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

Brief Summary of Committee Meeting
November 2-3, 2023

Introduction

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) met on November 2-3, 2023, to discuss various topics related to newborn screening and genetic disorders. Committee members received updates about the National Center for Newborn Screening System Excellence (NBS Excel), Cooperative Newborn Screen System Priorities Program (NBS Co-Propel), and an opportunity to volunteer for the National Academies "Newborn Screening: Current Landscape and Future Directions" study. Updates were given on a National Academies of Science, Engineering and Medicine (NASEM) newborn sequencing workshop and the NewSTEPs program. Recent work on the decision-making matrix and conflict of interest process were presented. Members attended one of four listening sessions and then reconvened to discuss the nomination and evidence review process. Finally, updates were given about the ongoing evidence-based reviews for Duchenne muscular dystrophy (DMD) and Krabbe disease. The meeting was open to the public and public comments were provided.

NASEM Workshop Update: Next Generation Screening – The Promise and Perils of DNA Sequencing of Newborns at Birth

Natasha Bonhomme, an organizational representative for Expecting Health, provided a recap of the NASEM workshop "Next-Generation Screening – The Promise and Perils of DNA Sequencing of Newborns at Birth." The workshop focused on the benefits, risks, and ethical concerns of newborn DNA sequencing. It addressed the equity of next-generation screening in the U.S. and involved various stakeholders, including families and health system representatives. The sessions covered a range of topics, from the practicality of implementing DNA sequencing at scale to its impact on precision health. Key workshop discussions focused on the balance of benefits and harms, the importance of engaging underrepresented voices, the need for responsible and equitable deployment, and the challenges of integrating sequencing into existing health systems. The workshop emphasized building trust, respecting ethical considerations, and ensuring that developments in sequencing translate into real health benefits. The NASEM Workshop concluded with plans for a study to examine and improve the current newborn screening systems and processes in the U.S.

Committee Discussion

a. A Committee member noted that the Committee functions with divergent definitions for the term *newborn screening* and asked if the term was defined in the workshop. It was clarified that the concept of state-based newborn screening was not part of the workshop. Instead, moderators of the workshop attempted to ask clarifying questions aimed at identifying the context of words such as *screening*.
b. A Committee member asked about the next steps after the workshop. It was explained that the final step for the workshop was the creation of the report. However, it was noted that the conversation continued and continues in other places, such as the International Consortium on Newborn Sequencing (ICoNS).
c. A Committee member asked for clarification about the types of sequencing that had been discussed and whether it was DNA sequencing technologies or genomic/exome sequencing. It

was clarified that the workshop was about genomic sequencing. Encouragement was given to be precise in language and not use the word *sequencing* as a shortcut.

d. A Committee member expressed concern about the implementation of genomic/exome sequencing as a part of newborn screening. It was clarified that the talk concerned sequencing during the newborn period but may or may not have included state-based newborn screening.
e. A Committee member asked if targeted next-generation sequencing was discussed, such as looking at particular genes for specific conditions. It was clarified that the workshop did not go into this level of detail.
f. An organizational representative noted that the infrastructure does not currently exist for widespread genomic sequencing in state newborn screening programs.
g. A Committee member proposed a conceptual framework that involved defining the requirements that would be needed to have full genomic sequencing for newborns as a state-based program.

Public Comment

Two written comments and 18 oral comments were provided to the Committee. Commenters included representatives from EveryLife Foundation for Rare Diseases, Expecting Health, Parent Project Muscular Dystrophy, Muscular Dystrophy Association, Cure MLD, the MLD Foundation, Hope for PDCD Foundation, as well as parents of children living with genetic conditions. Comments covered providing studies related to the costs of delayed diagnosis, as well as sharing firsthand experiences with Pyruvate Dehydrogenase Complex Deficiency (PDCD), Krabbe, Duchenne Muscular Dystrophy (DMD), and Metachromatic Leukodystrophy (MLD).

ACHDNC Decision Matrix Tool

The Committee Chair convened a small group in October 2023 that consisted of current and past Committee members to discuss potential updates to the Decision Matrix Tool. The Committee Chair described proposed changes to the ACHDNC Decision Matrix Tool as changes to align with current Committee practices and not to "move goal posts" or change the criteria for nominating conditions. Key changes to the Decision Matrix include reclassifying the grading system into designations: "A" (high certainty of substantial net benefit), "B" (moderate certainty of substantial net benefit or high certainty of moderate net benefit), "C" (moderate to high certainty of little or no net benefit, or net harm), and "I" (low certainty, indicating insufficient evidence to assign designation). Conditions with an "A" designation would be recommended to the Secretary for inclusion in the Recommended Uniform Screening Panel (RUSP), while "B" designation conditions may be recommended after further discussion and a separate vote. Those with "C" or "I" designations would not be forwarded for inclusion. The proposed changes also include separating the public health impact, feasibility, and readiness assessment from the evidence-based decision to add or not add a condition. The Committee Chair will convene a separate ad hoc topic group to discuss potential updates to the assessment for public health impact, feasibility, and costs.

Committee Discussion

a. A Committee member suggested replacing *state health departments* with *newborn screening system* to better encompass the laboratory and follow-up and clinical care.
b. A Committee member asked if a condition classified as a "C" would still undergo a feasibility analysis. It was stated that the ad hoc topic group that will be convened to discuss the public health impact assessment will discuss this question.

c. A Committee member asked for clarification about the process of an "A" designation automatically moving to a recommendation to the Secretary. It was clarified that it would be recommended to move directly to the RUSP from an evidence standpoint. However, a public health readiness, feasibility, and impact assessment would still be required before an official recommendation is made.
d. A Committee member suggested changing *current estimate of total cost* to a *range of costs* on the proposed questions for assessment since costs are based on the general approach.
e. An organizational representative noted that the proposed changes to the Decision Matrix tool did not have an adequate assessment of the follow-up and clinical requirements of the newborn screening system.
f. An organizational representative noted that, if feasible, the relative access to care for affected babies, especially in terms of cost, should be considered. It was clarified that treatment costs were not included. Another organizational representative noted that recommending an expensive condition to the RUSP could weaken or strengthen inequities depending on external factors.
g. An organizational representative noted that both the "C" and "I" designations would not be forwarded to the Secretary, but the "I" designation also indicated that evidence gaps would be identified and shared with nominators. They suggested potential changes to this language to ensure feedback is provided to all nominators despite the designation.
h. An organizational representative described a state resource for the Committee to review as it revises the Decision Matrix Tool. The resource is a report generated for a state prior to implementation of a condition and includes various factors associated with cost.

ACHDNC Conflict of Interest

Committee member Jennifer Kwon proposed recommendations for how the Committee could assess conflicts of interest (COIs). The proposed changes to the COI process focused on ensuring evidence-based decisions were free from undue influence, particularly from special interests, politics, and advocacy. Members would disclose financial, business, professional, and intellectual conflicts before meetings. Decisions on participation restrictions would be made based on these disclosures, ranging from no restrictions to recusal from discussions and/or votes. Financial interests covered investments and relationships that could affect decision outcomes, with a disclosure threshold set at $1,000. The proposal also distinguished organizational representatives, who should not be subjected to the same COI standards as voting members but should disclose funding sources annually. This revised approach aimed to maintain transparency and integrity in decision-making processes.

There was a proposal to separate the organizational representative part of the proposal, add language around the federal grant exception to exclude cases where there was an opportunity for financial benefit, and include duality of interest. It was decided to consult with legal advisors before finalizing this process.

Committee Discussion

a. A Committee member noted the value of transparency about duality of interests from Committee members, even in cases when the factors did not rise to a COI and to distinguish between duality of interests and conflict of interests.
b. A Committee member asked whether these changes would also apply to the Evidence Review Group and Expert panels. The concept was described as important, but further legal consultation was needed.

c. A Committee member asked whether this proposal was a shift from the typical process of disclosing a conflict. It was confirmed that the proposed process is different than how conflicts are usually handled by the committee. Instead of an annual conflict of interest review, a topic-specific COI assessment would be done prior to each meeting and disclosures would include potential financial, professional, business, and intellectual conflicts.
d. An organizational representative commented on having required disclosures for the percentage of the budget related to a specific topic. They also noted that although the organizational representatives represent a specific organization they also have personal interests that may be a conflict. It was clarified that organizational representatives would have different types of disclosures because they did not vote.
e. An organizational representative asked why federal and nonprofit grants were excluded. A Committee member responded based on experience with the US Preventive Services Task Force (USPSTF) and explained that federal grants were peer-reviewed with a well-defined process and were granted to an institution instead of an individual, so they should not be counted as a COI. The organizational representative suggested tracking this with nonprofit grants and noted that federal grants may result in profit (i.e., through patents).
f. An organizational representative suggested that the disclosures should include personal financial interests of organizational representatives because their testimony was considered. There was a proposal to design a disclosure system agreeable to organizational representatives.
g. An organizational representative noted that representatives of large groups might not know the financial scope of the entire organization. There was an indication that the phrase *to the best of your knowledge* could be used to address this situation.
h. A Committee member asked whether the disclosures would be public even if they did not result in an action. For Committee members, the disclosure would be kept private. The idea was to maintain confidentiality of individuals and their investments. There was a follow-up about whether a conflict needed to be publicly announced or not. The specifics of this issue required additional discussion.

Listening Sessions: Considerations for Nomination and Review Processes

The ACHDNC hosted four listening sessions for the Committee and the public related to the Committee's nomination and review processes. The four listening sessions groups comprised: Family and Representative Organization, Laboratory, Clinician, and Public Health. The listening sessions were structured around three guiding questions about the nomination process, and six guiding questions on the evidence-based review.

Committee members presented overviews of the listening session discussions, which had several overlapping themes. Regarding the nomination process, key points included: the need to decrease the burden on nominators when submitting a nomination package and the importance of establishing additional mechanisms to accommodate the review of multiple conditions. Regarding the evidence-based review, key points included: the need to review parent/family outcomes and not just treatment outcomes, how to balance and weigh relative benefits and relative harms, and the need to develop a robust long-term follow-up system for those identified by NBS to acquire more data. The Committee discussed the significance of FDA approvals in identifying new conditions for the RUSP, handling false positives in rare diseases, and the responsibility shift towards physicians. The possibility of expanding the Committee's scope beyond newborn screening to include additional strategies was raised, highlighting the need for careful deliberation to avoid overextending scope.

Newborn Screening Excel / Newborn Screening Technical Analysis and Evaluation Program (NewSTEPs)

Mr. Jelili Ojodu, representing the Association of Public Health Laboratories (APHL), provided an update on their newborn screening initiatives, notably the Newborn Screening Technical Assistance and Evaluation Program (NewSTEPS). The program recently received supplemental funding to address issues discussed in previous Committee meetings. Mr. Ojodu outlined four primary areas of focus: (1) standardizing the naming and counting of conditions in newborn screening, (2) secondary testing to reduce false positive results, (3) health equity in screening, and (4) measuring long-term outcomes and quality of life in newborn screening. APHL formed workgroups and communities of practice to tackle these areas, aiming to bring uniformity to how states name and count conditions and improve secondary testing capabilities. They planned to establish a community of practice focused on health equity. Lastly, they are collaborating with RTI International and regional networks to assess and develop metrics for long-term follow-up and quality of life in newborn screening.

Duchenne Muscular Dystrophy Evidence-Based Review: Phase 1 Update

Dr. Alex Kemper provided a comprehensive overview of DMD, an X-linked progressive disease-causing muscle function loss, primarily in males. He detailed the genetic basis of DMD, its progression from early childhood to adulthood, and associated dystrophinopathies. The screening section highlighted the use of creatine kinase, particularly the CK-MM isoform, and discussed the absence of DMD in current state newborn screening programs despite past and smaller ongoing screening initiatives. Treatment strategies were discussed including supportive care, physical therapy, nutritional management, and various pharmacotherapies like glucocorticoids and gene therapy. Dr. Kemper also reviewed ongoing activities such as literature reviews, key informant interviews, and development of a decision-analytic model that underscored the challenges in defining outcome measures and establishing a relevant time horizon for DMD screening and treatment.

Committee Discussion

a. A Committee member asked whether this review was progressing within the nine-month window. It was noted that the review process was proceeding within the time frame.

Krabbe Disease Expedited Evidence-Based Review: Phase 1 Update

Dr. Kemper provided an overview of the Committee's actions related to Krabbe disease. In August 2023, an expedited review was approved based on an updated nomination, marking the first instance of such a review. The focus was on infantile Krabbe disease, characterized by onset before 12 months, reduced galactocerebrosidase activity, and high psychosine levels in dried blood spots. The expedited review update included an updated evidence review, focused specifically on infantile Krabbe disease with specific biomarkers, a search of new published data and grey literature, and an updated survey of states using psychosine as a second-tier test. The review included an assessment of the developmental trajectories of infants identified through newborn screening and treated with hematopoietic stem cell transplantation (HSCT) in early infancy and updated decision analytic modeling to reflect the new screening target.

Committee Discussion

a. An organizational representative noted that DMD and Krabbe had been added to the Minnesota screening panel and they have begun the implementation process.

b. A Committee member asked whether there was a mechanism available to the Committee to prevent a newborn screening lab from calling borderline levels (i.e., a psychosine level of 9) as infantile Krabbe disease. A Committee member clarified that the Committee provided recommendations to the Secretary for adding conditions to the RUSP. States then decide what they want to screen and how. Therefore, the Committee did not have the power to prevent a screening lab from making a referral for evaluation and diagnosis reporting out borderline levels.
c. A Committee member asked whether psychosine cutoff levels were arbitrary. It was clarified that levels of ten and greater strongly predict having the infantile form. Levels between 2-10 indicate infants who might be at risk for a later, non-infantile phenotype. It was noted that infants with infantile phenotypes had much higher psychosine levels than ten.

New Business

1. Based on information shared during the Listening Sessions, a Committee member suggested pausing the acceptance of new nominations while the Committee considered revisions to the decision matrix tool and the nomination process. They suggested that any current nominations currently under review should continue through the existing process. Another Committee member noted that multiple groups were preparing nomination packages that should also be considered. A Committee member recommended a mechanism for groups currently working on a nomination package to determine how to best proceed. As a result of this discussion the Committee will pause acceptance of new nominations for at least six months as they make decisions about the nomination process and decision matrix. Current and potential nominators should contact HRSA staff for guidance.
2. An organizational representative mentioned the lawsuits involving newborn screening programs in Michigan and New Jersey over newborn blood spots. There was a suggestion that other organizations with an interest in newborn screening using blood spots may want to reach out to APHL to help support their work or work independently to support the Michigan Department of Health.
3. A Committee member discussed proposed FDA rules about laboratory developed tests. Most tests used for confirmation and diagnosis of rare diseases, including for newborns, are not available as FDA-authorized kits. The FDA has generally exercised enforcement discretion over most of these lab-developed tests but is increasingly concerned about the safety and effectiveness of these tests, which lack active FDA oversight. The FDA seeks public input on the proposed rule, which will tighten FDA's enforcement of oversight and monitoring of these tests. There is a concern among laboratories and clinicians that the regulatory requirements proposed by the FDA would make these tests inaccessible because of the high costs and burden associated with complying with these requirements. The FDA accepted public comments until December 4, 2023.
4. The meeting scheduled for February 1-2, 2024 would likely be rescheduled.

Committee Votes

Motion #1: Motion to accept the meeting summary from the meeting on August 10-11, 2023.
Voice vote in favor / 0 opposed. Motion carried.