recruitment rate is approximately 68 percent and they have been testing and evaluating multiple virtual recruitment strategies.

Since 2018, they have enrolled 18,000 individuals across North Carolina with the most concentrated recruitment rates in larger cities. In terms of race/ethnicity, White individuals account for 57 percent of recruitment (as compared to the 63 percent identified through the 2020 Census), African American individuals six percent (as compared to 22 percent identified through Census), and Asian individuals 8 percent (as compared to 3 percent identified through Census).

Dr. Bailey reviewed the mobile application, white board videos, and telegenetic counseling technologies that are used virtually. These technologies have been convenient for families and include functions such as language interpreters, screen-sharing, automated reminders, and audio-video recording. They also provide online educational content about different disorders. Their data system is comprehensive and includes mechanisms for data sharing and security, as well as a follow-up tracker and data visualization tools.

Going forward, they will be moving towards multiplexing a larger number of disorders and have recently received a grant to include Angelman syndrome, Prader-Willi syndrome, and Dup 15q syndrome. They also received a planning grant to develop a very large targeted sequencing panel that they hope to start in 2022. Their goal going forward is to develop flexible systems for responding quickly to newly nominated conditions.

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

- A Committee member asked if these projects have used individual-level social media data for the families, such as cell phone or email, for their outreach approach.
    - Dr. Bailey said that they do not conduct targeted outreach through social media but rather have an algorithm approach that uses age and other filters. They receive phone and other contact information from hospitals and newborn screening cards.
    - Dr. Wasserstein said they receive a list of all the babies born that includes contact information.
- A Committee member asked if the percentage of births that are being reached is known so that they can compare the online recruitment rate to the in-person recruitment rate. He also asked about the cost of advertising on social media and if those costs could be compared to in-person recruitment. Finally, he asked if both projects intend to collaborate and share lessons, especially in terms of parent preferences.
    - Dr. Bailey answered that North Carolina has approximately 120,000 births a year and they are recruiting a little over 600 per month, which is about two-thirds and not near the ScreenPlus recruitment rate. He said that one of their goals is to test different recruitment, laboratory, and follow-up methods to evaluate cost effectiveness. Some strategies, such as the patient portal, have been very cost effective and others, such as social media, are not quite as effective. They are also committed to collaboration and endorse data coordinating centers to help pull all the data together systematically.
    - Dr. Wasserstein said that each program presents a unique recruitment method. Although the in-person recruitment has been successful, there is long-term value for online methods. They are complementary and shared experiences may help find an optimal path going forward.

- An organizational representative asked if the subjects who declined but completed the survey still needed to be consented as research subjects. Dr. Wasserstein answered that they do collect information on individuals who decline and they are not consented, but the data is de-identified and non-trackable.
- An organizational representative asked Dr. Bailey if anyone involved in Early Check can participate in the telegenetic sessions or if they are targeted only to individuals with an out-of-range finding. Dr. Bailey answered that a phone call is the first mechanism of contact for a positive screen and then it depends on the nature of the disorder in terms of how quickly to bring them in. For example, they may use a combination of strategies for Fragile X, which is not as time-sensitive as other conditions.
- An organizational representative asked if the communication strategies used during recruitment had any effect on general public health communication and education for newborn screening. For example, he asked if they evaluated whether participants understand the difference between public health newborn screening communication campaigns and the research program that they enroll in.
    - Dr. Wasserstein answered that when they began their first pilot screen, one of their concerns was that parents may opt out of general newborn screening. There were differences in the script used between the research screening program and the routine screening, but no one opted out of the routine screening.
    - Dr. Bailey responded that they did not see any reduction on routine newborn screening either.
- An organizational representative asked if there were any parents who regretted receiving results even though they consented and if the incidence was at the expected incidence for the general public.
    - Dr. Wasserstein answered that they have not yet had a positive screen. They have found that parents experience less stress and anxiety when disorders are detected through newborn screening versus through a diagnosis.
    - Dr. Bailey said that they had a similar finding. They followed up on maternal stress and anxiety after receiving a positive screen for carrier status and compared it with those with a negative screen. They did not find any differences. In qualitative interviews, there is sometimes a short-term anxiety, but not long-term. It is challenging to compare parents who received information through the research project with parents who go through the diagnostic odyssey – there can be no within-family comparison. It is a complicated question to answer.

### *New Business*

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

Dr. Powell asked Committee members if there was new business to share. Hearing none, Dr. Powell thanked Committee members and said that the next Committee meeting will take place virtually on February 10 and 11, 2022.

### *Adjourn*

Dr. Powell adjourned the Committee meeting at 1:05 P.M.