Advisory Committee on Heritable Disorders in Newborns and Children

Advisory Committee on Heritable Disorders in Newborns and Children
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March 23, 2023

Parent Project Muscular Dystrophy
1012 14th Street, NW, SUITE 500
Washington, DC 20005

Dear Parent Project Muscular Dystrophy:

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) appreciates your nomination of Duchenne Muscular Dystrophy (DMD) for inclusion on the Recommended Uniform Screening Panel (RUSP). During the Friday morning public testimony, families and advocates shared their personal stories about DMD and their hopes for its inclusion on the RUSP. It takes a lot of courage to speak at the meeting, and we heard loud and clear why newborn screening is so important to the DMD community. We also recognize the years-long effort by advocates, families, friends, clinicians, and scientists to bring the nomination to the Committee.

As you know, a review of the DMD nomination package was conducted by the Nomination and Prioritization Workgroup, as part of the Committee's formal review process. Their findings were presented to the Committee during the February 9-10, 2023 meeting, which determines whether to forward a condition for evidence review. The Committee recognizes DMD as a medically serious condition with a well-described case definition, an available screening test and second-tier confirmatory test, available effective treatments, and pilot studies that have successfully detected cases of affected newborns. However, based on review of the nomination package, the Committee concluded they had insufficient information to move the nomination forward in the process and voted to not submit DMD for full evidence review. We would like to meet with you in the coming month to discuss key outstanding questions identified in the Committee deliberation.

In order to decide whether to advance the nomination to the next step of evidence review, the Committee will require additional information in the following areas:

Characteristics of the screening test – There were no data or estimates provided on the rate of false positives for the screening test. The data on false positives in the pilot studies indicate a high rate of false positives in the setting of a rare disease and a low positive

predictive value which is not sufficiently addressed in the nomination package. This creates challenges in assessing clinical utility as is described below. Finally, the package would benefit from a more detailed discussion of the evidence for and approach to false negatives tests in premature infants.

Confirmatory test/diagnostic process – It is unclear whether the proposed confirmatory testing that requires next generation (NG) sequencing is feasible to implement. Please provide more information on the availability of the proposed confirmatory testing and any additional information that describes how state newborn screening programs can access and implement confirmatory testing for DMD. Also, it would be useful to have evidence on the frequency of, clinical importance of, and approach to variations of unknown significance (VOUS).

Clinical Utility – There is insufficient evidence that newborn screening detected cases have better outcomes than those detected clinically or through another alternate detection strategy (such as screening though routine care) compared with population-based screening. This is an essential element for the committee to consider when deciding to move ahead with a full evidence review, and represents a gap that needs to be addressed in the nomination package. In fact, the nominators noted that screening for DMD with CK-MM is not time-critical in the newborn period (p 17 nomination package).

Also, to allow the Committee to better weigh the potential benefits and harms of adding DMD screening to the RUSP, we would like you to please consider providing even rough estimates of the anticipated outcomes from screening a cohort of newborns, such as the US birth cohort (approximately 4M newborns), including:

- the number/percent of false negatives,
- the number/percent of all screening positives,
- the number/percent of false positives determined by confirmatory testing,
- the anticipated impact/harms of these false positive tests and confirmatory testing on newborns and their families,
- the number/percent of those expected to benefit by earlier diagnosis and the magnitude of those expected benefits, and
- the number/percent of those treated expected to be harmed by treatment and the magnitude of those harms.

Finally, if available, please provide published data from sibling studies, additional outcome studies and long-term treatment studies which will address important evidence gaps and strengthen the nomination.

The Committee encourages you to resubmit the nomination when the above items have been addressed. Upon receipt of the completed nomination package, the Committee will review the updated nomination package to present and determine whether to move DMD forward for a full evidence review.

If you have any questions about the additional information requested, would like additional technical assistance, or have questions, please contact me at achdnc@hrsa.gov.

Thank you for your nomination of DMD for inclusion on the RUSP. I look forward to hearing from you soon.

Sincerely yours,

/s/

Ned Calonge, MD, MPH
Chairperson

ATTACHMENT: Committee Summary of DMD Nomination Requirements and Key Considerations Presentation

Cc: Leticia Manning, MPH
Acting Designated Federal Official
Health Resources and Services Administration