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

Brief Summary of Committee Meeting
August 10-11, 2023

Introduction

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) met on August 10-11, 2023 to discuss various topics related to newborn screening and genetic disorders. The Committee received updates on two recently awarded grant programs; State Newborn Screening Systems Priorities Program (NBS Propel) and the National Center for Newborn Screening System Excellence (NBS Excel), as well as an upcoming program: Cooperative Newborn Screening System Priorities Program (Co-Propel). The Committee heard presentations on moving Duchenne muscular dystrophy (DMD) to a full evidence review, adopting an expedited evidence review process, considering equity in newborn screening, and moving Krabbe disease to an expedited evidence review. The meeting was open to the public and public comments were allowed.

Duchenne Muscular Dystrophy (DMD)

A summary of the status of the DMD nomination package was provided. A nomination package was delivered to the Committee in June 2022 and the Committee did not recommend DMD to full evidence review. The DMD nominators submitted a revised nomination package in June 2023.

Public Comment

Public comments on DMD were made by five people, comprised of parents, parent advocacy groups, medical researchers, and physicians. Parents shared personal stories of having children with DMD and advocated for including this condition in the Recommended Uniform Screening Panel (RUSP). Multiple speakers advocated for DMD to advance to full evidence review and shared the advantages of early detection and emerging therapeutic opportunities. An argument was also made that adding DMD to the RUSP would promote equitable and timely diagnoses, especially in minority groups that may experience later detection.

Nomination Summary

Dr. Chanika Phornphutkul presented a summary of the review of the ACHDNC Nomination and Prioritization (N&P) Workgroup and the additional information provided by the nominators in the resubmitted nomination package. Dr. Phornphutkul provided a brief overview of the condition, clinical presentation, treatment/management, and the N&P Workgroup's review of eight key questions addressed to support their findings.

The Workgroup recommended that the Committee move the nomination of DMD forward for a full evidence review. Additionally, there was a recommendation to define DMD as an elevated CK-MM with subsequent molecular testing to avoid/limit false positives and to provide evidence/data of clinical utility from pilot studies or retrospective sibling case studies.

Committee Discussion

a. A Committee member summarized the differences between the resubmission and the original submission. Additional information was provided that the case definition had also become more targeted.
b. A Committee member commented that the implementation of newborn screening would likely provide needed evidence.
c. A Committee member reviewed the Committee's charge of protecting the integrity of compulsory population-based newborn screening. They commented that advocacy, parent, and pharmaceutical interests do not support research into the potential harms of newborn screening. They pointed out that statements in the nomination package potentially overstated the strength of evidence. Another Committee member agreed with these concerns. A comment was raised that it is inaccurate to say that family and parent groups are not interested in considering harms.
d. A comment was made about the benefits of adding DMD to the RUSP. A committee member clarified that the persistence of elevated CK-MM would be the defining characteristic used for newborn screening.
e. A comment was made that the diagnosis for DMD is straightforward and children with DMD will have a persistent CK-MM value. There is improved technology and an assay worked well in a pilot study after establishing cut-off values. A Committee member asked about the calibration process for the assay in the pilot test. The process of setting thresholds was described.
f. A Committee member stated that the pilot data was run through the Collaborative Laboratory Integrated Reports (CLIR) tool from the Mayo Clinic, which reduced the number of borderline determinations. A Committee member asked if this also picked up Becker cases in screening. The response was that none were found.
g. A Committee member cautioned about requiring that a molecular test be part of the newborn screening component. It was recommended that programs have the ability to parse out a molecular test as a part of the affirmatory post-screening, rather than as a part of the newborn screen because the gene is very large.
h. A question was raised about mutations associated with Becker muscular dystrophy and how diagnosis would work under the revised case definition. A Committee member stated that this was unclear and would need to be discussed. Two Committee members stated their interpretations.
i. A comment was raised about false positives, and that there should be consideration about interpreting the results in terms of a broader differential diagnosis.

Expedited Evidence Review Process

Dr. Ned Calonge presented a proposal for an expedited evidence review process. The final step for recommending a new condition to the RUSP involves discussion and synthesis of the evidence review and vote. If the vote does not result in a recommendation to add the condition to the RUSP, the nominators may elect to submit new evidence and/or other revisions to qualify as a material change within one year of the vote. A material change must be a change in the scope of the condition nominated and/or substantial new evidence for the nominated condition.

Dr. Calonge said that the Committee would consider and vote whether the revised nomination package should be considered for expedited review. If the vote failed, the Chair would summarize the issues leading to the decision to the nomination group. If the vote passed, the review would be evaluated for prioritization, and the updated evidence would be reviewed.

The proposed expedited evidence review process was amended to include:

- The vote must be held within nine months after approval of expedited review.
- The expedited review should include responses to the Chair's letter and may include additional new evidence.
- Additional new research on issues not included in the original discussion may be uncovered during the review process.
- An explicit communication would be added that a topic approved for expedited review may still end in a decision against the recommendation of the condition to the RUSP.

The conditionally approved proposal was amended before the Committee reconvened on the subsequent day to include verbiage better describing the process and incorporated caveats raised during the initial discussion.

Committee Discussion

a. A Committee member raised a concern that care must be taken around the communication of this process to be clear to nominators that being responsive to concerns is not a guarantee that the expedited review will result in a desired outcome. It was pointed out that a gap review may uncover new evidence that may or may not be supportive.
b. A Committee member asked whether the Committee works in isolation after the package is resubmitted or if there was a mechanism to communicate with the nominators. The existence of a Technical Expert Panel was brought up; the process of asking subject matter experts occurs currently.
c. It was clarified that any new information could be added to the submission for expedited review, not just information directly responsive to comments from the initial application.
d. A Committee member asked about the rationale for a one-year deadline. It was clarified that this decision was experience-based and the process of other review groups as an evidence review becomes outdated.
e. A Committee member expressed that they needed to see a more finalized document describing the process before voting. It was suggested to postpone the vote until a more finalized document was completed. Another Committee member expressed an interest in not postponing the vote.
f. A Committee member asked about possible safeguards for nominators bringing a nomination package prematurely and bringing in the evidence later using the expedited process.
g. A Committee member asked if there would be guidance about how the evidence review should be performed regarding the expedited process. Language was added to incorporate a Committee vote.
h. A Committee member stated that they would prefer that Committee members not have to justify their votes.
i. A Committee member asked who determined whether the expedited review package incorporated a material change. It was clarified that the Chair makes the material change determination, but it was up to the Committee to decide if the material change was sufficient to move the condition to expedited review.
j. A Committee member asked for clarification of the timelines in the expedited process. Language was added, providing time constraints for steps in the process.
k. A Committee member asked how the review group would prioritize conditions they are working on when expedited reviews are introduced. It was clarified that prioritization within the queue would need to be decided by a Committee vote.

l. A Committee member asked whether a rejected expedited review process precluded a future expedited review process. It was clarified that there needed to be a closure to this process.
m. A question was raised regarding the need for an expedited review request to change both the scope and make a material change. It was clarified that the expedited process application need only change the scope or make a material change.
n. A question was raised regarding when the nine-month timeline begins. It was clarified that the nine-month deadline started when there was a decision to do an expedited review.
o. A question was raised about which data points might be used to reevaluate the process once two expedited reviews were completed. Committee members mentioned including whether deadlines were kept, soliciting feedback from nominators, and evaluating resources and staff.
p. A concern was raised that the implications of the expedited procedure being adopted were not being fully considered. It was clarified that the new process was a standard procedure and not binding.

<u>Expedited Review Process</u>

The following outlines the process for an expedited review:

1. If the committee vote results in not recommending a condition to be added to the RUSP, the chair sends a letter to the nominators summarizing the issues leading to the decision (per current practice, within 60 days of the ACHDNC meeting).
2. Within one year of the chair's letter, nominators may resubmit a re-nomination package for expedited review.
3. Requests for an expedited review must include responses to the chair's letter and may include additional new evidence or information on other relevant issues.
4. The request must outline at least one material change and include supporting data/documents.
    - A material change involves a change in scope of the condition nominated and/or substantial new evidence for the nominated condition.
    - If there is a change in scope, it is preferable that there is also new evidence provided in support of the nomination.

    Chair's letter and nomination for expedited review caveats:

    > The nomination package resubmission must address committee questions and comments described in the chair's letter to the nominators. However, nominators should realize that the chair's letter only includes issues that were raised in the discussion—there may be other reasons a committee member voted against adding the condition. The committee does not want to create expectations that addressing the issues in the letter alone will result in a changed vote for any member.

5. The chair reviews the re-nomination package and, with input as necessary from ERG and N&P Workgroup, determines if it qualifies as a material change.
    - This step is likely to involve ongoing discussion with the nominators and will be performed as expeditiously as is practical for all participants.

6. If the chair concludes that the renomination constitutes a material change, the package will be presented and discussed by the full committee for consideration for an expedited review. If the chair concludes there is not a material change, the nominators and the rest of the committee

will be notified. The condition will return to the list of conditions for future nomination and prioritization.

7. The committee should vote on whether to move the condition nomination to an expedited review, to be conducted by the ERG.

8. If the vote fails, the chair will summarize the issues leading to the decision in a letter to the nomination group, and the condition will return to the list of conditions for future nomination and prioritization.

9. If the vote passes, and if necessary, the N&P workgroup will prioritize the review, considering other topics in the prioritization queue, in order to determine timelines/deadlines.

10. The ERG will follow standard systematic review processes to identify relevant research published since completing the previous review.
    - The ERG may find additional new research on issues not included in the original review and committee discussion (and chair's letter) that could impact the decision to recommend the condition be added to the RUSP.

11. The ERG will work with the technical evaluation panel (TEP) and revise the review to include the new evidence and/or address any revision in scope; this may involve additional modeling.

12. When the review is complete, the condition will be scheduled for presentation, discussion, and vote for recommendation for inclusion on the RUSP at a regular committee meeting.
    - A vote on the condition must be held within 9 months after approval of expedited review.
    - If the vote is not to recommend, the condition will return to the list of conditions for future nomination and prioritization.

Focusing on Equity After Newborn Screening

Dr. Amy Houtrow shared a presentation titled "Focusing on Equity After Newborn Screening." Dr. Houtrow explained that health equity ensures everyone has an equal chance to attain their best health, but structural barriers like racism, classism, and ableism create disparities. Dr. Houtrow emphasized that there are a lot of injustices in our current health system and changes can be made through policy interventions.

Committee Discussion

a. A Committee member highlighted that newborn screening could improve diagnostic health equity but may not improve health outcomes without improvements in the health care system. It was emphasized that it is important to build equity activities with the people who will benefit from and need the equity activities.
b. A Committee member mentioned that long-term follow-up programs were increasingly being set up and asked what changes might help equity. There was a suggestion to collect social determinants of health information to help tailor the type of interventions needed.
c. A question was asked about whether equity should be considered when reviewing nominations. It was acknowledged that the observation of a delayed diagnosis in marginalized racial groups was raised for many conditions.

d. A question was raised about the type of systemic solutions that might exist. A report by the National Academy of Medicine describing how to reduce child poverty while simultaneously raising money was referenced. It was also mentioned that the United States has not signed on to United Nations proposals for issues like the Rights of the Child, or to the Rights of Persons with Disabilities.
e. Comments were made about the importance of rurality as a barrier to care and the importance of family partnership.
f. A comment was made about how the diagnosis of DMD requiring a genetic test would increase the cost of diagnosis and science may be ahead of our ability to provide equitable care.
g. A comment was made about the importance of collecting better data from long-term follow-up to identify appropriate strategies and interventions.

Public Comment

Public comments were made by eight people, comprised of individual parents, advocacy group leadership, and physicians. Parents and physicians shared personal stories and professional experiences advocating for the inclusion of Krabbe disease into the RUSP. Parents and advocacy group leadership brought attention to additional conditions that would benefit from newborn screening, including adrenoleukodystrophy (ALD), metachromatic leukodystrophy (MLD), and congenital cytomegalovirus (cCMV). Updates were also provided about relevant newborn screening programs.

Krabbe Disease Re-Nomination and Vote to Move Krabbe to Expedited Review

A summary of the Krabbe disease timeline was provided. The ACHDNC voted not to recommend Krabbe disease for inclusion into the RUSP at the February 2023 meeting. The ACHDNC Chair sent a letter to the nominators in March 2023. The nominators resubmitted a nomination package in July 2023. The nomination package met the criteria for expedited review—it had been less than a year since the vote, and a material change was included in the new nomination.

The Committee voted on whether to move Krabbe to expedited review.

New Business

1. A Committee member suggested a potential source of information: the National Academy of Medicine project looking at newborn screening and genome sequencing. It was clarified that the project was at a preliminary stage.
2. An update was given that the National Academies had a workshop on Next-Generation Sequencing on June 7th.
3. A comment was made that the concept of "harms" had been introduced multiple times and that there may be a need for a more in-depth discussion.

Committee Votes

Motion #1: Motion to accept the meeting summary from the meeting on May 4-5, 2023.

Voice vote in favor / 0 opposed. Motion carries.

Motion #2: Motion to move Duchenne Muscular Dystrophy forward to a full evidence-based review.

12 in favor / 1 opposed / 0 abstention. Motion carries.

Motion #3: Motion to conditionally approve the expedited evidence review process, with a commitment to finalize the language and timeline of the process.

13 in favor / 0 opposed / 0 abstention. Motion carries.

Motion #4: Motion to move Krabbe Disease forward to an expedited review.

13 in favor / 0 opposed / 0 abstention. Motion carries.