Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Minutes of November 3-4, 2022

In-Person and Virtual Meeting

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Term End Date: June 30, 2026

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Genetic Alliance
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Vice President of Strategic Development

March of Dimes
Siobhan Dolan, MD, MPH
Professor and Vice-Chair for Research
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National Society of Genetic Counselors
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Boston Children's Hospital
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DAY ONE: Tuesday, November 3, 2022

Welcome, Roll Call, Committee Business

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

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

Committee members in attendance were:

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

Organizational representatives in attendance were:

- American Academy of Family Physicians, Dr. Robert Ostrander
- American Academy of Pediatrics, Dr. Debra Freedenberg
- Association of Maternal & Child Health, Ms. Karin Downs
- American College of Medical Genetics & Genomics, Dr. Marc Williams
- Association of State and Territorial Health Officials, Dr. Scott Shone
- Association of Women's Health, Obstetric and Neonatal Nurses, Dr. Shakira Henderson (Day 2)
- Child Neurology Society, Dr. Margie Ream
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Department of Defense, Dr. Jacob Hogue
- Genetic Alliance, Ms. Natasha F. Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Gerard T. Berry

Dr. Calonge introduced two new Committee members. Dr. Jannine Cody is a Professor of Pediatrics at the UT Health Science Center at San Antonio, where she developed the multidisciplinary Chromosome 19 Clinical Research Center. Dr. Cody's daughter, Elizabeth, was born with a rare chromosome abnormality called 18q, which is easily diagnosed yet not much information existed about medical management on maximizing the potential of individuals living wit h18q. As a result, Dr. Cody founded the Chromosome 18 Registry and Research Society, which brings together more than 3,000 families affected by chromosome 18 abnormalities. Dr. Ashutosh Lal is a pediatric hematologist-oncologist practicing at the University of California San Francisco (UCSF) Benioff Children's Hospital, Director of the UCSF Benioff Children's Hospital Thalassemia Clinical Program and Iron Disorder Program, and Professor of Clinical Pediatrics at UCSF. Dr. Calonge also introduced a new organizational representative for the Association of Maternal and Child Health Programs, Ms. Karin Downs, who recently retired from the Massachusetts Department of Public Health where she was the Maternal and Child Health Director for the Title V program and Director of the Division of Pregnancy, Infancy, and Early Childhood within the Bureau of Family Health and Nutrition.

Dr. Calonge welcomed Dr. Jeff Brosco as the new Director of the Maternal and Child Health Bureau (MCHB) Division of Services for Children with Special Health Needs. Dr. Brosco is a historian and physician who teaches and practices general pediatrics and developmental behavioral pediatrics at the University of Miami Miller School of Medicine. He has held several leadership positions supporting children with special care needs and his research focuses on history, policy, and ethics in child health.

Dr. Calonge provided an update of Committee business. In May 2022, the Committee voted in favor of recommending the addition of guanidinoacetate methyltransferase (GAMT) to the Recommended Uniform Screening Panel (RUSP), and the final decision from the Department of Health and Human Services Secretary (the Secretary) will be posted on the ACHDNC website when it is received. On June 29, 2022, the Committee received a nomination for Duchenne muscular dystrophy. The Nomination and Prioritization Workgroup has begun their review of the nomination and will continue to provide updates to the Committee. Dr. Calonge said that he expects the new Capacity and Prioritization Workgroup will convene shortly after this meeting to begin the development of criteria and processes for prioritizing the review of nominated conditions.

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

Department of Defense Newborn Screening System

***Jacob Hogue, M.D.,* Lieutenant Colonel, Medical Corps, US Army Chief, Genetics, Madigan Army Medical Center**

Lt. Col. Jacob Hogue provided an overview of the Military Health System (MHS) as context for how the Department of Defense (DoD) supports newborn screening. MHS is an overarching system that is responsible for health care delivery and medical education across DoD, serving approximately 9.6 million beneficiaries. The Defense Health Agency (DHA) is a relatively new organization within DoD that was mandated by Congress and formed in 2013 to lead military direct (i.e., military treatment facility or MTF) and contract (civilian) health care delivery. One

of DHA's goals is to implement the rapid adoption of best practices to reduce variation across the MHS. DHA is also responsible for MHS Genesis, an electronic health record systems that allows for data sharing across the entire MHS. Reduced variation in health care delivery and support for data sharing across MHS are important because families, and their infants, tend to frequently move locations. DHA also delivers the TRICARE Health Plan, a program that pays for care delivery by civilian providers. In addition, DoD supports the Exceptional Family Member Program for families that require specialized medical services for a chronic condition.

The most common procedure in MHS is childbirth and there are approximately 120,000 births each year in MHS, with half occurring in MTFs and half in civilian hospitals. The first policy for newborn screening in DoD began in the Army in 2002, requiring all MTFs to provide newborn screening for at least four tests. Following the formation of the Committee, there have been 29 primary conditions and 25 secondary conditions recommended for the RUSP. As disparities in the implementation of screens across states emerged, DoD became concerned about state differences and the frequency of location changes in military families.

TRICARE Management Agency requested a study of military newborn screening in 2006, which resulted in a recommendation to adopt expanded screening. This recommendation led to a policy change in 2011 and a central contract was put in place to support all newborn screening with one central laboratory, ensuring that all newborns received the same screening across states. The contract expired in 2016 with a number of concerns. One concern, for instance, was that implementation of a broad set of tests was occurring across multiple states, reducing screening disparities. In addition, the contract did not support screening follow-up and treatment, which created challenges—particularly in remote areas with reduced access to the MHS direct care system. MHS then moved newborn screening back to state programs in 2016.

Currently, each military service has a separate newborn screening policy and the recent transition to DHA may eventually create a unified policy. MTFs within the continental United States (CONUS) are encouraged to use state screening programs and to establish a plan for follow-up and treatment. MTFs outside of the continental United States (OCONUS), including Alaska, have different processes. For instance, Alaska sends their newborn screens to Iowa and confirmed newborns may be treated in different states. The United Kingdom sends newborn screens to Wisconsin but generally provides treatment in Cambridge or London. Landstuhl, Germany has a large MTF that can provide direct care for infants. Across CONUS, MHS has 11 geneticists, 14 genetic counselors, and a genetics lab that processes much of the genetic testing from MTFs. Although genetic testing and counseling is conditionally covered by TRICARE, genetic counselors are not currently considered authorized providers by TRICARE and there are challenges in obtaining reimbursement. This is a particular challenge for areas without access to direct care at MTFs.

Lt. Col. Hogue said that the transition to DHA may provide the traction needed to change policies and expand services for the newborn screening program. This year, DHA created a Clinical Genomics and Precision Medicine Support Service, which has outlined goals for expanding laboratory services and addressing challenges in the workforce, MHS Genesis information entry, and pharmacogenomics. He summarized that DoD is committed to providing

medical care for military-connected children, aligning their newborn screening program with states, and expanding coverage and availability of genetic testing and counseling.

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

- Dr. Calonge asked how the variation in newborn screening between states impacts active duty families. Lt. Col. Hogue answered that infants are screened in the state in which they are born. This means that an infant born in Washington state will be screened for that state'snewly added conditions because Washington has added them to their panel, but an infant born in Hawaii—which has not added those conditions—will not. Although there are still between-state disparities, the greater challenge that DoD will focus on in terms of policy change is follow-up and treatment.
- Dr. Calonge said that the DoD and MHS could be an ideal setting to consider quality improvement metrics related to time to screening positivity, time to confirmatory testing, and time to treatment. He asked if DoD had the resources and the direction to take on that type of quality improvement. Lt. Col. Hogue answered that they do not currently have a unified policy or available data to conduct an assessment. They have looked more closely at OCONUS newborn screening challenges in terms of timing and customs processing.
- A Committee member asked about the potential for delays and turnaround time overseas. Lt. Col. Hogue said that he had recently talked to people in Korea, Germany, and the United Kingdom and found that the challenge is in differences between the direct and indirect systems. Most babies are born out-of-network and therefore newborn screening occurs out-of-network. If there is an abnormal result, the follow-up stage will involve screens sent to MHS facilities in Wisconsin or PerkinElmer Genetics. Lt. Col. Hogue said that the turnaround time for overseas screening is generally efficient. The challenge has been with the small number of screens that are held up due to shipping or customs problems.
- A Committee member asked for an example describing how short-term follow-up works in the military system. Lt. Col. Hogue said that it depends on the availability of a pediatric specialty care provider. In Madigan Army Medical Center, the process will be very similar to a civilian hospital. The MTF has a pediatric endocrinologist and the ability to send confirmatory testing to the same laboratories as the Washington State newborn screening program. The process diverges in locations that do not have pediatric specialty providers. In this case, the short-term follow-up responsibilities fall on the general pediatrician. One of DoD's goals is to better align with state programs to facilitate earlier access to specialty care. OCONUS MTFs have more challenges and will often reach back to Lt. Col Hogue to work towards a follow-up plan.
- A Committee member asked how treatments are reimbursed through TRICARE and if reimbursement has been a challenge for families. Lt. Col Hogue said that he did not have insight into how TRICARE provides coverage. He has, however, experienced challenges with access to newer, more expensive treatments. Each military hospital has its own pharmacy budget, which is relatively small. If a one-time expensive treatment is needed, the hospital will have to find a way to cover it within that budget. Often, it is faster to send the individual out-of-network to get quicker access to treatment, even when the MTF has available providers for the treatment.

- A Committee member asked for guidance in how a clinician can better navigate TRICARE, which had been a particular challenge in coverage for metabolic formula during the formula shortage. Lt. Col Hogue said that he has heard similar challenges from civilian providers. Most of their challenges with TRICARE are in specialty pharmacy and genetic testing. Lt. Col. Hogue suggested that working with the closest pediatrician inside MHS may be the best way to facilitate care and ensure the patient is connected to the necessary systems.
- A Committee member asked if military families could be eligible for care at centers that excel in or are conducting research on a particular condition. Lt. Col. Hogue said that the short answer is yes and that it happens fairly regularly. Depending on the care needs and the availability of treatment in the region, MHS may authorize insurance coverage and provide travel for both the individual and their family for a period of time. Challenges arise when the family asks TRICARE to cover something that they want rather than need. Clinical trials are not covered by TRICARE or any other insurance because it is not an inherent part of clinical treatment. TRICARE will also not pay for travel to clinical trials.
- An organizational representative asked whether physician assistants and nurse practitioners had been providing genetic counselling and if MHS had considered the genetic counseling laws in the states in which they were practicing. Lt. Col. Hogue answered that they had conducted a study of primary care providers who were provided with extensive training in basic genetic counseling. While it had some effectiveness in the short-term, it did not work well in the long-term. They found that the primary care providers were not comfortable providing genetic counseling, despite the training. Physician assistances and nurse practitioners who do provide genetic counseling do so because they feel genetic testing is warranted and there is no other access to genetic counseling. It is a circumstance in which the policy does not match provider knowledge and comfort level.
- An organizational representative talked about the lack of continuity for the coordination of follow-up in MHS. Often a provider will try to contact a person for follow-up. but the family has been transferred or deployed. Providers then spend hours trying to solve how to ensure the child is appropriately cared for. The representative asked if there was any overarching policy or services that could support continuity. Lt. Col. Hogue said that his facility aims to have one person in charge of follow-up. MHS is a large system and people are assigned a pediatrician after a baby is born. However, there is a lot of mobility both in providers and in families. Some facilities address this by having one number that a state screening lab can call so that individual can establish follow-up care. As DHA pushes out best practices, there may be development of a standard pathway, but currently there is no such unified policy.
- An organizational representative asked if DoD had policies for front-end education to raise awareness in screening awareness or back-end education that is condition-specific after a diagnosis. Lt. Col Hogue said that there is a policy for what to do if a family declines newborn screening. For everything else, the goal is to align with state programs. Although there is no broad DoD or DHA policy for educational requirements, the education is provided nonetheless as a part of good medical care.
- An organizational representative asked whether DoD has access to the American College of Medical Genetics (ACMG) Newborn Screening ACT Sheets. Lt. Col Hogue answered

that they do and that, depending on the state, they may be more reliant on those sheets than on the state program for follow-up information.

- An organizational representative asked whether medical foods, which are commonly excluded by commercial insurance plans, were covered by TRICARE. Lt. Col Hogue answered that the did not know the specific details, but that TRICARE had a change a few years ago that provided some coverage for medical foods. The coverage, however, was imperfect and incomplete.
- An organizational representative asked if MHS or TRICARE has a way to provide timely approvals for out-of-network subspecialty care. Lt. Col. Hogue said that DoD is a federal system and is not necessarily obligated to follow state policies. Although they do try to align with states, there may be circumstances in which MHS follows federal rules, which can help reduce barriers to timely approvals for specialty care. The challenge is not as much a between-state issue as it is a between-TRICARE region issue.

Roundtable Discussion: State Implementation of Conditions Recently Added to the RUSP

Dr. Calonge introduced a panel representing state newborn screening programs that range in size, location, program structure, and legislative processes to better understand the challenges and enabling factors in implementing RUSP conditions.

New Disorder Implementation in Texas NBS Program

***Susan M. Tanksley, PhD*, Deputy Laboratory Director, Texas Department of State Health Services Laboratory**

Dr. Susan Tanksley said that Texas has a statute stating that it will screen for RUSP conditions *as funding allows*. Although Pompe disease and mucopolysaccharidosis type I (MPS I) have been on the RUSP for an extended period, Texas has not had the funding needed to implement the screens because they required new technology and additional lab space. They were able to rapidly add X-linked adrenoleukodystrophy (X-ALD) and spinal muscular atrophy (SMA) because the screening protocols were built on existing technologies and there was less expense involved.

Dr. Tanksley reviewed the Texas NBS evaluation process for implementation. They create a cost estimate that includes both laboratory and follow-up costs, a projected timeframe for implementation, the technology and retrofits needed to support the new conditions, and the various methods (including first and second tier screens) available for the new conditions. Because they have been waiting for the funding needed to implement Pompe disease and MPS I and II, they developed these estimates quite a while ago. However, they anticipate receiving a sizable amount of funds leftover from the end of the fiscal year within the next few months, which will enable implementation. Although Texas does not conduct true pilot studies, it does conduct an extensive validation study to look at performance metrics, reference range for their large population, and the impact of additional screening on the assay. They consider how to integrate and test the new screening within their existing workflow and meet with specialists to develop and refine follow-up protocols. They also evaluate staffing needs in the context of current workforce challenges. Finally, they evaluate their communication and education tools to provide information about the new screening for both health care providers and families.

Oklahoma NBS Program
***Lisa Caton, MS, RN,* Director of Screening and Special Services, Oklahoma Department of Health**
Ms. Lisa Caton said that Oklahoma's process for adding new conditions recently changed due to legislation that requires Oklahoma to be consistent with the RUSP to the extent practicable. This means that they need to be more proactive and start their analysis of a condition as it seems likely to be recommended by the Committee. As the Committee is reviewing a condition, the Oklahoma NBS program will be starting their feasibility and readiness assessment to evaluate existing lab processes, staffing, costs, and the availability of specialists to accept referrals.

Once this assessment is complete, they present their findings to the Infant and Children's Health Advisory Committee, who then makes a recommendation to the Commissioner of Health. Once the Commissioner of Health signs off, the NBS program begins the work needed to add the condition to their panel. This legwork is done in tandem with the Committee's review. Previous to the new legislation, there might be a one-and-a-half to two-year process before adding a new condition.

California NBS Program
***Richard Olney, MD, MPH*, Division Chief, Genetic Disease Screening Program, California Department of Public Health**
Dr. Richard Olney said that California was the first state to be aligned with the RUSP. Their statues were modified in 2016, setting a two-year implementation phase for adding a new condition after its adoption to the RUSP. As a result of this mandate, California implemented Pompe disease in and MPS I in 2018 and SMA in 2020—almost exactly two years after their inclusion in the RUSP.

During these two years, they evaluate the multiple pieces needed to implement a new condition, including cost, methods, and new laboratory or instruments needed. California's procedures tend to be relatively elaborate in terms of interpreting data and reporting results and follow-up data. For newer disorders, the program uses contracts with commercial labs for confirmatory testing. They coordinate with specialists to develop educational materials, which can be challenging if the specialty had not previously been a part of the newborn screening system. These components are tied together through their online screening information system (SIS). California does not have an advisory committee or internal approvals because adding new RUSP conditions is now automatic. Instead, they follow the Committee's recommendation as a roadmap. Dr. Olney said that the procurement and contracting processes for staffing can be challenging and prolonged. There is a process for approving new positions and the recruitment and hiring phase can be convoluted and time-consuming.

NBS Policymaking in Washington State
***John D. Thompson, PhD, MPA, MPH*, Director, Newborn Screening Program, Public Health Laboratories, Division of Disease Control & Health Statistics, Washington State Department of Health**
Dr. John Thompson said that Washington does not have specific rules to align their newborn screening program to the RUSP, but the State Board of Health has authority to implement new newborn screening. The Board will convene an ad hoc Newborn Screening Advisory Committee,

either parent or physician advocacy or from the Committee's recommendation. For example, when the recommendation for MPS II was signed by the Secretary, Dr. Thompson immediately alerted the Board and their internal policymakers in his division in the Department of Health.

The Board evaluates candidate conditions using five criteria: 1) available screening technologies sensitive for the population, 2) available diagnosis and treatment, 3) prevention potential and medical rational, 4) public health rationale, and 5) cost benefit. Washington has a separate requirement through the Administrative Procedure Act stating that, before adopting a rule, an agency will determine if the probable benefits are greater than the probable costs. Washington meets this requirement with a decision tree analysis to compare outcomes for no screening and screening. They make a final determination in the form of a cost benefit ratio and net benefit for screening program, and the Advisory Board uses this information to make a recommendation to the State Board of Health.

Dr. Thompson highlighted some common challenges. For instance, it is difficult to evaluate intangibles such as stress caused by a diagnostic odyssey or a screening test that creates large numbers of false positives. In addition, Washington must receive legislative approval to increase spending. The legislature only meets once a year, creating a significant barrier for implementing a new condition that requires new staff or technology.

Florida's Process to Implement a New Condition
***Roberto Zori, MD*, Professor, Chief of Clinical Genetics and Metabolism**
University of Florida; Chair, Florida Genetics and Newborn Screening Advisory Council
Dr. Roberto Zori said that Florida's statutes state that a condition approved by the Committee must be implemented within a year of its approval. The Newborn Screening Section uses that year to prepare a presentation for the Advisory Council, which then uses that information and provides an approval (or not) or a request for more information. If it is approved, then there is a year-and-a-half maximum period of time to implement the new condition, unless the Advisory Committee requested more information.

This process ensures that there is immediacy in implementation, but there are challenges in maintaining precision and accuracy. There are many moving parts that need to be completed within a year. For instance, there is an evaluation of cost per screening tests, methods, compatibility, staffing and space, data system updates, updated provider education, technical assistance for birthing facilities and follow-up processes, and website updates. Concurrently, there is a legislative request for funds that needs to be submitted during the appropriate legislative cycle. Within a year, the Advisory Council votes to approve or not, but they can request additional information if they are uncertain about safeguards or the accuracy of information. Advisory Council only meets twice a year and a request for additional information could significantly delay the process. There are also lobbyists and legislators who push for faster movement.

Dr. Zori said that there are problems with this push to move a condition faster into implementation. First, there is a need to ensure minimal risk to patients, which takes time. Second, parents can become stressed while they wait for confirmatory testing. Finally, there is a

chance of missing a positive screen. Adequate time is needed to ensure that these risks are safeguarded.

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

- Dr. Calonge asked panelists if there was a certain step of the process that was the most challenging or took the longest and if there were resources available to help the program overcome those challenges.
    - Dr. Tanksley said that the cost estimate for Pompe disease and MPS II was approximately $7 million and annual ongoing costs were expected to be even more. The program receives seed funding, which is helpful, but if there is not already funding in the works, the $300,000 to $400,000 that they receive in seed funds will not be enough for implementation. They were grateful to receive CDC funds, which helped develop their second and third tier tests but was not enough to do all of the work. Having enough funding would set the program up for success.
    - Ms. Caton said that prior to the change in their statute language, the challenge was the length of time needed to get through the rule change process. Removing that barrier was helpful. Going forward, the barrier will be lab capacity to add new conditions, which will depend on the available methodologies and whether new equipment, lab space, staff hiring, and staff training would be needed.
    - Dr. Olney said that the staffing process was a major challenge. Getting funds for a position takes time, but the actual hiring process is the barrier. When California implemented adrenoleukodystrophy, they used a contracting process to hire contact staff. It still took time, but it was a solution. Funding is not as much an issue in California because screening is mandated, which puts more weight on funding requests. Laboratory-developed testing can also be a prolonged process and having an FDA-approved assay can help facilitate the process.
    - Dr. Thompson said that the budget preparation and approval process is the longest, most challenging issue. For example, the Board of Health approved the addition of ornithine transcarbamylase (OTC) deficiency to their panel. Dr. Thompson immediately began the internal policy process to add the condition to the budget proposal for the governor's office. The budget proposal for the condition will needed to be added to the House and Senate budget when their sessions start in January. There are several hurdles to overcome before the fee increase is approved and implementation can move forward.
    - Dr. Zori said that said that the biggest challenge in Florida was money and time. There is a lot to be done within one year and the Advisory Council does not have a lot of time to assess its preparedness. It would be helpful to have guidelines at the federal level to outline what needs to be in place for each condition. Because of the short timeframe, it is very important to get it right the first time. A second review would help highlight things that were forgotten or need to be corrected. It would be helpful to review it in terms of risk factors so that the system can be optimized. There should be an automatic review process to fix these issues before legislative funds to be released. In addition, there is no set procedure for what happens when a budget is not approved but the clock is still ticking.

- Dr. Warren said that MCHB will release a funding opportunity in November 2022. They anticipate funding 25 applications to receive $345,000 for five years.
- A Committee member talked about unintended consequences in newborn screening policies. For instance, in Texas, there is a mandate to screen for secondary conditions. Secondary conditions were not meant to be newborn screening targets but rather reminders for clinicians about the different conditions they might encounter when looking at primary conditions. In Washington, there is a mandate to screen for ODC deficiency when there is no appropriate screening that is sensitive or specific. The Committee member asked the panel to address three questions: 1) whether the Committee should consider eliminating the terminology for secondary screening, 2) what impact would result on state newborn screening programs if the Committee made a recommendation to add a condition only if an appropriate second tier test was available to minimize false positives, and 3) the actions that the Committee could take to improve state's ability to implement newborn screening recommendations, recognizing the limited options for action available to the Committee.
    - Dr. Tanksley said that she has chaired a task force through the Association of Public Health Labs (APHL) for more than a year and one of their recommendations was to determine whether secondary conditions should be on core set of conditions or eliminated altogether. Despite clear communications on the purpose of secondary conditions, the information is interpreted differently across states. In terms of requiring a second-tier test for confirmation, there has been a lot of recent emphasis on reducing false positives. New conditions screened with tandem mass spectrometry have better positive predictive values, but the same could not be said about the original panel. There has been discussion about improving screening for existing RUSP conditions, but the effort has not had much traction. The additional funding coming from MCHB might be good support for quality improvement efforts related to this.
    - Ms. Caton agreed that there is a lot of confusion over the primary and secondary panels. The general public and legislation tend not to differentiate between the two and may continue asking when a secondary screen will be added to a panel. Requiring second tier testing to reduce false positives is a good idea, but there also needs to be solid first tier tests because such a requirement would create a huge burden on programs. Additionally, the Committee has been adding new conditions much more efficiently and it is difficult for programs to keep up, much less have time for quality improvement. One idea is for the Committee to recommend a condition for a trial period before being added to the RUSP so that more long-term data could be collected and the burden on states could be reduced.
    - Dr. Olney also agreed that a re-examination of secondary conditions on the RUSP should be conducted. In terms of what the Committee could do to help, one idea is to re-examine current RUSP conditions to determine whether they should remain or not. There could be an evaluation of real-world data that the Committee could use for a re-evaluation process.
    - Dr. Thompson said that a requirement for a second-tier test would be great for some programs, but not for those that do not have capacity, expertise, or space. A lot of the second and third tier tests are molecular, and he had recently participated in a webinar that addressed the fact that few newborn screening

programs have a strong molecular component. His program is currently hosting an APHL fellow, who is working on method development and program improvement., including for second tier testing. In terms of what the Committee could do, the MCHB funding is so important to states, which could use the funds for quality improvement, data analysis, or health information exchange. There are not a lot of funding opportunities that provide significant amounts over several years. Often, funding opportunities are small or short durations, and it is difficult to justify the resources need to apply.

    - Dr. Zori said that the secondary criteria is a big problem in his state. Recently, their legislature decided to move faster to add SMA, which meant that there was even less time to review. Because hearing was a second-tier test for cytomegalovirus (CMV), the process went around the Advisory Committee and straight to legislature. Lobbyists have good intentions, but they can also make it difficult to complete an analysis on precision and unintended harm. Going forward, it may be time for the Committee to stop adding new conditions to the RUSP and to focus on fixing systems through a federal quality improvement initiative. This would provide some foundation to demonstrate the importance of precision and accuracy to legislature. It would also improve the system for new conditions to be added in the future. There is also a need for guidelines on optimal practices that could be used to measure what is being met or not. Finally, it would be beneficial to provide grants to all 50 states instead of 25. It should not be a competition but rather a way to help each state get to a good project.

- A Committee member suggested that the Committee could create a recommendation that motivates states to push through quality improvement efforts as hard as they push through new conditions. Dr. Calonge responded that the Secretary's recent request for a report back on findings after implementation speaks to his expectation for quality assessment and improvement going forward.
- An organizational representative commented that there should be caution about the definition of secondary conditions. In the representative's state, resources and benefits cannot be provided to a child unless it is a screened condition. Others consider a condition secondary if it was not screened during the newborn screening period.
- An organizational representative talked about the need to be better communicators with the public, even if there is disagreement among experts. In addition, there may be opportunities for pediatric testing as a way to take pressure off of the newborn screening program. It would also be helpful if state programs communicated their challenges to all stakeholders, who want to have a better sense of what is happening at the real-world level. Finally, the representative talked about fielding several requests for reviews of the same educational materials and suggested the need to share materials and not reinvent the process in each state.
    - A Committee member commented that it is not the fault of advocates for pushing things through. State legislatures are not doing due diligence to understand the potential for unintended consequences. The organizational representative agreed that there is a need for states, advocacy organizations, and legislators to work together because if they do not, the newborn screening program may collapse under its own weight.

    - Dr. Zori added that his program responded to expanded screening by creating a workgroup and engaging with three other states to develop a document outlining how to expand newborn screening. He agreed that lobbyists have priorities that differ from the state program, particularly around timelines. But by engaging with lobbyists, there can be a sharing of perspectives and a better understanding of what needs to be in place before adding a condition.
- An organizational representative suggested that using an implementation science framework would be better to evaluate the heterogeneity across state newborn screening. Quality improvement tends to work best in homogeneous settings.
- An organizational representative said that individuals who are caring for patients with positive newborn screens are really struggling, in part because of the pandemic and even before the addition of new conditions. It has become difficult to provide adequate care, which should be considered during these discussions. Dr. Calonge added that state laboratories are also responding to COVID-19 and monkeypox testing. There is competition for the same workforce across different programs. Understanding how best to support programs with implementation is very important for moving forward.

Public Comments

Marianna Raia

Ms. Marianna Raia is Associate Director of Programs at Expecting Health. She provided an overview of their programs, which aim to instill leadership and confidence in individuals and families to help them drive change and ensure that the newborn screening process is a positive experience for all. Expecting Health has reached more than 18,000 families through training and education and has an extensive partnership network to help connect families to support. She welcomed the Committee and other meeting attendees to engage with their training programs and to reach out for potential collaboration.

Dylan Simon

Mr. Dylan Simon is the Director of Policy for the EveryLife Foundation of Rare Diseases. He provided clarity about their legislative processes and activities that aim to strengthen the newborn screening system. Specifically, EveryLife Foundation works with state leaders and the rare disease community to pass state legislation to align state screening programs to the RUSP. State RUSP alignment has three components: 1) auto-inclusion to vote for inclusion to add a new RUSP condition to the state panel, 2) a specific timeline within which to add a new RUSP condition, and 3) allocation of resources to support the addition of a new RUSP condition. He invited the Committee to reach out with any questions about their legislative efforts.

Kim Stevens

Dr. Kim Stevens is President of Project Alive, Co-chair of the EveryLife Foundation Newborn Screening Diagnostics Working Group, and parent advocate. She encouraged the Committee to provide more formalized opportunities for stakeholder engagement and provided five recommendations to meet this aim: 1) ensure that Committee is composed of professional diversity that reflects its full network of stakeholders, 2) add a patient advocate as a Committee member to properly represent the patient experience, 3) add a public comments section dedicated to advocates speaking about conditions currently in the RUSP nomination review process, 4) take more time to respond to public comment to develop a deeper dialogue with the Committee's

stakeholders, and 5) include the perspective of the patient experience in panel presentations and discussions.

Heidi Wallis
Ms. Heidi Wallis has a 19-year-old daughter and five-year-old son with GAMT deficiency. While her daughter is intellectually disabled, her son was able to be diagnosed at birth and was treated with a readily available supplement. The GAMT Deficiency Association for Creatinine Deficiencies has a strong network of researchers and a large patient registry and would welcome the opportunity to work with labs to help implement this screening.

Nikki Armstrong
Ms. Nikki Armstrong is the Newborn Screening Program Manager for Duchenne Newborn Screening and spoke on behalf of the Parent Project Muscular Dystrophy and the Duchenne patient community. She provided an update of the efforts that Parent Project Muscular Dystrophy has conducted in preparation for Duchenne screening and treatment. Notably, they published outcomes from a survey conducted with physicians to better understand their readiness for Duchenne newborn screening. They have also compiled a list of care recommendations endorsed by experts. Duchenne has five FDA-approved therapies and more in the research pathway. However, babies must be identified early for the best outcomes and newborn screening would provide that opportunity.

Amanda DeRossett
Ms. Amanda DeRossett has a six-year-old son with Krabbe disease. He was the first child to be identified by the Kentucky newborn screening program and was able to quickly receive a transplant. Although her son was born in a Kentucky hospital, the family lived on the border in Tennessee, where Krabbe disease is not screened. If they had not decided to cross the state lines, her son might not be here today. She believes that every parent, regardless of state, should have the same opportunity to treatment that her son was provided.

Kelly Denora Bonacoursa
Ms. Kelly Donora Bonacoursa has a one-year-old daughter with Krabbe disease. As an active duty military family, their careers and plans to move overseas were halted with the diagnosis. They live in Virginia, a state that does not screen for Krabbe disease, largely because the condition is not on the RUSP. Since her diagnosis, her medical care has amounted to more than $500,000. Her daughter receives 24/7 in-home nursing, hospice, and palliative care to support her difficulties with eating and other developmental delays. As the disease progresses, her care will become more complex, and she has a very short life expectancy. Ms. Bonacoursa urged the Committee recommend the addition of Krabbe disease to the RUSP so that other families could access early diagnosis and intervention.

Hema Rangarajan
Dr. Hema Rangarajan is a physician specializing in bone marrow transplant for children and Associate Professor of Pediatrics at Nationwide Children's Hospital and Ohio State University in Columbus, Ohio. She described her team's experience in the care and transplant for two infants diagnosed with Krabbe disease through newborn screening. Both children are now toddlers, are free from transplant-related complications, and are making steady developmental gains. Dr.

Rangarajan emphasized that this success serves as an example of an in-state pediatric transplant center's ability to conduct an expediated transplant process.

Stacey Pike Langenfeld
Ms. Stacey Pike Langenfeld is Co-founder and President of Krabbe Connect. She reviewed the unsuccessful 2009 nomination submission for Krabbe. There were three concerns that led to it not being added to the RUSP: 1) the disease not being well-defined, 2) the lack of information on the best screening method, and 3) uncertainty about the benefits of treatment. In the last few years, there have been advances in understanding the subgroups of Krabbe, the validation of an effective second-tier screening for psychosine, several peer-reviewed articles on successful transplant intervention, and clinical trials for gene therapy. She urged the Committee to consider these advances as they continue their evaluation of the recent nomination package for Krabbe disease.

Lisa Brackville
Ms. Lisa Brackville's daughter was diagnosed with Krabbe at six-and-a-half months old and died at 20 months of age because she was not eligible for treatment. Ms. Brackville has spent five years advocating for more equitable newborn screening programs and helped take the legislature and funding barriers out of Pennsylvania's newborn screening program. In addition, her advocacy helped lead the Pennsylvania Newborn Screening Advisory Board to add Krabbe to the panel, resulting in the identification of four positive screens. She said that no parent should have to bury their child when newborn screening provides an opportunity for treatment.

Krabbe Disease 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**
Dr. Alex Kemper presented an interim summary of the Evidence-Based Review Group's review of Krabbe disease. The Evidence-Based Review Group conducted two group calls with the Technical Expert Panel and a series of key informant interviews with experts and advocates. Krabbe disease was not recommended for the RUSP in 2009 because there were several gaps in understanding, including concerns about the definition of early infantile form, the screening and treatment algorithm, the benefits of stem cell transplantation, and over-referral and follow-up. There have been advances since 2009, including the addition of psychosine testing to decrease false positives and reduce unnecessary referrals.

Krabbe disease is an autosomal recessive lysosomal storage disease and leukodystrophy caused by homozygous or compound heterozygous pathogenetic variants in the gene coding for glucocerebrosidase (GALC). Krabbe is associated with low GALC enzyme and elevated psychosine in early infancy and the expected birth prevalence of Krabbe disease is approximately 1 per 100,000. Classification in Krabbe disease has evolved to better reflect its epidemiology and different clinical usage. The nomination of Krabbe disease focuses on the first 36 months; therefore, the Evidence-Based Review Group also focused its review what is expected in the first 36 months of life.

Dried blood spot for GALC enzyme activity is the first-tier screening for Krabbe and second tier testing for psychosine can reduce false positives and help stratify risk. Molecular analysis can

also identify variants with known severity. An expert panel recommended psychosine levels of more than 10nmol/L as strongly predictive of early infantile Krabbe disease, indicating a time critical need for follow-up. Identified infants are immediately referred for diagnosis and genotyping can further stratify high, low, and no risk treatment pathways. Ten US states currently offer Krabbe disease newborn screening, nine of which use psychosine at some point in the screening algorithm.

Dr. Kemper reviewed evidence from New York's newborn screening for Krabbe disease, which did not include psychosine screening at the time. Nearly two million infants were screened between 2006 and 2014. Of these, 620 infants had low GALC enzyme activity, of which 348 were referred for follow-up and five infants were confirmed with infantile Krabbe disease. In Illinois, nearly 500,000 infants were screened between 2017 and 2020, with 838 infants identified with GALC enzyme activity and another 288 infants identified by a repeat GALC screen. Illinois used psychosine as a second-tier test, which identified two newborns with psychosine levels between 10 and 35, six newborns with levels between 2 and 5, and 178 with levels less than 2 (pseudodeficiency). Dr. Kemper presented data across seven states showing a prevalence of referrals ranging from 0.6 to 13.8 per 100,000 screened. Confirmed Krabbe disease ranged from 0.0 to 1.8 per 100,000 infants. Infants identified as at risk for late-onset Krabbe disease ranged from 0.0 to 2.3 per 100,000 screened and the Evidence-Based Review Group is working with the state newborn screening programs to understand their follow-up to better characterize the follow-up and status of these infants.

Diagnosis for Krabbe disease includes an additional clinical test for GLAC enzyme and psychosine concentration, and molecular testing if it had not already been conducted. Diagnosis can be confirmed with additional information from magnetic resonance imaging (MRI), nerve conduction, electroencephalogram (EEG), auditory and visual evoked potentials, and cerebrospinal fluid (CSF). Treatment is hematopoietic stem cell transplantation (HSCT) for presumed early infantile Krabbe disease, ideally within 30 days, and later HSCT for other phenotypes. Gene therapy as a treatment for Krabbe is currently in clinical trial and not available for clinical purposes.

Dr. Kemper reviewed evidence for treatment outcomes. In a 2018 study, 19 participants who had received HSCT by two months of age from a single center between 1996 and 2010 showed no difference in 5- and 10-year survival by early (less than 30 days) or later (more than 30 days) HSCT. Importantly, there were significant differences in functional outcomes. Walking was higher in early HSCT (90 percent) than later HSCT (17 percent); communication higher in early HSCT (100 percent) than later HSCT (50 percent); and feeding by mouth higher in early HSCT (90 percent) than later HSCT (17 percent). Seizure incidence was lower in early HSCT (0 percent) than later HSCT (33 percent). Dr. Kemper cautioned that this study had a small number of participants.

In 2016, New York screened approximately two million infants. Of these, 348 were referred, of which two were lost to follow-up and five were diagnosed with early infantile Krabbe disease. Of these five infants, four received HSCT ranging from age 24 to 41 days. After treatment, two infants died of complications, one was non-ambulatory and had developmental delays at eight years old, and one had developmental delays and failure to thrive at five years old. In a 2022

study of HSCT treatment outcomes in six infants with early onset Krabbe disease, five surviving children were evaluated for neurologic delays between 30 and 58 months after treatment. All had developmental delays, particularly in gross motor skills, but they were still alive.

Dr. Lisa Prosser reviewed the plan for evaluating population-level health outcomes for Krabbe disease newborn screening. This analysis will use an annual US cohort of 3.65 million newborns to project both outcomes with newborn screening and clinical identification. Screening outcomes will include positive screens, risk, projected transplants, and mortality. Clinical identification outcomes will include identified cases and mortality. Modeling is a systematic approach for decision-making in uncertain conditions and projects ranges of short-term outcomes to support the decision-maker's determination that the alternative is expected to yield the most health benefit. It can also identify key parameters that drive results and areas that need more information.

Dr. Prosser said that the second technical expert panel reviewed the model structure and underlying assumptions and provided input about classification and screening outcomes. Their input is reflected in the revised model, which is anticipated to project up to three-year outcomes. The model will use data from multiple states to project hypothetical pathways to different positive screen and treatment outcomes. The model will also simulate clinical presentation of Krabbe disease in order to compare these outcomes with hypothetical screening outcomes. Dr. Presser will finalize the results in the next few months, then input data and project outcomes for analysis before the final results are shared with the Committee.

Dr. Kemper reviewed progress of the Public Health Impact Assessment, which will be conducted by APHL. APHL will interview individuals in newborn screening programs in nine states that offer Krabbe newborn screening. The assessment will consider staffing, funding, competing priorities, administrative challenges, and legislation. APHL will also survey states that are not offering Krabbe newborn screening.

Committee Discussion

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

- Dr. Calonge referred to the New York data, which showed that five of the nine high-risk children were later confirmed and received a transplant, and asked how the four other children were ruled out. Dr. Kemper said that they are trying to collect that information from the program.
- A Committee member asked if Dr. Kemper could confirm that psychosine testing resulted in no false positives that were referred for transplant. Dr. Kemper answered that infants with early infantile Krabbe disease that should be treated with transplant will all have elevated psychosine levels. There is a single case report of an infant who had a psychosine level that was not quite at 2, but who was confirmed with infantile Krabbe disease. The cutoffs for psychosine levels are artificial because the disease is a spectrum and psychosine levels are likewise a spectrum.
- A Committee member asked if psychosine screens were a simple or complex analysis. Dr. Kemper said that he understands it is more complicated than, for example, GALC enzyme analysis, which can be easily multiplexed.

- A Committee member asked about the timing of transplant for late infantile and later onset Krabbe disease and whether optimal timing was determined by pre-symptomatic MRI or other indicators. Dr. Kemper answered that their work has focused on the youngest children but that he understands that a constellation of findings determines timing. Another Evidence-Based Review Group member added that timing is based on signs of active disease. The later the onset of disease, the slower its progression. Early onset Krabbe disease progresses rapidly and needs an immediate evaluation process. Later onset Krabbe affords a little more time for evaluation.
- A Committee member noted the importance of using the right comparison group. To compare children who received transplant to children who did not, there needs to be confidence that those who were transplanted had similar genotypes and psychosine concentrations to those who were not. It is evident that transplanting a child who presents with symptoms at six months old will have very different outcomes than a child who was transplanted at one month of age. The Committee member asked if there was a summary of the data supporting the utility of psychosine and if the evidence was overwhelming for psychosine or not. Dr. Kemper said that the evidence he has reviewed shows that psychosine clearly reduces the number of infants that are referred and that this finding has been embedded into classification algorithms. Psychosine can therefore be considered a "game-changer" for Krabbe newborn screening.
- A Committee member commented on the challenge of evaluating the entirety of data. The Committee works with problematic data and small numbers, but it would be helpful to have enough granularity in the Evidence-Based Review Group's final report to help Committee members see the bigger picture.
- A Committee member asked about the stability of psychosine as a measure and whether it was considered a bioMarcer for disease progression or if it was the same over the course of disease. Dr. Kemper answered that there were studies that measured changes in psychosine over time but that he would have to review the data and make sure that it is included in their report.
- An organizational representative noted that much of the Committee's discussion has been informed by states that have instituted universal newborn screening for Krabbe and that it is fortuitous to have the wealth of data. Other conditions only have pilot study data because mandatory screening has not been implemented in states. The representative wondered if it was reasonable for the Committee to consider a recommendation for more funding for a number of states to institute screening for these more complicated conditions. A Committee member responded that the Committee might not be empowered to make such a recommendation and that there would be some discomfort in suggesting that some states institute a screen while others do not. The recommendation could be to fund every state, although that may come with other complications.

DAY TWO: Wednesday, November 4, 2022

Welcome and Roll Call

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

Blueprint for Change: Access to Care for Children and Youth with Special Health Care Needs and Their Families

Dennis Kuo, MD, MHS, **Professor of Pediatrics Chief, Division of Developmental and Behavioral Pediatrics, University of Rochester Medicine/Golisano Children's Hospital**

Dr. Dennis Kuo provided an overview of the *Blueprint for Change: A National Framework for a System of Services for Children and Youth with Special Health Care Needs* (the Blueprint) and its implications on the newborn screening system and the RUSP. He began by describing a system as not only its components, but also its context in terms of an underlying philosophy and a journey to health and wellness. For instance, MCHB envisions a nation in which all mothers, children, and families reach their full potential. "Potential" is defined not as an absence of disease, but rather a journey of full growth and development. Children and youth with special care needs (CYSHCN) encompass children with conditions recommended for the RUSP, which are based on the potential net benefit for screening and the availability of effective treatment. But the journey does not end with diagnosis and treatment because many RUSP conditions involve ongoing specialty care management needs across the lifespan. The Blueprint sets the context that underlies the system of care for CYSHCN and provides a roadmap for the journey through the system. It therefore also provides context for the comprehensive, longitudinal management of RUSP conditions and a roadmap for the Committee to consider conditions going forward.

Despite the incredible work by HRSA and MCHB to improve the system for CYSHCN, it remains fragmented, especially in terms of comprehensive, coordinated care; the transition from pediatric to adult health care systems; and ongoing inequities in care access. MCHB convened a steering committee in fall 2019 to address these gaps. Work continued in fall 2020 with a national summit of 150 experts to develop focus areas. By 2021, the vision and focus areas were drafted and in June 2022, the Blueprint was released in a supplement of *Pediatrics*.

MCHB had six indicators of a coordinated, comprehensive, family-centered system of services for CYSHCN: 1) families as partners, 2) a medical home, 3) adequate insurance, 4) early and continuing screening, 5) community-based services, and 6) transition into adulthood. The Blueprint was based on these six indictors and updated to include four interdependent focus areas that center around the issues that families consider the most important to strengthen the system of care. These are: 1) Health Equity, 2) Family and Child Wellbeing and Quality of Life, 3) Access to Services, and 4) Financing of Services. Specifically, the Blueprint outlined calls:

- For health care systems to measure outcomes that are meaningful to children and families.
- To design a system that is build around the needs of children and families, not just a diagnosis or treatment protocol.
- To address the upstream and downstream factors that prevent CYSHCN from a fair and just opportunity to be healthy.
- To support a service system that support access, equity, and integration, and eases the financial burden on families.

Dr. Kuo provided examples of how the Blueprint could be applied to newborn screening by highlighting the comprehensive system of care needed to support children with sickle cell

disease and its related costs, the transition from the special education system to adult health care systems in children with hearing loss, and the multiple specialists needed to support a child with SMA. He also emphasized that there is an opportunity to use human-centered design to ensure that the journey through the system is not only adequate, but also a delightful experience for families.

Dr. Kuo outlined several guiding questions for how the Committee's Workgroups could consider the Blueprint and its four focus areas in their deliberations. The Education and Training Workgroup could consider how the Blueprint should be used to address the broad system of service partners that should be included; the systemic barriers to screening, testing, and follow-up; and collaboration with community and family partners (i.e., family health information centers, federal agencies). The Follow-up and Treatment Workgroup could consider the need for continuous screening for co-morbidities (i.e., developmental delays and mental health); systemic barriers to service access (i.e., systemic racism, distribution issues, telehealth regulations); and the importance of care navigation, care integration, and family support. The Laboratory Standards and Procedures Workgroup could consider financing and payment for screening and follow-up, system access for false positives and negatives (i.e., training, learning collaboratives, data-driven outcomes, regional oversight), and service access to follow-up (i.e., structural barriers, family navigation through the system).

Dr. Kuo summarized that there is a need for pilot studies to propose newborn screening algorithms or treatment protocols to provide the data necessary to inform evidence review. There is a need to understand the system and what could be achieved if the system were optimized. The Blueprint for CYSHCN provides a way to frame system and research initiatives that can pave the way for a more predictable journey and improved health outcomes.

Discussion

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

- A Committee member asked what top three concrete steps could be taken toward a more delightful system. Dr. Kuo answered that the first step would be to ensure that the right stakeholders are not only at the table, but are true partners in the conversation. This requires some level of training, support, and compensation for time. There should at least two or three individuals who reflect the community and are part of the conversation. The second step is addressing diversity, equity, and inclusion. A lot of organizations are creating diversity, equity, and inclusion efforts, but have not quite opened up completely because it involves extremely vulnerable conversations. Efforts have to go past conversations and into data, and there are best practices that organizations can take. For instance, the organization can look at their own makeup and perhaps conduct blind reviews during recruitment. These need to be standard practices in order to truly address the structural issues. The third step would be to ensure that there is no penalty in insurance plans for families with CYSHCN. Dr. Kuo shared a personal story of his own child with special needs who transitioned to adult health care. Her medication costs are $60,000 a year and she is only able to be covered by insurance because of the Affordable Care Act. There should be a mandate that people with special health care needs are not financially penalized. The idea that having people share in the buy-in to control health care utilization is not one that is well-supported by research.

- A Committee member asked if the Blueprint would also accommodate the need for very early diagnosis and treatment in conditions in which diagnosis is made prior to birth. Dr. Kuo said that the Blueprint does have room for those conditions because its focus on the lifespan, which includes maternal health and the prenatal environment.
- A Committee member commented on the 85 percent of CYSHCN who are not in well-functioning programs and asked if there was something about the other 15 percent that could be informative. Dr. Kuo answered that there are more complex differences the further one dives into the data. The National Survey of Children's Health is a composite measure and the areas that get the least favorable responses are medical home and transition to adult care. Within those areas are further differences by condition, developmental factors, behavioral factors, immigration status, and racial/ethnic factors. For instance, the issues in the medical home may be related to a financing system that does not value counseling or provide the resources needed for comprehensive care. Learning collaboratives and partnerships with adult health care systems are needed to support transition. A child from an immigrant family will have language barriers and difficulty navigating and access care. There may be a need to partner with community services. Although a lot of progress has been made, the landscape of children's health has changed because children who would not have survived in the past are living today. There is a need to understand the combination of metrics and to have many stakeholders at the table, especially those at ground level, such as families.
- A Committee member asked if there had been any consideration to training adult physicians who do not know how to care for an adult with congenital heart disease or a growth hormone deficiency. Dr. Kuo said that the issue does get a lot of attention. There has been some debate about how long young adults should stay in the pediatric system, but there is a point in which the young adult begins to have needs that are unfamiliar to pediatric providers. Conditions, such as Down syndrome, have much longer life expectancy and are now facing new onset conditions that are not understood or were even seen before. There have not yet been systemic initiatives to address this, but there have been local efforts with individual learning collaboratives. Med-peds and family physicians have skills needed to take care of young adults. Working with family partners and thinking about a continuum of care rather than an hand-off from one system to another would be a good start.
- A Committee member said that the scope of deficiencies highlighted in the Blueprint seem overwhelming and asked how Dr. Kuo suggests the document be used. Dr. Kuo answered that the Blueprint was mean to be aspirational. There have been numerous examples of policy and financial initiatives that have worked, and there have been substantial advances in understanding over the last few decades. For instance, Medicaid coverage today is vastly different than it was years ago. It is important to look at policies as a way to strengthen justice and to provide children with coverage, food security and access to care. Another area the Blueprint can be used is in thinking holistically. This involves thinking differently, bringing different stakeholders to the table, and imagining in solutions in new ways. The Blueprint provides a way to have discussions with families at the center. These discussions will start to make a difference, little by little. Some of the principles in the Blueprint did not come from the health field. For instance, the concept of a delightful experience came from the IT sector. It is important to draw from lessons outside the field.

- A Committee member asked how the Blueprint can address complex disorders such as intellectual disability and the transition not just from primary pediatric care but also the various subspecialities involved. Dr. Kuo said that the definition of CYSHCN includes children with intellectual and developmental disability who are in a complex system. The pandemic highlighted how one system that falls apart for this population will cascade to failures other systems. The Blueprint is framed with a civil rights lens, which begins to touch on issues such as guardianship and supported decision-making. These are relatively new research areas, but there are indications that empowering and recognizing the rights of a child and young adult results in improved health care, educational, and functional outcomes. It is not enough to recognize the need for a care coordinator and consequently provide a care coordinator. The care coordinator also needs training in the journey, empathy, and cultural humility and responsiveness. The Blueprint helps frame the discussion about lived experience, equity, and fairness as a foundational point to questions about access, navigation, training, and allocation of resources.
- Dr. Calonge asked about the dissemination plan for the vast and diverse set of stakeholders who could be impacted by the Blueprint. Dr. Kuo answered that the Blueprint has catalyzed action across multiple levels, from social media messaging and presentations to decisions about funding and policy. New York has been using the Blueprint to move discussions toward how to move through the journey together. In his personal talks with colleagues, he has found that they consider the Blueprint to be a "game-changer" because it completely resets the discussion.
- Dr. Michael Warren commented that MCHB has begun to incorporate the Blueprint in their Title V Block Grant guidance, as well as in grant-making opportunities such as the CYSHCN Research Network that is looking at quality-of-life measures and a new funding opportunity to support a national center on systems of services to address the idea of a well-functioning system.
- An organization representative reminded the Committee that having difficult conversations—such as what is needed to advance diversity, equity, and inclusion—is something that is asked of families who share their personal experiences. In addition, there has been a focus on funding lab and state initiatives and less funding in important areas such as family engagement and public education. It can be frustrating to hear about the importance of family involvement when the financial component has not caught up. Dr. Kuo agreed that there is a long way to go, but that just having this conversation is a significant advance from a few decades ago.
- An organizational representative commented that, except for the heavier focus on diversity, equity, and inclusion, efforts 20 years ago were not dissimilar to a lot of the ideas outlined in the Blueprint. The representative talked about a project to involve parents and advocates in disseminating their needs and vision to the medical homes. But they were preempted by insurance companies and the government, who co-opted the medical home and moved it from a family-centered home to a payer-centered home that had no resemblance to the vision that parents had. Dr. Kuo responded that he shared this perspective and that there were no easy answers, but that being humble and responsive, bringing the right people to the table, and focusing on equity and lived experience will uncover questions that had not previously been considered. For instance, he was part of a group that talked about the transition between early intervention and special education as

one of the hardest challenges to overcome, which was not something he was taught in medical school. He reiterated the importance of centering conversations around families.

- An organizational representative asked how children identified as at-risk for late onset conditions are addressed with the Blueprint and how family-centered approaches can facilitate access to care for family members who may need to be screened after a child has been identified. Dr. Kuo answered that the answer involves team-based care, which will look different in different care settings. There needs to be a system to not only screen but also to continuously collaborate with schools or other settings across the lifespan to promote development.
- An organization representative talked about the fragmentation that occurs between the diagnostic testing at 20 weeks prenatal and newborn screening. There is an enormous window of missed opportunity. Medical records can worsen the situation because prenatal data and newborn records are not connected, and neither will be sent to a community physician. The representative asked whether the Blueprint could be used as framework for data collection. Dr. Kuo agreed that data from different health care systems is a major challenge and that there needs to be advances in terms of human-centered design interfaces to make the connection useful. He emphasized the importance of having a conversation across systems, which can advocate that all of care is part of one system and that there is a continuum in the from prenatal to adulthood.

Follow-up and Treatment Workgroup Update

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

Dr. Kyle Brothers said that the Follow-up and Treatment Workgroup considered the three ideas they identified in the last meeting to determine one focus area that could have practical, concrete steps. The focus area the workgroup chose was the request for a blueprint for follow-up treatment as part of the RUSP nomination process. This would be a task both for the nominators to complete and for the Committee to develop guidance on. The Committee could also utilize the information to ensure the implementation of the screening was ready to go.

The preliminary ideas that the workgroup discussed for the blueprint were to include a breakdown of subgroups (e.g., pseudodeficiency, asymptomatic) identified in newborn screening, which would be different for every condition. Breaking this into subgroups would help the states understand what follow-up was needed for each subgroup. The nominators would also be asked to develop standardized terminology to use in both communications about implementation, but also as a starting point for data collection for outcomes in the follow-up stage. The nominators would be asked to provide guidance on follow-up needs specific to each subgroup, such as the types of evaluations, laboratory exams, and locations. This could provide states with a checklist of needs to implement the screen, which would highlight the resources they have and the resources they need to obtain. The blueprint should focus on whether the screened individual has the primary condition and not follow-up needed for asymptomatic individuals who may develop symptoms later.

Laboratory Standards and Procedures Workgroup Update

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

Dr. Kellie Kelm provided an overview of the Laboratory Standards and Procedures Workgroup discussion to identify ideas to help state programs. The workgroup identified two focus areas. One focus area was improvement in technology, which the workgroup felt was out of scope for their discussion. The other focus area was to support program development for a new condition. The workgroup talked about building on current processes to develop a "quick start" guide or worksheet "shell" for the implementation of a new RUSP condition. When the APHL conducts the Public Health Assessment, they create a fact sheet. There could be an expansion of this factsheet to include information that would be helpful in implementation. When a condition is added to the RUSP, there is a toolkit that is developed, but it is a long document that can be too much to present to a state advisory board. Another idea was to provide support for a champion or project manager. States found that having a champion was very helpful in driving all the pieces together, but some states do not have the resources. The Committee could develop a project plan or worksheet and states could have a project manager or champion meeting, using the worksheet as a checklist. There are different implementation considerations across states, but the worksheet would identify the different components needed for implementation so that states could identify what they have and what they need to bring in. It could also address second-tier testing so that states could share information.

In addition, the workgroup discussed the need to improve processes for conditions already on the RUSP, which may have new second-tier testing or other advances. The guidance could therefore be both prospective and retrospective to assess current performance and ways to improve. It would also provide data to support requests for resources to conduct second-tier testing. The workgroup also talked about how the current methodology for screening homocystinuria is not effective and has an unacceptable false negative rate. The workgroup was interested in gathering information about this issue to determine if there was something that could be implemented to improve the process.

Education and Training Workgroup Update

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

Dr. Jane DeLuca reviewed the ideas and solutions that the Education and Training Workgroup identified at the last meeting and highlighted the solutions that were feasible. The workgroup talked about goals for education and training and who the target was. Different categories of people have different education and training needs, and the Committee's Educational Planning Guide is a good resource spanning 31 different types of stakeholders across 28 distinct topics. Patient education is a priority, but there are training needs across the system. There are existing educational materials and training centers and there is an opportunity to centralize these resources into a repository. This would require gathering the resources, organizing them, and creating templates describing the existing materials. The core question that the workgroup considered was whether to focus on new conditions or on older conditions that still needed education.

The workgroup also discussed social media as a way of educating the public. There is a lot of potential for misunderstanding, some of which is passed through prenatal screening messages, Recent articles and resources on newborn screening from the New York Times could be potential areas of further confusion rather than clarity. The workgroup talked about partnering with government agencies to identify common areas that could lead to education collaborations, as well as with professional organizations, which have the ability to widely communicate messaging. Finally, the workgroup talked about the need for culturally appropriate education and training and the need to engage people from diverse cultures to understand their experiences of health care. Their three priority areas were combined into a single statement to partner with governmental agencies and professional groups working in similar spaces, and support the development, distribution, and awareness of diverse and culturally focused new and existing newborn screening educational programs and materials, ensuring coverage of basic genetics and newborn screening for all.

Discussion

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

- A Committee member asked when in the process the blueprint for follow-up would occur and if the blueprint would look different from state to state. Dr. Brothers answered that the blueprint would be submitted with the nomination package and would focus on the condition itself and its subgroups rather than how a specific state would implement it. States would then use the blueprint as a guide. Since it can be sometimes a challenge for the Committee to evaluate the subgroups, having this outlined in the nomination package would be helpful to that process as well.
- A Committee member said that there is limited information about the natural history, such as the penetrance and variability in expression of a given condition. The hope is that a blueprint could inform data collection from following individuals longitudinally to inform the understanding of the long-term mechanisms of the condition. Dr. Brothers agreed and said that the blueprint would focus on the short-term follow-up to understand what happens after an individual screens positive. The longer-term follow-up that looks at outcomes that occur with or without treatment is not necessarily part of this recommendation. However, it is critical to interdigitate both short- and long-term follow-up to understand the natural history.
- A Committee member asked who the target audience would be for the blueprint and how the blueprint would be different from developing guidelines for the management and treatment of disease.
    - Dr. Brothers answered that the guidance would not be on the treatment of disease but rather on what happens when a child screens positive. There is still an open question about whether clinical practice guidelines are needed to inform this initial step. In some instances, there is a big difference between an individual who screens positive and an individual who has the condition. There could be room for professional societies to help inform that guidance for the first step. The first target audience would be the Committee in the decision-making process. The second target audience would be the states as a starting point for implementation. It would provide the states with a standard terminology and definitions, which would be helpful in reporting and with quickly identifying what resources will be needed for implementation.

    - Dr. Calonge added that this issue became clear in the review of New York's data on Krabbe, in which nine children were identified as high-risk, but only five were confirmed with the condition.
    - Dr. Brothers said that it also ties in with the idea about secondary conditions. There is a need not only for a case definition for a specific condition, but also separate case definitions and standardized terminology for each of the sub-situations that occur when an individual screens positive.
    - Dr. Calonge said that a lot of this information could be generated from the Evidence-based Review Group because they look closely at treatment. It may be an additional information source for the blueprint.
- A Committee member commented that the purpose of newborn screening is to take care of a child identified with a serious and chronic condition. The conversation about short-term or long-term guidelines raises a larger concern about putting imaginary boundaries on what is in the state's purview. In order to implement screening for new disorders, there has to be a conversation about integrating long-term considerations for implementation.
- An organizational representative agreed that long-term follow-up needs to have a place in Committee conversations at the time the recommendation is made. It may not be in the purview of the Committee and there may be limitations in terms of available resources. But it would be beneficial to partner with NIH to help the Committee work through how to consider long-term outcomes, particularly for individuals who do not have the classic disease but who will likely have a problem that surfaces later in life.
- An organizational representative said that ACMG develops Act Sheets that addresses what should be done with a positive screen and also addresses issues that come up with different phenotypes from screenings. The Act Sheets are all regularly revised to reflect best practices and Committee members are welcomed to review them for gaps. ACMG is also investing more resources into the Newborn Screening Translational Research Network to use standardized terminology, which includes all of the phenotypic terms directly relevant to newborn screening. However, the current resources are clearly not adequate to provide long-term follow-up for every disorder. There is also an issue with data access. While it is relatively easy to access health care data, some of the other data that would be useful for assessing long-term outcomes, such as school data, are harder to access. It is important to remember that states ultimately make the final decision. There is explained clinical variance, which may be addressed differently across different states to reflect their population. But most of the challenge is unexplained clinical variance, which needs to be reduced. ACMG also supports the creation of standards and guidelines for testing, and these are also being regularly reviewed and revised. Any ACMG member should take advantage of public review processes to make comments.
- An organizational representative said that asking nominators, who are often parent advocacy groups, to develop this blueprint can be a challenge for some organizations that do not have the resources. It could become an equity concern. The representative asked if the workgroup considered how nominators would collect that information. Dr. Brothers answered that the workgroup did extensively discuss this issue but that it was not presented because it was not a part of the charge. There likely will need to be multiple stakeholders involved, with states playing an active role to clarify the quality of testing.

There needs to be a plan, including for funding, to help nominators who do not have the resources.

- An organizational representative suggested that there are simple messages about screening that are getting lost in translation amongst both providers and the public. The recent New York Times article was written by a journalist who did extensive research but still translated information in a way that will tap into the mistrust of the public. There is much more work to be done on these simple messages that could help with follow-up and that can be embedded into blueprints for laboratories and in professional provider education.
- A Committee member asked whether the Committee would be able to collect more genetic data on conditions that are diagnosed through second tier or subsequent testing in order to further strengthen first tier testing or shorten the diagnosis process.
    - Another Committee member suggested that, while there is not policy or tradition of going back to review data after implementation, the Committee has mentioned several times the need to review and update current RUSP conditions.
    - Dr. Warren said that HRSA will evaluate the available resources to determine if this activity is possible.
- An organizational representative commented on the need to be more explicit about diversity, equity, and inclusion across all of the workgroups. One missing piece has been the self-reflection of implicit biases that health care providers have and how that is affecting families today. It is important to take the Blueprint one step further by making explicit what is meant by centering families. As was mentioned earlier, families have been made very vulnerable by being asked to present on their painful experiences. Providers and staff need to likewise be vulnerable in looking at their own biases and how those can inadvertently contribute to less-than-ideal experiences.
- An organizational representative talked about how newborn screening provides the opportunity to objectively identify individuals, irrespective of pre-existing bias. For example, severe combined immune deficiency disorder was considered to primarily be a disorder in individuals of Northern European descent until newborn screening was initiated and 80 percent of cases were found in individuals not of Northern European decent. The question is whether those who have been identified have equitable access to the services needed or not.

Committee Discussion on Action Items on Advancing Newborn Screening System

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

Dr. Calonge reviewed all three workgroup's priority areas and identified one tangible, discrete area for each workgroup that could be addressed within the next year. For the Education and Training Workgroup he suggested identifying how to create or modify the existing education and training materials to include cultural awareness for populations that are traditionally overlooked and/or marginalized so that the information is more equitable.

For the Laboratory Standards and Procedures Workgroup he indicated interest in creating the quick guide and project planning "shell" to help states identify the elements needed for implementation, such as staffing, equipment, and test interpretation. The quick guide could be developed in coordination with the Committee's recommendation process so that the guide could

be included in the recommendation letter to the Secretary. This would help the Secretary feel less concern about the burden being placed on states to implement new conditions.

For the Follow-up and Treatment Workgroup he suggested they consider developing the blueprint and identifying the elements that need to be included. He added that he recognized the challenge being given to the nominating groups and suggested that there may be ways to expand current processes, such as the Evidence-based Review, to include a small expansion on treatment and follow-up. There could be a template to build this methodology using an existing condition such as SMA.

- A Committee member asked what resources are available to support these charges. Dr. Calonge said that there are staff available to coordinate times to meet and Zoom available for virtual meetings. ~~He suggested that having information flow from the Evidence-based Review Group and Committee member expertise can at least inform a framework within a year.~~ The Committee charge is a little broader than making recommendations to add new conditions to the RUSP. If there are concrete suggestions to improve the implementation of recommendations, there is nothing in the Committee charter that prevents a specific request to increase resources.
- An organizational representative asked workgroup members to be cognizant that some of the work in their priorities has already been done by partners and to not duplicate efforts. In addition, there is information available from the last two Committee meetings' presentations on challenges in the system and the overlap of public health and medicine that should be reviewed. He reiterated the importance of not pushing forward without reflecting on the past.
- An organizational representative said that there have been some lawsuits in newborn screening that should be on the agenda for 2023 that could be informative. A Committee member agreed that this was an important topic to review because it speaks to the potential harms of compulsory newborn screening on the people.

New Business

***Ned Calonge, MD, MPH*, Committee Chair**
Dr. Calonge invited Committee members and organizational representatives to share new business or announcements.

Dr. Parisi announced that NIH has an open request for information on feedback for future research needs and infrastructure support for newborn screening research

Dr. Calonge thanked Committee members and said that the next Committee meeting will be virtual on February 9 and 10, 2022.

Adjourn

Dr. Calonge adjourned the Committee meeting at 1:00 P.M. E.T.