Nomination and Prioritization Workgroup Report on: *Duchenne's Muscular Dystrophy*

Advisory Committee on Heritable Disorders in Newborns and Children Nomination and Prioritization Workgroup:

Kyle Brothers
Carla Cuthbert
Chanika Phornputkul
Ned Calonge
Shawn McCandless

Presented by:
Ned Calonge, MD, MPH

February 10, 2023

Nomination of Duchenne Muscular Dystrophy

Nominator	Niki Armstrong, MS, CGC, and Pat Furlong, Founder and President (Parent Project Muscular Dystrophy [PPMD])
Co-Sponsoring Organizations	Muscular Dystrophy Association (MDA) Duchenne RUSP Submission Workgroup*
Advocate Organizations	PPMD and MDA

*Duchenne RUSP Submission Workgroup Members:
Niki Armstrong, MS, CGC, PPMD
Pat Furlong, PPMD
Annie Kennedy, Everylife Foundation
Jerry R. Mendell, MD, Nationwide Children's Hospital
Katerina S. Kucera, PhD, RTI
Michele A. Lloyd-Puryear, MD, PhD, Consultant
Dorota Gruber, DHSc, MS, CGC, Cohen Children's Medical Center at Northwell Health
Anne M. Connolly, MD, Nationwide Children's Hospital
Richard Parad, MD, MPH, Brigham and Women's Hospital
R. Rodney Howell, MD, Emeritus Professor and Chairman of Pediatrics
Amy Brower, PhD, American College of Medical Genetics and Genomics
Edward C. Smith, MD, Duke Children's Neuromuscular Program
Paul Melmeyer, Muscular Dystrophy Association

DMD Condition Information

- DMD is:
  - An X-linked neuromuscular disease with progressive muscle damage and weakness in both skeletal and heart muscle; and primarily affects males, although females can be variably affected.
  - Associated with highly elevated levels of creatine-kinase. Diagnosis is based on genetic testing to identify likely disease-causing variants in the *DMD* gene or muscle biopsy. Deleterious variants in *DMD* are associated with other forms of disease:
    - Becker muscular dystrophy
    - *DMD*-associated dilated cardiomyopathy (*DMD*-DCM)
  - Known to occur in approximately 1/5,000 live male births (Mendell, J. et. al). Females with a pathogenic variant in *DMD* can be clinically affected.

DMD—Clinical Presentation

- DMD is a progressive neuromuscular disease of childhood. All patients with DMD experience loss of ambulation, followed by loss of upper limb use, progressive impairment of pulmonary function, and progressive cardiomyopathy.
- Children affected with DMD often have significantly delayed developmental milestones (motor function, global developmental delays, and delayed onset of ambulation and other early motor skills).
- It is noted that irreversible muscle damage begins as early as fetal life.
- Typically diagnosed at 4-5 years of age with loss of ambulation in early adolescence and death related to pulmonary or cardiac disease often in their 30s

DMD—Treatment and Management

Treatment:

- 4 FDA-approved exon skipping therapies available for DMD-teplirsen, golodirsen, casimersen, and vitolarsen. These are considered the standard of care for eligible patients (those with an amenable pathogenic variant, about 30% of DMD).
  - Therapies are provided via weekly intravenous infusions.
  - Optimal age to initiate this treatment not established, experts recommend offering it at time of diagnosis even if corticosteroids not yet appropriate.
- Corticosteroids are standard of care and recommended to begin prior to onset of physical decline (average initiation at 5.9 years).
  - Optimal age to initiate use not established.
  - Current practice guidelines recommend discussing use at time of diagnosis.
- Additional therapies in development in various stages of clinical trials.

DMD—Treatment and Management

- Treatment typically begins as clinically indicated, usually at time of diagnosis (4-5 years).
- No evidence on early treatment benefit because of the diagnostic delay, clinical course, heterogeneous nature of DMD, and rarity of the condition

DMD—Treatment and Management

Management:

- DMD requires a multidisciplinary team led by a neurologist/physical medicine rehabilitation specialist and includes: cardiologists, therapists, genetic counselors, pulmonologists, orthopedists, and others.
- Physical, language, and speech therapy and early intervention services have shown to improve quality of life and early functioning

Core Requirements for Nomination

1. Validity of the laboratory test
   - yes
2. Widely available confirmatory testing with a sensitive and specific diagnostic test
   - There is an FDA-approved screening test (creatinine kinase MM—CK-MM)
     - GSP processor is high throughput and similar to other GSP tests used commonly in NBS
   - Confirmatory testing requires NG sequencing which is not necessarily “widely available”

3. A prospective population-based pilot study

   --Yes, from New York, North Carolina, and Zhejiang province, China

Key Questions to Address

1. Is the nominated condition(s) medically serious?
2. Is the case definition and the spectrum of the condition(s) well-described to help predict the phenotypic range of those children who will be identified based on population-based screening?
3. Are prospective pilot data from population-based assessments available for this disorder?
4. Does the screening test(s) have established analytic validity?
5. Are the characteristic of the screening test(s) reasonable for the newborn screening system (among other aspects, a low rate of false negatives)? Is there a widely available and CLIA and/or FDA approved confirmatory test/diagnostic process?
6. Are there defined treatment protocols, FDA approved drugs (if applicable) and is the treatment(s) available?
7. Do the results have clinical utility? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

Key Question 1: Is the nominated condition(s) is medically serious?

Yes

This is a health condition with morbidity that negatively impacts daily function and quality of life. All patients experience loss of ambulation, loss of upper limb use, and progressive impairment of pulmonary function, and progressive cardiomyopathy.

Death related to pulmonary/cardiac disease often occurs in third decade of life

Clinical Presentation:

- Muscle Weakness (calf hypertrophy, difficulty rising from the floor)
- Delayed motor development
- Delayed onset of ambulation and other early motor skills
- Frequent falls
- Difficulty with stairs
- Overall, can be heterogeneous and non-specific

Key Question 2: Is the case definition and the spectrum of this condition well described, to help predict the phenotypic range of those children who will be identified based on population-based screening?

Yes

- X-linked disorder, primarily affecting males, though females can be affected
- 1/3 of male individuals with DMD have a de novo pathogenic variant
- Genetic testing identifies pathogenic/likely pathogenic variants and/or
- Muscle biopsy confirms diagnosis
- There are other variants including Becker muscular dystrophy that may also be diagnosed and could benefit from early detection
- Patients are typically clinically identified between 4-5 years of age

Key Question 3: Are prospective pilot data (U.S. and/or international) from population-based assessments available for this disorder?

Yes

Newborn Screening Program	Year Screening Began	Number of Newborns Screened	DMD Newborns Identified
NY State Pilot	2019	39,495	4 male confirmed, 1 female carrier
NC RTI Early Check Pilot	2020	7,428	1 with pathogenic variant
Zhejiang Pilot		18,424	4

Key Question 4: Does the screening test(s) have established analytic validity?

Yes

Screening Tests for DMD

- Primary Newborn Screening Assay
  - Measures creatine Kinase MM (CK-MM)
  - Assay performed using genetic screening processor instruments (available via PerkinElmer)
- Second Tier test
  - Genetic analysis of *DMD* gene via next generation sequencing
- There are different cutoffs for different ages complicating the question of analytic validity, for example, false negatives in premature infants, which creates concerns about Question 6

Key Question 5: Are the characteristics of the screening test(s) reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?

- No

NOTE: this question must also address false positives

- NY (10/19-9/21): 36,781 screened, 296 borderline (repeat recommended), 42 referred, 4 confirmed (4 males, and 1 female carrier)
  - False negative rate: not reported
  - False positive rate: 0.1%/0.9% (positive/borderline)
  - PPV: 11.9/1.5% (positive/borderline)
  - NPV: not reported
- RTI (NC) (in first year): 7,428 screened, 54 screened positive and referred, 1 confirmed (1 possible carrier
  - False negative rate: not reported
  - False positive rate: 0.7%
  - PPV: 1.9%
  - NPV: not reported
- Cure Duchenne-Brigham Women's Hospital supplemental DMD NBS (7/21-5/22): 4,777 screened, 122 screened positive, 0 confirmed
  - False negative rate: not available
  - False positive rate: not available
  - PV: not available
  - NPV: not available

- There will be newborns with high CK levels that don't have a pathogenic variant, and the false positive rate is high given the low incidence.

- Based on an estimate of 4,000,000 US births annually and NY/NC rates, expect 400-500 positives identified annually

Key Question 6: Is there a widely available and CLIA and/or FDA approved confirmatory test/diagnostic process?

No (not FDA approved)

194 labs across the U.S. are able to provide confirmatory testing for DMD

Key Question 7: Are there defined treatment protocols, FDA approved drugs (if applicable) and is the treatment available?

Yes

Treatment:

- Exon-skipping therapy provides significant benefit for 30% of cases (defined via NGS testing)
- Corticosteroid therapy
- Speech and physical therapy

- However, evidence of treatment prior to usual clinical diagnosis is limited/unavailable

Key Question 8: Do the results have clinical utility? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

- Answering this question about clinical utility must include evidence and a discussion about the benefits of screening the harms/potential harms of screening and treatment with enough specificity for the committee to judge whether a full evidence review is warranted
- This answer should include estimates, based on available data, of the frequency of all positives, the proportion of false positives and the processes and impact of determining these, and the frequency and magnitude of benefits associated with treatment, and the frequency and magnitude of harms from treatment
- Finally, the answer should provide 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)

Key Question 8: Do the results have clinical utility? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

- There are benefits from available therapy as noted in the slide for Question 7; the benefits are significant and described as “delay in pulmonary function” and “delay in loss of ambulation” with the longest follow reported for 4 years (exon-skipping therapy) and 10 years (corticosteroids)
- It is likely that the harms from therapy are outweighed by the benefits; however, long term data and data quantifying on the frequency and severity of harms appear to be sparse
- There remain questions regarding VOUS

Key Question 8: Do the results have clinical utility? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

No

- There are potential harms of a population-based screening program that must be considered in determining the balance of benefits and harms in clinical utility; there was insufficient evidence provided on potential harms to make a decision on clinical utility based on balancing harms and benefits
- 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

Key Questions - Summary

YES 1. Is the nominated condition(s) ***medically serious***?

YES 2. Is the ***case definition*** and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.

YES 3. Are ***prospective pilot data*** from population-based assessments available for this disorder?

YES 4. Does the screening test(s) have established ***analytic validity***?

NO 5. Are the ***characteristics of the screening test(s)*** reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?

NO 6. Is there a widely available and CLIA and/or FDA approved ***confirmatory test/diagnostic*** process?

YES 7. Are there defined ***treatment*** protocols, FDA approved drugs (if applicable) and is the treatment(s) available?

NO 8. Do the results have ***clinical utility***? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

Gaps noted by N&P workgroup

- Reasons for recommendation to not be moved forward
  - perhaps most important gap is limited evidence on whether NBS screening-detected cases have better outcomes
  - Benefits of treatment based largely on expert opinion, lacking published data.
    - Lack of sibling studies
    - Lack of outcomes studies
    - Lack of long-term treatment studies
  - NBS may not be the appropriate place to screen for DMD, there are other screening timepoints
  - Cutoffs for different ages challenging
  - Treatment
    - Unclear benefits of EARLY treatment
    - Uncertainty around benefits of exon skipping and long-term corticosteroid use; and
    - Age of timing of treatment

Nominations and Prioritization Group Recommendations

The Advisory Committee SHOULD NOT move the nomination of Duchenne Muscular Dystrophy forward for a full evidence review

Additional thoughts

- At this time, the compelling evidence to consider adding DMD to the RUSP is not clear or has not yet been developed
- This was an appropriate submission for review:
  - There is a test that can identify affected children
  - There is experience with population-based pilots
  - There is new effective therapy

Additional thoughts

- It would be helpful for nominations to summarize the information that would allow the N&P workgroup to evaluate the estimated impact of screening some number of children
- For example, if you screened 100,000 newborns:
  - how many would test positive;
  - of these, how many would test negative on second tier or otherwise be determined to be falsely positive;
  - what is the impact on these newborns and their families;
  - of those truly positives, how many will benefit from treatment and what will be the nature and magnitude of that benefit;
  - of those treated, how many will be harmed by the treatment and what will be the nature and magnitude of that harm

Additional thoughts

- It was not the intention of the N&P workgroup to appear to be changing the criteria for nominations to be approved for a full evidence review, yet this nomination is accompanied with significant uncertainty about the likelihood of a full evidence review revealing more relevant data so that the Committee can make an informed decision.
- Our field is changing with new testing approaches, new therapies, and more complexity in the conditions being considered; our evaluation methods need to reflect this
- It is certain the evidence for newborn screening for DMD and other conditions will evolve and may well fill in the gaps where there is uncertainty