ACHDNC
Advisory Committee on Heritable Disorders in Newborns and Children

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

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ACHDNC Nomination and Prioritization Workgroup:

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***Denotes changes to original presentation from February 10, 2023**

Nomination of Duchenne Muscular Dystrophy (DMD)

Nominators	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

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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- eteplirsen, golodirsen, casimersen, and viltolarsen. 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).
- Limited evidence on early treatment benefit because of the diagnostic delay, clinical course, heterogeneous nature of DMD, and rarity of the condition
- FDA recently approved new ELEVIDYS gene therapy*

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

Summary of Re-Submission*

Additional Information provided:

1. New case definition: Highly elevated levels of CK-MM, followed by persistently elevated CK levels, and a pathogenic or likely pathogenic variant in the *DMD* gene
2. Specific treatment available for 30% of DMD cases
3. Gene therapy age of treatment 4-5 years but average age of diagnosis in DMD cases without family history is 6.9 years
4. One sibling outcomes study

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)?
6. Is there a widely available and CLIA and/or FDA approved confirmatory test/diagnostic process?
7. Are there defined treatment protocols, FDA approved drugs (if applicable) and is the treatment(s) available?
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?

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

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)?

Yes

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

Updated Information*

- State labs will need to define and optimize cut-offs to reduce false negatives and positives
- 2nd tier molecular testing should be required
- Technology continue to evolve so NBS for DMD would likely result in less false positives

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)
- ELEVIDYS gene therapy*
- Corticosteroid therapy
- Speech and physical therapy

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

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 loss of pulmonary function” and “delay in loss of ambulation” with the longest follow-up reported 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 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?

Yes/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 some evidence that newborn screening detected cases that access early intervention and therapies may have improved outcomes

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***?
YES	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?
YES/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?

Nominations and Prioritization Group Recommendations

The Advisory Committee SHOULD move the nomination of Duchenne Muscular Dystrophy forward for a full evidence review

Additional recommendations from the N&P Workgroup:

- Recommend DMD be defined as an elevated CK-MM and subsequent molecular testing to avoid/limit false positives.
- Provide evidence/data of clinical utility from pilot studies or retrospective sibling case studies