Health Resources and Services Administration
Advisory Committee on Heritable Disorders
in Newborns and Children

Brief Summary of Committee Meeting
January 29-30, 2024

Introduction

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) met on January 29-30, 2024, to discuss various topics related to newborn screening and genetic disorders. Committee members received updates about the Family Outcomes of Newborn Screening project; two presentations on family perspectives research; a Phase 2 update on the Duchenne-Muscular Dystrophy Evidence-based Review; updates on revisions to the ACHDNC Decision Matrix Tool, Nomination Package, and Nomination and Evidence-Based Review Process; and an expedited evidence-based review and committee report on newborn screening of Krabbe Disease.

Family Outcomes of Newborn Screening: Project Overview Update

Don Bailey, Jr., PhD, Med

Dr. Bailey described the background and objectives of the Family Outcomes in Newborn Screening Project, focusing on the significance of evaluating family outcomes in newborn screening (NBS) programs. The project seeks to create a framework for assessing family outcomes in NBS using diverse stakeholder inputs, literature reviews, and feedback from the Committee to finalize and publish a comprehensive set of outcomes.

Committee Discussion

Committee members and organizational representatives asked questions and provided comments related to the incorporation of health equity into the study; how newborn screening stakeholder groups would be identified; and the importance of understanding family outcomes for individuals with positive, false positive, and negative screening results.

Research on Family Perspectives

Families' Search for Meaning and Value in Rare Genetic Diagnoses

Sara Ackerman, PhD, MPH

Dr. Ackerman explored the broad utility of diagnostic genome sequencing, particularly for families dealing with rare genetic diagnoses. The presentation emphasized the need to expand the definition of utility to encompass clinical outcomes and personal dimensions like emotional, cognitive, and social factors. Dr. Ackerman described the Program in Prenatal and Pediatric Genomic Sequencing (P3EGS) study, which underlined complexities families encounter in navigating service and support landscapes and the disparities underserved families face in using genomic information effectively.

The "Value of Values": Expanding Assessment of Net Benefits and Harms through Social Science Data

Aaron Goldenberg, PhD, MA, MPH

Dr. Goldenberg emphasized the growing need for integrating social science data into NBS practices and research among evolving NBS practices such as expanding NBS panels, genomic screening, and residual dried blood spot use. The presentation highlighted the lack of data on public and parental values, the underutilization of available data, the anecdotal nature of data on harms or benefits, the lack of systematic integration of social science data into evidence reviews, strategies for integrating values and perspectives into decision matrices, and the role of social science data in policy development.

Committee Discussion
Committee Members and Organizational Representatives provided comments and asked questions regarding how the evidence types described in the presentations might be used for Committee decisions; the importance of combining qualitative and quantitative data in consented studies; possible tools to measure resiliency; and the scarcity of studies related to how families deal with uncertain results.

Public Comments

Four written comments and ten oral comments were provided to the Committee on day one from Cure MLD, Muscular Dystrophy Association, Parent Project Muscular Dystrophy (PPMD), medical practitioners, and parents of children with a heritable disorder.

Seven oral comments were provided to the committee on day two from the National MPS Society, Hunter's Hope, Forge Biologics, medical practitioners, and parents of children with Krabbe disease.

A Committee member made an inquiry to Dr. Joanne Kurtzberg's public comment regarding Dr. Kurtzberg's experience with the availability of hematopoietic stem cell transplantation (HSCT) donors for patients from non-white backgrounds. Dr. Kurtzberg, a cord blood banker and transplant expert, explained the advantages of using cord blood for HSCT, noting its rapid donor procurement, lower requirement for matching, and superior engraftment in certain conditions like Krabbe disease. Dr. Kurtzberg highlighted the efficiency of finding cord blood donors through the National Marrow Donor Program, the quick process of donor workup and shipping, and a 95% success rate of finding suitable donors for non-Caucasian patients, including babies with Krabbe disease.

Duchenne Muscular Dystrophy Evidence-Based Review: Phase 2 Update

Alex R. Kemper, MD, MPH, MS
Dr. Kemper provided a comprehensive update on the evidence-based review of Duchenne Muscular Dystrophy (DMD). The talk highlighted legislative advancements for DMD newborn screening in Ohio, New York, Minnesota, Arizona, and Illinois. Dr. Kemper described various treatments, including drugs like Eteplirsen, Golodirsen, Viltolarsen, and Casimersen, gene therapy, and glucocorticoid therapy, focusing on their outcomes and approval statuses. The presentation also addressed the correlation between dystrophin levels and functional outcomes, the benefits of early identification, non-pharmacologic interventions, and the impact on individuals and families.

Committee Discussion
Committee members and organizational representatives discussed topics related to DMD and the process used by the Evidence Review Group, including but not limited to the following: the role of the Technical Expert Panel (TEP); the importance of patient-centered outcomes; and exon skipping treatments for DMD.

ACHDNC Decision Matrix Tool: Public Health Assessment

Ned Calonge, MD, MPH
Dr. Calonge presented on suggested revisions to the Decision Matrix Tool for Public Health Impact Assessment (PHIA) and outlined a comprehensive approach to evaluating the readiness and needs of pilot states for implementing new testing protocols for NBS-identified conditions. Phase I focuses on surveying pilot states to assess their requirements for implementation, such as new equipment, lab space, staff needs, legislative changes, and financial appropriations. It considers the time and cost associated with confirmatory testing, treatment initiation, and whether additional funding would be needed for follow-up. Phase II extends the survey to more states, summarizing information from the

pilot states to gauge whether states could implement testing within two years if a condition were added to the RUSP, identifying the resources and support needed. The process emphasizes gathering data on the estimated time and cost of implementation, the proportion of states ready for implementation within two years, and those requiring additional external support, with a strategy to include both states that could quickly move towards implementation and those facing challenges.

Committee Discussion

Committee members and organizational representatives discussed topics related to the Decision Matrix Tool PHIA, including: the importance of considering staffing needs for follow-up activities; the timeline and feasibility for implementation of testing if a condition is added to the RUSP; the selection criteria for states involved in Phase II of the PHIA; survey response rates; and legislative alignment in states. It was suggested that the ad hoc group working on PHIA take into consideration the meeting presentation and discussion and meet to discuss further and share updates with the Committee in the future.

ACHDNC Nomination Package Revision

Ned Calonge, MD, MPH

Dr. Calonge discussed the current challenges and proposed revisions to the nomination process for conditions to be included in the RUSP. The presentation highlighted the burdensome process for nominators, including the extensive effort required to compile a nomination package for conditions, unclear terminology used on the nomination form, and lack of space for additional information. The ACHDNC Nomination Process Revision presentation proposed a two-step process for nomination. In the first step, nominators would answer four key questions about the availability and effectiveness of screening tests, confirmation of diagnosis, identification of infants with the condition through a population-based project, and whether early identification leads to better health outcomes. If affirmative, the nominators would submit peer-reviewed publications for each question. The ACHDNC Chair, select ACHDNC members, and HRSA staff would review the information submitted and determine readiness for the second step. The second step involves completing a detailed nomination package, describing the condition, screening process, the net benefit of screening, and other considerations. The process aims to streamline the nomination procedure, provide clear guidelines, and ensure a comprehensive evaluation of the condition's suitability for newborn screening.

Committee Discussion

Committee members and organizational representatives discussed topics related to the nomination process, including but not limited to the following: the role of benefits and harms to families; the complexity of incorporating questions related to family impact; and challenges of the nomination process for nominators.

ACHDNC Nomination and Evidence-Based Review Process Proposal

Ned Calonge, MD, MPH

The proposal addressed whether the ACHDNC should evaluate the complete spectrum of peer-reviewed evidence when considering new policies or recommendations. It emphasized that the primary focus has been on the benefits and harms to the individual child and recommended considering the impacts on the family and society, including considerations of equity. Financial and geographical factors for the family, psychological effects, opportunity costs to the public health system, and the overall harms and benefits were highlighted as crucial areas of concern. Furthermore, it was proposed that any harms and benefits considered should be supported by peer-reviewed evidence directly relevant to the condition being reviewed, underscoring the importance of evidence-based decision-making.

Discussion
Committee and meeting participants discussed the role of secondary conditions in the nomination process; challenges related to the availability of peer-reviewed evidence for harms and benefits; how evidence of benefits and harms is used in decision making processes; recommendations to support expedited medical research to support condition nominations; and the importance of the Committee and HRSA staff engagement with nominators.

Dr. Calonge announced that a Federal Registry Notice (FRN) will be available for people to submit written comments on the ACHDNC Nomination and Evidence-Based Review Process and encouraged both in-person and virtual participants to provide comments.

Newborn Screening or Krabbe Disease: An Expedited Evidence-Based Review

Alex R. Kemper, MD, MPH, MS
Lisa Al. Prosser, PhD
The Evidence Review Group (ERG) provided a presentation sharing their findings that indicated that using psychosine levels ≥10 nM as a criterion for the second-tier test could effectively identify Infantile Krabbe Disease, with cases detected having significantly high levels of psychosine. Additionally, no false negatives were reported with psychosine ≥10 nM, suggesting a low risk of missing Infantile Krabbe Disease cases. The review highlighted variations in screening practices across states and the outcomes for infants identified through screening and treated with hematopoietic stem cell transplantation (HSCT) showed promising survival rates compared to those identified through clinical symptoms.

Committee Discussion
Committee members and organizational representatives discussed topics and asked questions related to the evidence-based review of infantile Krabbe disease, including: clinical studies described during the presentation; the impact of newborn screening for Krabbe disease; modeling of the proportion of families who received HSCT; the complexity of HSCT; and second tier testing using psychosine in state labs.

During Committee discussion, an organizational representative from the Society for Inherited Metabolic Disorders (SIMD) shared the society's unanimous decision against adding Krabbe disease to their research and care panel, citing concerns about the effectiveness of the proposed therapy, its feasibility within the recommended timeframe, and the financial and healthcare access inequities it may cause. Despite their commitment to supporting affected families, they emphasized the need for additional evidence on the utility of transplants, FDA approval for treatments, and better access to care before reconsidering their decision.

Committee Report: Newborn Screening for Krabbe Disease

Shawn E. McCandless, MD
Jennifer M. Kwon, MD, MPH, FAAN
Drs. Kwon and McCandless served as Committee liaisons to the External Review Group (ERG) for the review of infantile Krabbe disease and provided a presentation summarizing the screening approach for infantile Krabbe disease using two-tiered dried-blood spot screening approach, characterized by low galactocerebrosidase (GALC) enzyme activity and a psychosine level of ≥10 nM to improve specificity and reduce the follow-up of uncertain late-onset cases. They highlighted infantile Krabbe Disease as an autosomal recessive disorder leading to neurodegeneration and early childhood mortality, with hematopoietic stem cell transplant (HSCT) being the only treatment, albeit with associated risks. Data from state programs and outcomes from 11 screened cases were reviewed, showing a survival benefit

for those receiving HSCT early. They presented on treatment-related mortality, equity in donor availability, and the readiness of state labs for implementation. The Committee liaisons did not recommend including infantile Krabbe disease as a core condition on the RUSP based on a balance of potential benefits and harms, alongside the challenges of diagnosis and treatment coordination.

Committee Discussion

Committee members and organizational representatives discussed topics and asked questions related to infantile Krabbe disease, including: concerns regarding treatment-related mortality; the Committee's role in determining screening criteria for infantile Krabbe disease; risks and benefits of HSCT; and the importance of ensuring families have the choice to screen or not screen. After Committee discussion, the Committee posed a motion to recommend adding infantile Krabbe disease to the Recommended Uniform Screening panel (RUSP) as a core condition. The motion was carried.

New Business

None.

Committee Votes

Motion #1: (Mistry / Caggana) Motion to approve the meeting summary from the meeting on November 2-3, 2023.

13 in favor / 0 opposed. Motion carries.

Motion #2: (McCandless / Kwon) Motion to recommend adding Infantile Krabbe disease as defined by low GALC enzyme activity AND psychosine ≥10nM for inclusion as a core condition on the Recommended Uniform Screening Panel.

10 in favor / 3 opposed. Motion carries.