Public Health Impact Assessment Fact Sheet for Duchenne Muscular Dystrophy (DMD) Newborn Screening

This fact sheet provides newborn screening programs with background information on Duchenne Muscular Dystrophy (DMD) so they can complete a public health impact assessment survey that evaluates their program's readiness and feasibility to add DMD onto their newborn screening panels. The factsheet discusses background information pertaining to the condition, screening methods, resources/materials, personnel requirements, screening results from pilots, costs, short-term follow up, and treatment for DMD. Contact Jelili Ojodu (jelili.ojodu@aphl.org) for more information.

Condition	Duchenne Muscular Dystrophy
Description	Duchenne muscular dystrophy (DMD) is a degenerative neuromuscular disorder caused by pathogenic variants in the *DMD* gene. DMD is an X-linked disorder, primarily affecting males. Screening can detect elevated levels of the skeletal muscle isoform of creatine kinase (CK-MM) in blood. Currently, diagnosis is based on genetic testing to identify pathogenic/likely pathogenic variants. If no pathogenic variant is found, muscle biopsy is done to assess dystrophin levels to achieve a definitive diagnosis. Reading frame of the variant and dystrophin levels can be helpful in distinguishing between DMD and Becker Muscular Dystrophy (BMD), a milder form of the disorder. However, there is heterogeneity in the clinical presentation and it can be challenging in some cases to clinically distinguish between DMD and BMD. Infants and children with DMD experience motor delays and can have other delayed developmental milestones. Neuromuscular symptoms such as calf hypertrophy, difficulty rising from the floor, frequent falls, and difficulty with stairs typically present by ages 2-3 years [Ciafoloni et al]. Loss of ambulation (e.g., wheelchair use) in early adolescence is common and death is often related to pulmonary or cardiac disease (median age of death= 24 years) [Paramsothy et al].
Detection	It is estimated that 1/5000 US males ages 5 to 9 have DMD or BMD (DBMD) [Romitti et al]. Prospective consented screening studies show similar findings for birth prevalence. The North Carolina Early Check project reported a birth prevalence of 1/3400 male newborns for DBMD [Kucera et al]. The New York Parent Project Muscular Dystrophy (PPMD) consented screening project reported a birth prevalence 1 in 6200 male newborns for DBMD [Tavakoli et al]. Newborn screening has the potential of identifying females with DMD variants as well as other non-DMD disorders. Some estimates show that 2-20% of female heterozygotes with a P/LP variant develop some symptoms, ranging from mild muscle weakness to something similar to Becker muscular dystrophy [Gruber et al].

First-Tier Screening Methods	
Screening Strategy and Markers	The first-tier screen for DMD measures the elevation of the skeletal muscle isoform of creatine kinase (CK-MM) in dried blood spots.

Second-Tier Screening Methods	
Screening Strategy and Markers	The screening strategy for DMD entails a first-tier assay using a GSP Immunoassay to measure CK-MM levels. Algorithms can vary and include a repeat CK-MM and final lab report or a second-tier molecular test and lab report. Cutoffs should be adjusted for birthweight and/or gestational age. Other biological and demographic considerations may improve sensitivity and specificity. PerkinElmer developed a CK-MM kit that has been approved by the FDA. The kit relies on a PerkinElmer GSP analyzer, which is used in 41 states to screen for other conditions [Hartnett et al].

Newborn Screening for DMD	
State Mandates and Pilot Projects	New York and Ohio have mandates to add DMD to their state newborn screening panels. Additionally Minnesota's Advisory Committee has recommended adding newborn screening for DMD. There are three prospective consented screening studies for DMD that have been completed or are ongoing: NY PPMD (completed), North Carolina Early Check, and Boston Brigham and Women's Hospital-Cure Duchenne. For the NY project (9 hospitals in NY), cutoffs were age-adjusted to reflect the differences in CK-MM over time. If a specimen had a CK-MM higher than the cutoff, it was re-tested in duplicate. Borderline results led to a request for a repeat specimen. Any specimen above the CK-MM cutoff, was sent to a contract laboratory for molecular testing to test for *DMD* gene deletion or duplication [Hartnett et al]. The North Carolina Early Check project relies on a similar algorithm [Kucera et al]. The NY project molecular analysis for DMD consisted of the following tiers: *DMD* sequencing and microarray-based comparative genomic hybridization analysis, followed by a gene panel covering 47 neuromuscular disease genes (if necessary) followed by a 90 to 104 gene panel (if necessary) [Hartnett et al]. Challenges remain regarding molecular testing's ability to distinguish between DMD and BMD [Tavakoli et al, Kucera et al].

Resources and Materials	
Minimum Instrumentation, Equipment and Requirements Necessary to Process 100,000 Specimens Annually	First-tier requires the PerkinElmer analyzer.
Equipment Suppliers and Availability of Kits, Reagents and Consumables	FDA approved kit from PerkinElmer. Each kit includes reagents to run 12 plates. Also needed: CK/MM buffer, shaker, incubator.

Workstation Resources and Capacity	
Instrument Time	4 hrs 50 min/plate, 26 plates/15 hrs.
Minimum Space Requirements	No additional space is needed.
Staff Time	May not need additional staff or minimal since it is added to other tests.

Other Considerations	
LIMs Adjustments	Variable (dependent on vendor). LIMs revisions for new conditions may require additional staff time and cost for initial set up.
Availability of Quality Control Materials	CDC has QC materials available.

Short-Term Follow-Up	
Description	Patients confirmed to have DMD based on elevated CK-MM and genetic testing should undergo follow up with a geneticist/genetic counselor to gain an understanding of the diagnosis and to assess risks to other family members. Patients should then be followed by a neuromuscular specialist or neurologist with expertise in DMD to monitor strength and developmental milestones and to ensure proper follow up over time with other specialists such as cardiology. Elevated CK-MM can be associated with neuromuscular conditions other than DMD. Patients with persistently elevated CK-MM, with or without genetic confirmation of another condition, should also see a neuromuscular specialist, neurologist or geneticist for further evaluation.
Case Definition	Elevated CK-MM and a pathogenic/likely pathogenic variant in the *DMD* gene associated with DMD.
Diagnostic Method & Criteria	Elevated CK-MM and pathogenic variants.

Current Treatment	
Description and Current Treatment Guidelines with Clinical Identification	DMD patients are typically followed by primary care physicians and neuromuscular centers. Treatment guidelines vary depending on whether the individual is in an ambulatory or non-ambulatory stage. Steroid therapy (e.g., glucocorticoids) is the standard of care for DMD and used to slow disease progression. Steroid therapy is typically not recommended until age 4 and its efficacy in young children is not well understood. One study shows a delay in loss of ambulation for boys (median age = 7 years) given steroids for more than 3 years [Kim et al]. Four exon-skipping drugs have received accelerated approval from the FDA [Haber et al]. These therapies can be given to individuals who have pathogenic variants affecting the *DMD* gene in exons 45, 51, and 53, which account for ~68% of cases. Since the treatments are so new, data regarding their effectiveness is limited. Additionally, the primary endpoint for many exon skipping treatment studies is the change in dystrophin levels measured by a Western blot assay, which can be difficult to interpret due to limitations of the assay at low levels of dystrophin expression. Gene therapy received accelerated FDA approval for use in 4-5 year olds in 2023 based on limited data.

References

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