Module 2
How is Duchenne muscular dystrophy (DMD) diagnosed?

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Module summary

Patient outcomes have improved since the 1960s as DMD management strategies have evolved[1]

Accurate and timely diagnosis of DMD is crucial for early intervention[2,3]

Detection of *DMD* gene mutations and low or absent dystrophin are used to confirm a diagnosis of DMD[4,5]

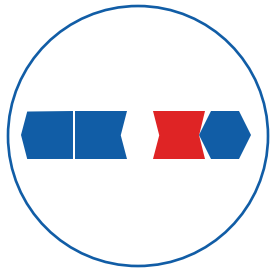
CK and genetic testing, and muscle biopsy are used to diagnose DMD[4]

Newborn screening involves assessment of CK levels followed by a confirmatory genetic test[4,6]

With emerging treatments that may be most effective with early intervention, there is renewed interest in newborn screening[4]

A diagnostic delay of ~2 years persists, despite introduction of a diagnostic algorithm[4,7]

The average age at confirmed diagnosis is 4.9 years[7,8]



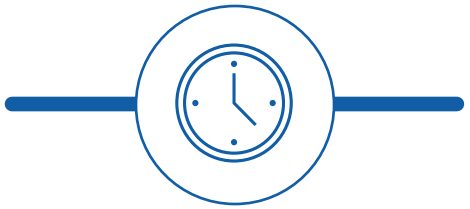
Certain *DMD* mutations lead to total absence or nearly undetectable levels of dystrophin in individuals with DMD[5]

Genetic testing to determine the type of mutation in the DMD gene will dictate the therapeutic approach[9]

CK, creatine kinase; DMD, Duchenne muscular dystrophy.

1. Goemans N, et al. *Eur Neurol Rev*. 2014;9:78–82; 2. Mendell JR, et al. *Ann Neurol*. 2012;71:304–313; 3. van Ruiten HJA, et al. *Arch Dis Child*. 2014;99:1074–1077; 4. Birnkrant DJ, et al. *Lancet Neurol*. 2018;17:251–267; 5. de Feraudy Y, et al. *Ann Neurol*. 2021;89:280–292; 6. Hartnett MJ, et al. *Int J Neonatal Screen*. 2022;8:50; 7. Ciafaloni E, et al. *J Pediatr*. 2009;155:380–385; 8. Thomas S, et al. *Muscle Nerve*. 2022; 66:193–197; 9. Aartsma-Rus A, et al. *J Med Genet*. 2016;53:145–151.

How could timely diagnosis improve care and outcomes in DMD?



Will allow for earlier initiation of multidisciplinary care and access to treatments, potentially resulting in improved survival[1–3]

Could help address sociodemographic disparities in the diagnosis of DMD[4]

Timely genetic counseling and assessment of carrier status[2,3]

Avoidance of unnecessary diagnostic testing (eg, liver biopsy) and reduction of psychologic burden associated with a prolonged “diagnostic odyssey”[3,5,6]

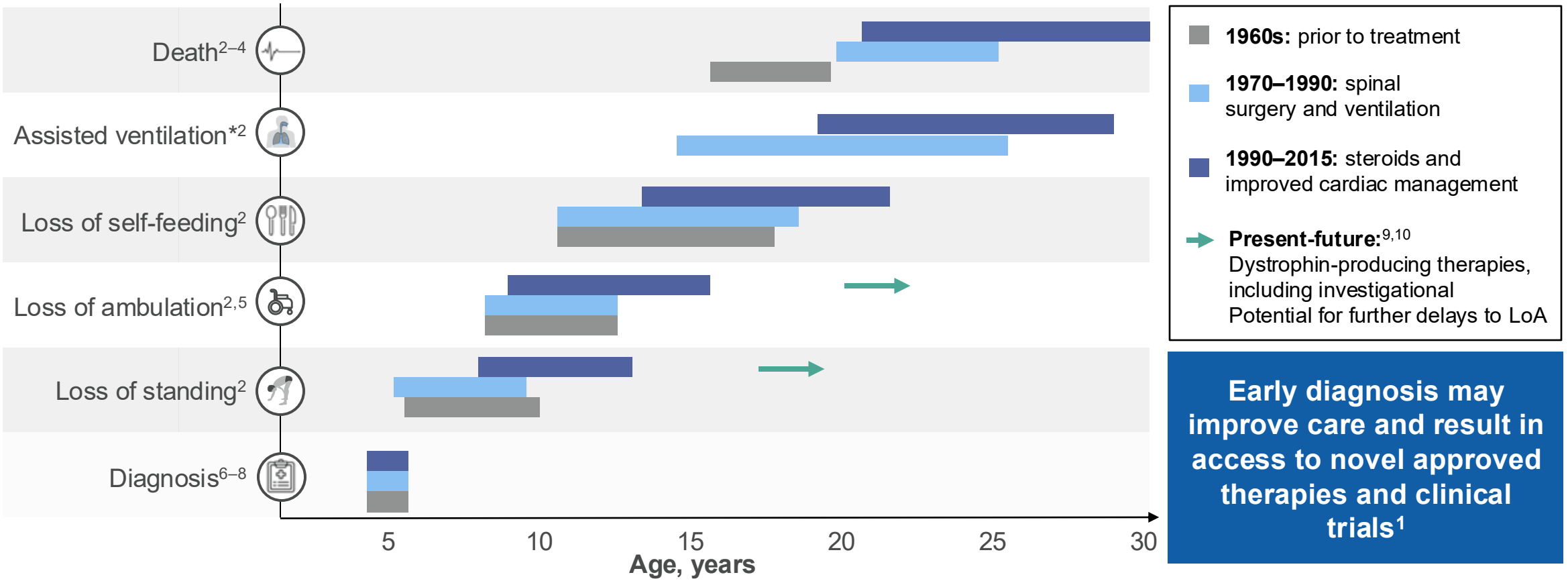
Accurate and timely diagnosis of DMD is crucial for early intervention[1,2]

DMD, Duchenne muscular dystrophy.

1. Mendell JR, et al. *Ann Neurol.* 2012;71:304–313; 2. van Ruiten HJA, et al. *Arch Dis Child.* 2014;99:1074–1077; 3. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:251–267; 4. Counterman KJ, et al. *Muscle Nerve.* 2020;61:36–43; 5. Carmichael N, et al. *J Genet Couns.* 2015;24:325–335; 6. Wright M, et al. *J Am Board Fam Med.* 2012; 25:536–540.

How have patient outcomes changed as DMD care has evolved?

Patient outcomes have improved since the 1960s as DMD management strategies have evolved[1,2]



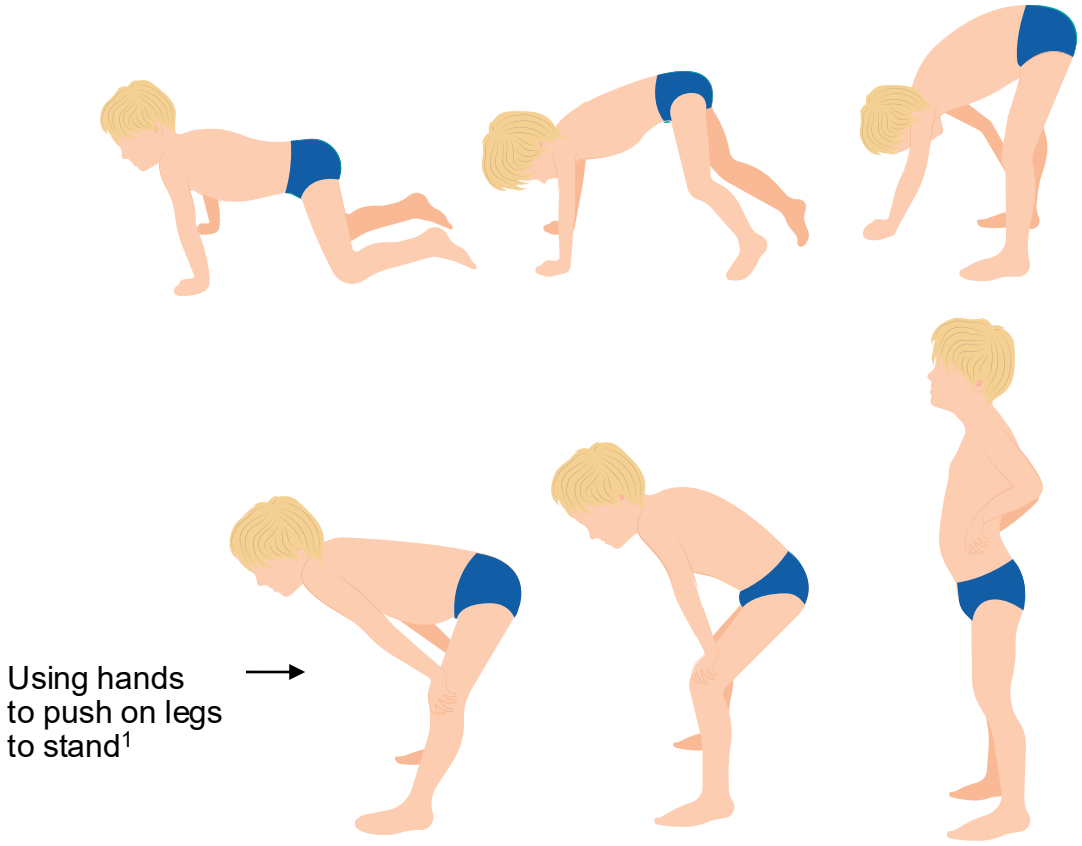
Early diagnosis may improve care and result in access to novel approved therapies and clinical trials[1]

Image based on approximate age ranges in Goemans N, et al. *Eur Neurol Rev*. 2014;9:78–82, Broomfield J, et al. *Neurology*. 2021;97:e2304–e2314, Paramsothy P, et al. *Neuromuscul Disord*. 2022;32:468–476, Kim S, et al. *J Child Neurol*. 2015;30:1275–1280, van Essen AJ, et al. The Natural History of Duchenne Muscular Dystrophy. Analysis of Data from a Dutch Survey and Review of Age Related Events. Doctoral Thesis, Groningen State University. 1997, Thomas S, et al. *Muscle Nerve*. 2022 Aug;66:193–197, and Ciafaloni E, et al. *J Pediatr*. 2009;155:380–385.

*Assisted ventilation does not apply in '1960s' illustration. LoA, loss of ambulation; DMD, Duchenne muscular dystrophy.

1. van Ruiten HJA, et al. *Arch Dis Child*. 2014;99:1074–1077; 2. Goemans N et al. *Eur Neurol Rev*. 2014;9:78–82; 3. Broomfield J, et al. *Neurology*. 2021;97:e2304–e2314; 4. Paramsothy P, et al. *Neuromuscul Disord*. 2022;32:468–476; 5. Kim S, et al. *J Child Neurol*. 2015;30:1275–1280; 6. van Essen AJ, et al. The Natural History of Duchenne Muscular Dystrophy. Analysis of Data from a Dutch Survey and Review of Age Related Events. Doctoral Thesis, Groningen State University. 1997; 7. Thomas S, et al. *Muscle Nerve*. 2022;66:193–197; 8. Ciafaloni E, et al. *J Pediatr*. 2009;155:380–385; 9. Fortunato F, et al. *Neuromuscul Disord*. 2021;31:1013–1020; 10. Deng J, et al. *Front Pharmacol*. 2022:13:950651.

What is an early sign of DMD?

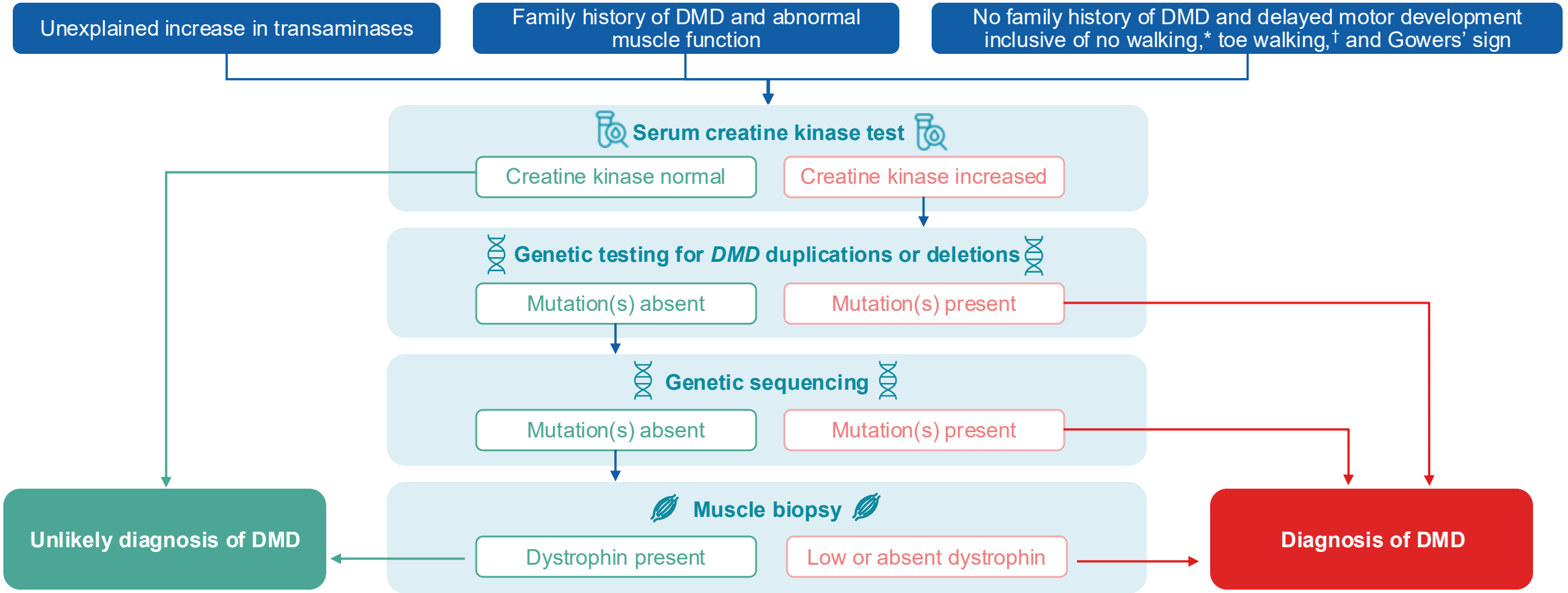


The Gowers' Maneuver is one of the most common early signs of DMD and should prompt testing for a potential diagnosis of DMD[2,3]

DMD, Duchenne muscular dystrophy.

1. Chang RF, Mubarak SJ. *Clin Orthop Relat Res.* 2012;470:1987–1991; 2 Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:251–267; 3. Doglio L, et al. *Eur J Phys Rehabil Med.* 2011;47:587–594.

How is DMD diagnosed?[1,2]



Detection of *DMD* gene mutations and low or absent dystrophin are used to confirm a diagnosis of DMD[1,2]

*By 16–18 months; †At any age but particularly <5 years old.
DMD, Duchenne muscular dystrophy.
1. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:251–267; 2. de Feraudy Y, et al. *Ann Neurol.* 2021;89:280–292.

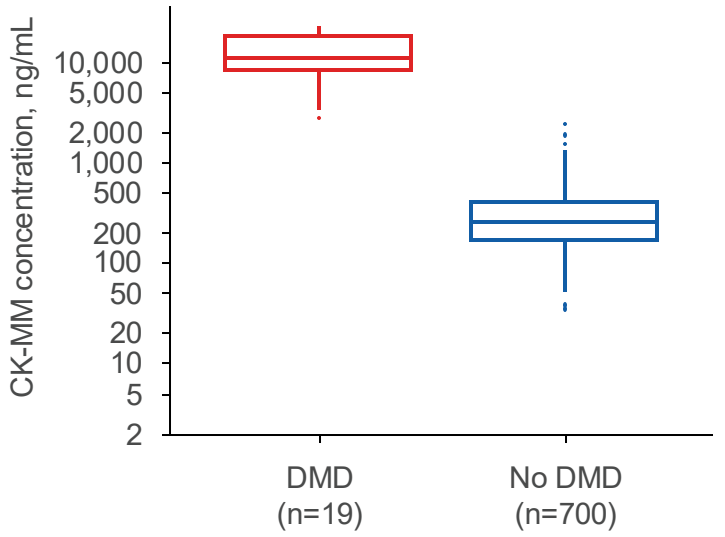
How is CK relevant to a diagnosis of DMD?

A CK test may be carried out during newborn screening, or as part of the evaluation for a young child with delayed motor development.[1,2]

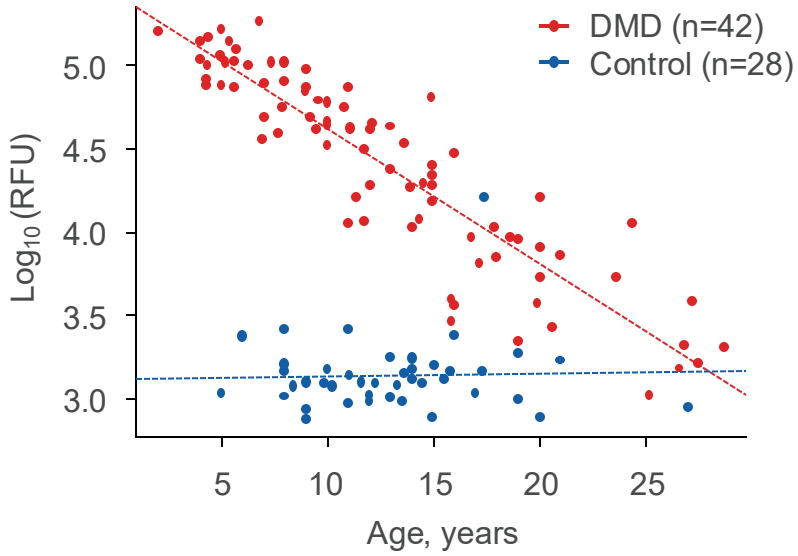
CK Isoenzymes Test[3]

- **CK-MM**
  Skeletal muscle damage
- **CK-MB**
  Cardiac muscle damage
- **CK-BB**
  Stroke, brain injury, or smooth muscle damage

CK-MM Concentration in Newborns (US Population)[2*]



CK-MM In Boys With and Without DMD[4†]



A finding of elevated CK usually results in a referral to a neurologist or neuromuscular specialist for definitive diagnosis, genetic counseling, and treatment[5]

CK, creatine kinase; CK-BB, serum creatine kinase from the brain; CK-MB, serum creatine kinase from the heart; CK-MM, serum creatine kinase from skeletal muscle; DMD, Duchenne muscular dystrophy; RFU, relative fluorescence unit.

*Image adapted from Timonen A, et al. *Int J Neonatal Screen*. 2019;5:27, licensed under a CC-BY 4.0 Creative Commons license; doi: 10.3390/ijns5030027.

†Image used with permission of The Author, from Hathout Y, et al. *Proc Natl Acad Sci USA*. 2015;112:7153–7158; permission conveyed through Copyright Clearance Center, Inc.

1. National Task Force for Early Identification of Childhood Neuromuscular Disorders. Early diagnosis makes a difference. Accessed May 09, 2025. https://childmuscleweakness.org/wp-content/uploads/2019/05/PrimaryCareProviderPacket.pdf;
2. Timonen A, et al. *Int J Neonatal Screen*. 2019;5:27; 3. Medline Plus. Creatine Kinase. https://medlineplus.gov/lab-tests/creatine-kinase/. Accessed May 14, 2025; 4. Hathout Y, et al. *Proc Natl Acad Sci USA*. 2015;112:7153–7158;
5. Ciafaloni E, et al. *J Pediatr*. 2009;155:380–385.

What is involved in DMD newborn screening?

Goals of DMD newborn screening:[1]

- To identify infants with DMD early and to initiate care with specialists earlier
- To prevent families from experiencing an unnecessary diagnostic odyssey
- To ensure that every individual with DMD and their family receives timely, helpful, and accurate resources at the time of diagnosis

With new therapies emerging, there has been a renewed interest in newborn screening; new treatments may be most effective if they are initiated early, before symptom onset.[2]

DMD newborn screening process[1,2]

1. **Dried blood spot collection**
2. **Assessment of CK-MM levels**
3. **Genetic testing if CK-MM is elevated**

CK-MM levels can be measured via GSP® Neonatal CK-MM Kit[3]

- The kit measures muscle-specific creatine kinase (CK-MM) in dried blood spots, helping to detect newborns affected by DMD[3,4]
- Assay is fully automated and ready for use[3]
- Analyte (CK-MM in dried blood sample) is bound to monoclonal CK-MM-specific antibodies[3]
- Used in New York DMD NBS pilot study; assay showed separation of individuals with DMD from unaffected newborns[4]

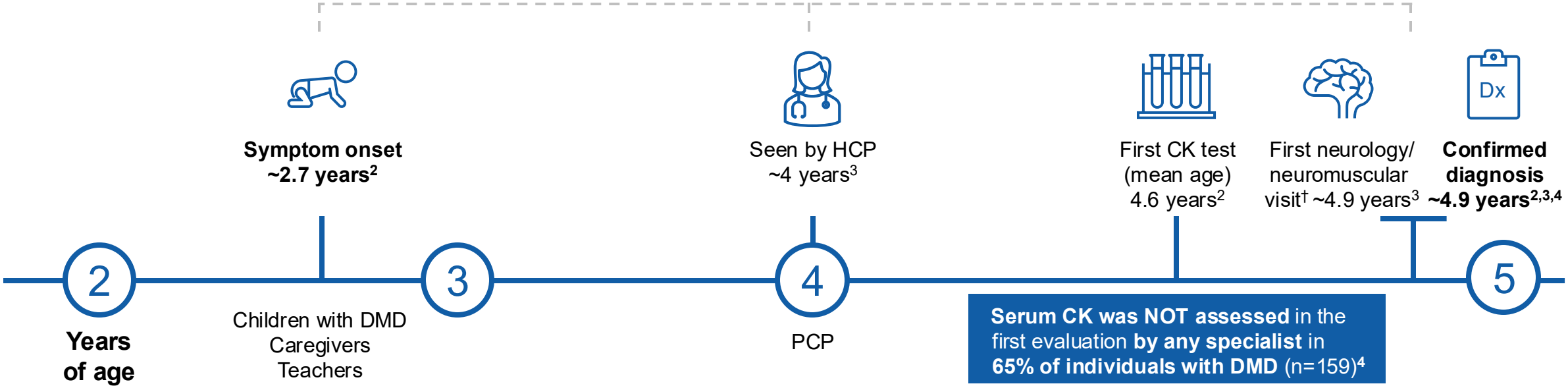
CK, creatine kinase; CK-MM, serum creatine kinase from skeletal muscle; DMD, Duchenne muscular dystrophy; NBS, newborn screening.

1. Hartnett MJ, et al. *Int J Neonatal Screen*. 2022;8:50; 2. Birnkrant DJ, et al. *Lancet Neurol*. 2018;17:251–267; 3. Timonen A, et al. *Int J Neonatal Screen*. 2019;5:27; 4. Tavakoli NP, et al. *Ann Clin Transl Neurol*. 2023;10:1383–1396.

What does the typical journey to a DMD diagnosis look like?

Despite introduction of a diagnostic algorithm, the time to diagnosis of DMD remains unchanged.[1–5]

2.2 years from initial notice of symptoms to confirmed diagnosis[2]*



A prolonged diagnostic journey is most often caused by a delay in checking CK[2,4]‡

*The schematic represents the typical journey to a DMD diagnosis. Individuals' journeys may deviate from the schematic; †Patients may be referred first to a wrong specialist (eg, orthopedist).[3] ‡Delays caused by delays in checking CK are especially pertinent in non-Hispanic black and Hispanic individuals.[2]

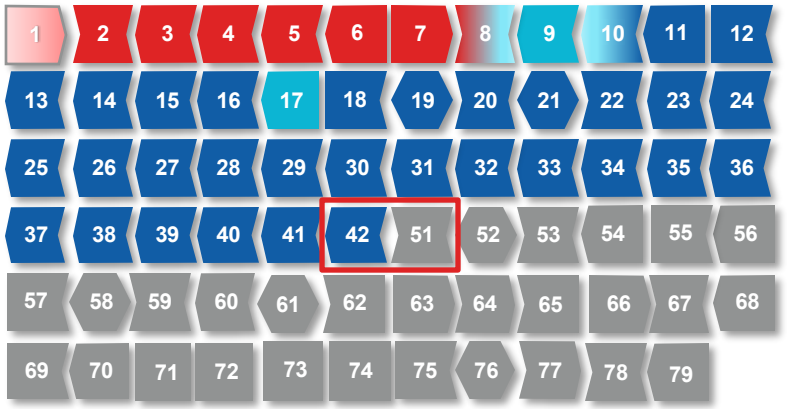
CK, creatine kinase; DMD, Duchenne muscular dystrophy; HCP, healthcare provider; PCP, primary care physician.

1. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:251–267; 2. Thomas S, et al. *Muscle Nerve.* 2022; 66:193–197; 3. Ciafaloni E, et al. Poster presented at 25th International Annual Congress of the World Muscle Society; September 30–October 4, 2020. Virtual format; 4. Ciafaloni E, et al. *J Pediatr.* 2009;155:380–385; 5. National Task Force for Early Identification of Childhood Neuromuscular Disorders. Early diagnosis makes a difference. https://childmuscleweakness.org/wp-content/uploads/2019/05/PrimaryCareProviderPacket.pdf. Accessed May 09, 2025.

How do *DMD* mutations affect dystrophin transcripts?

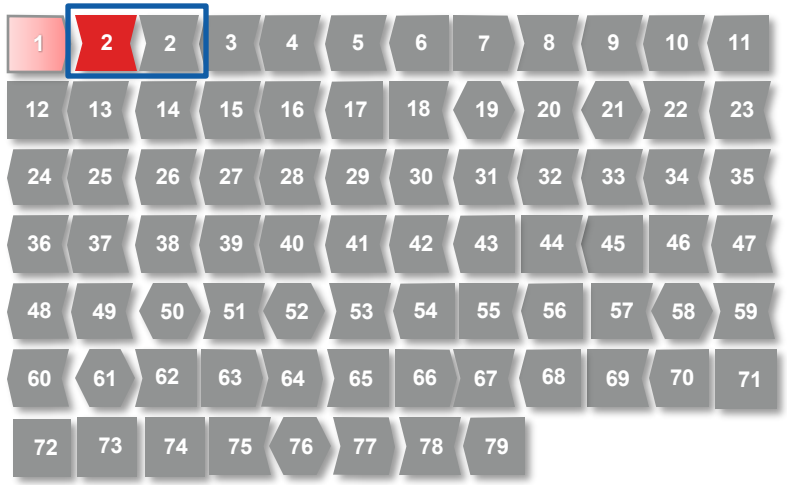
Certain *DMD* mutations lead to total absence or nearly undetectable levels of dystrophin in individuals with DMD.[1]

Large exon deletions



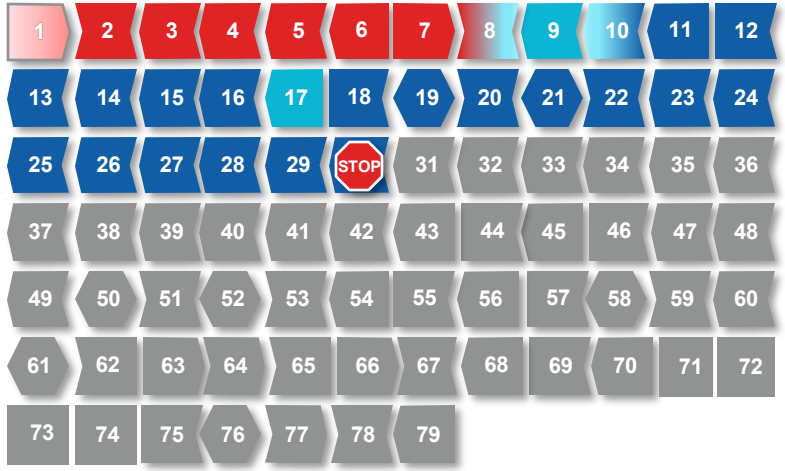
Reading frame disrupted resulting in premature termination of translation[2,3]

Duplications



Reading frame disrupted resulting in premature termination of translation[2,3]

Nonsense mutations



Premature termination of translation without reading frame disruption[2,3]

Genetic testing to determine the type of mutation in the *DMD* gene will dictate the therapeutic approach[2]

DMD, Duchenne muscular dystrophy.

1. de Feraudy Y, et al. *Ann Neurol.* 2021;89:280–292; 2. Aartsma-Rus A, et al. *J Med Genet.* 2016;53:145–151; 3. Dove: *DMD* Open-access Variant Explorer. https://www.dmd.nl/DOVE. Accessed September 24, 2025.

What are key differences between Duchenne muscular dystrophy and Becker muscular dystrophy?

DMD is caused by the lack of functional dystrophin, while in BMD, partially functional dystrophin is produced – resulting in a later onset and milder disease phenotype.[1,2]

DMD

~1 in 3,500 to 5,000 males born worldwide[3,4]

Typically out-of-frame or nonsense *DMD* gene mutations; no or very low levels of functional dystrophin produced[1,5]

Symptoms manifest in the first years of life – muscle fibrosis, motor delays, other delays, eg speech[6–9]

Loss of ambulation in early teens[10]

BMD

~1 in 19,000 males born worldwide[11]

Typically results from in-frame *DMD* gene mutations, producing partially functional dystrophin[1]

Symptoms manifest later in life (mean onset ~12 years)[2]

Loss of ambulation ~third decade of life[2]

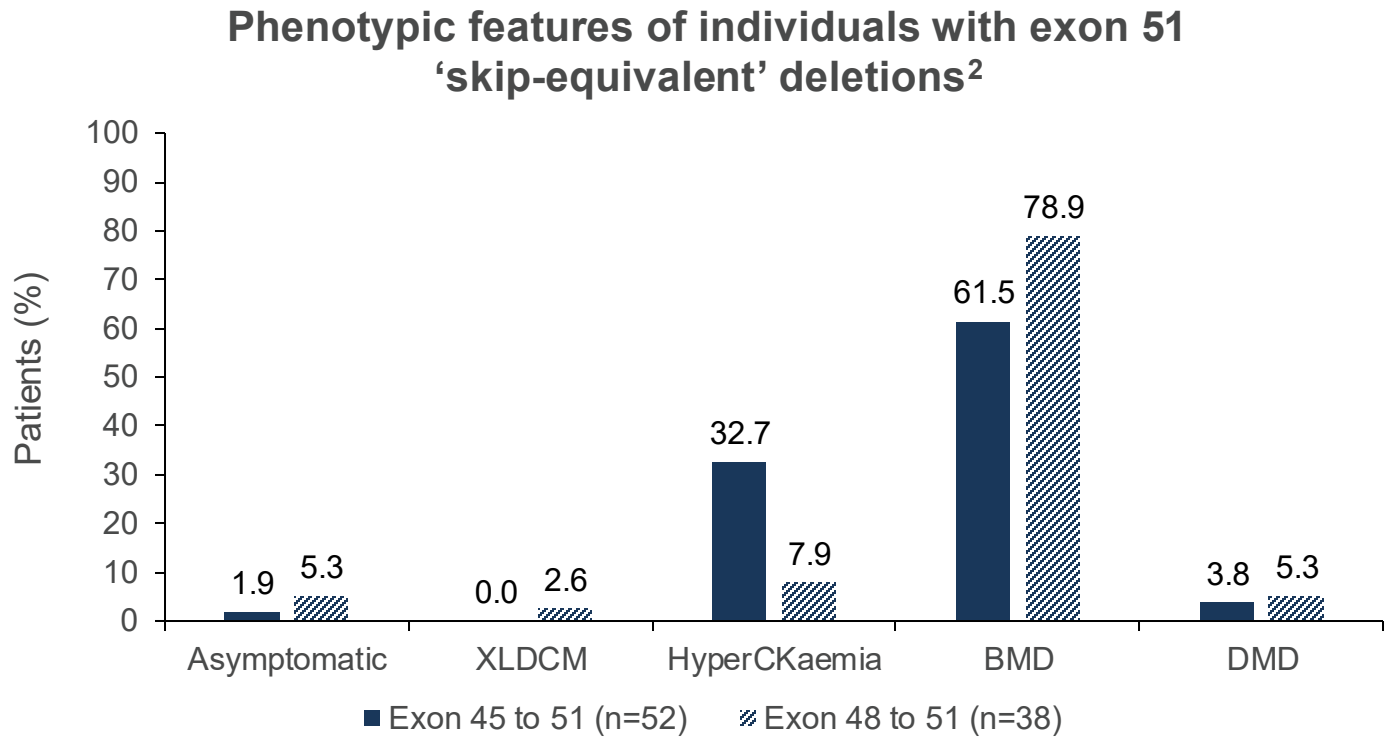
Although both DMD and BMD can result in progressive muscle degradation and loss of ambulation, DMD is characterized by earlier onset of symptoms, earlier loss of ambulation, and an overall poorer prognosis[1,2]

BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy.

1. Aartsma-Rus A, et al. *J Med Genet*. 2016;53:145–151; 2. Wilson K, et al. *Toxicol Pathol*. 2017;45:961–976; 3. Crisafulli S, et al. *Orphanet J Rare Dis*. 2020;15:141; 4. Emery AE. *Neuromuscul Disord*. 1991;1:19–29; 5. de Feraudy Y, et al. *Ann Neurol*. 2021;89:280–292; 6. Chen Y-W, et al. *Neurology*. 2005;65:826–834; 7. Peverelli L, et al. *Neurology*. 2015;85:1886–1893; 8. Van Dommelen P, et al. *Dev Med Child Neurol*. 2020;62:1198–1204; 9. Cyrulnik SE, et al. *J Pediatr*. 2007;150:474–478; 10. Bello L, et al. *Neurology*. 2016;87:401–409; 11. Kamdar F, Garry DJ. *J Am Coll Cardiol*. 2016;67:2533–2546.

What are the phenotypic features of individuals with exon 51 ‘skip-equivalent’ deletions?

- Phenotype depends on the quality of the dystrophin produced. Some genetic deletions can lead to production of a shortened but partially functional dystrophin, that leads to the mild BMD phenotype[1]
- Deletions that cause exon 51 to be ‘skipped’ typically produce mild phenotypes, and are rarely seen in individuals with DMD[2]



Individuals with exon 51 ‘skip equivalent’ deletions typically have a mild BMD phenotype[2]

BMD, Becker muscular dystrophy; CK, creatine kinase; DMD, Duchenne muscular dystrophy; XLDCM, X-linked dilated cardiomyopathy.

1. Duan D, et al. *Nat Rev Dis Primers*. 2021;7:13; 2. Waldrop MA, et al. *J Neuromuscul Dis*. 2020;7:217–229.