Module 3
How is motor function affected in Duchenne muscular dystrophy (DMD)?

Dyne | Medical Central

©2025 Dyne Therapeutics, Inc. All rights reserved. Date of preparation: September 2025. MED-00739.

Module summary

Muscle damage in DMD precedes appearance of clinical symptoms[1]

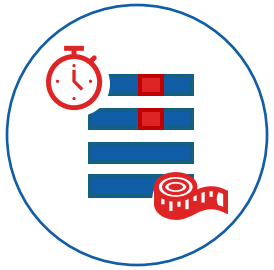
Fatty infiltration of thigh muscle tissue begins as early as 1–2 years of age[2]

The muscular effects of DMD are often evident before 5 years of age[3,4]

Effects initially include toe walking, difficulty with physical activity, waddling gait, and Gower's sign, progressing over time to include arm weakness and loss of motor skills[3–5]

Loss of ambulation is a clinically meaningful natural history milestone[3,5,6]

Age at loss of ambulation (typically in early teens) is an indicator of the severity of disease progression[6,7]



Several timed function tests, measures and scales are used to monitor progressive loss of motor function[7–9]

Examples include 6MWT, 10MWR, 4SC, TTR, SV95C, and NSAA[7–9]

SV95C is a digital objective endpoint of ambulatory performance in an individual's normal daily environment[9,10]

SV95C is qualified as a digital primary endpoint by the EMA in studies in boys with DMD ≥4 years old[10]

Biomarkers of muscle damage can allow for early detection of DMD, but are less suitable for monitoring disease progression[11–14]

Levels of CK, myoglobin, and transaminases are high in young individuals with DMD, then decline with age and muscle loss[11–14]

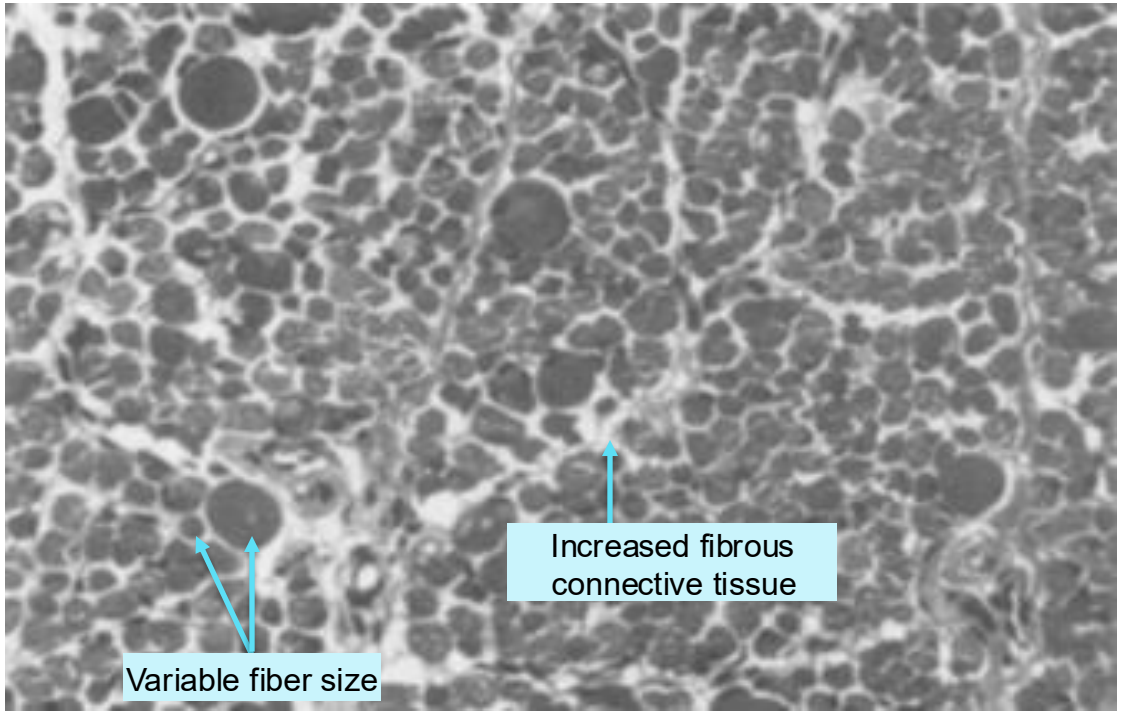
4SC, 4 Stair Climb; 6MWT, 6-Minute Walk Test; 10MRW, 10-Meter Walk/Run; CK, creatine kinase; DMD, Duchenne muscular dystrophy; EMA, European Medical Association; NSAA, North Star Ambulatory Assessment; SV95C, Stride Velocity 95th Centile; TTR, Time to Rise.

1. Bradley WG, et al. *J Neurol Neurosurg Psychiatry*. 1972;35:451–455; 2. Li W, et al. *Neuromuscul Disord*. 2015;25:375–380; 3. Birnkrant DJ, et al. *Lancet Neurol*. 2018;17:251–267; 4. Crossnohere NL, et al. *Am J Med Genet C Semin Med Genet*. 2022;190:169–177; 5. Bushby K, et al. *Lancet Neurol*. 2010;9:77–93; 6. Henricson EK, et al. *Muscle Nerve*. 2013;48:55–67; 7. Arora H, et al. *Muscle Nerve*. 2018;58:631–638; 8. Stimpson G, et al. *Eur J Paediatr Neurol*. 2024:53:123–130; 9. Servais L, et al. *Nat Med*. 2023;29:2391–2392; 10. EMA. Opinion on SV95C. July 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-primary-endpoint-studies-ambulatory-duchenne-muscular-dystrophy-studies_en.pdf. Accessed September 24, 2025; 11. Fortunato F, Ferlini A. *J Neuromuscul Dis*. 2023;10:987–1002; 12. Hathout Y, et al. *Proc Natl Acad Sci USA*. 2015;112:7153–7158 (and supplementary material); 13. Wright MA, et al. *J Am Board Fam Med*. 2012;25:536–540; 14. Rodríguez-Cruz M, et al. *Am J Phys Med Rehabil*. 2020;99:1121–1128.

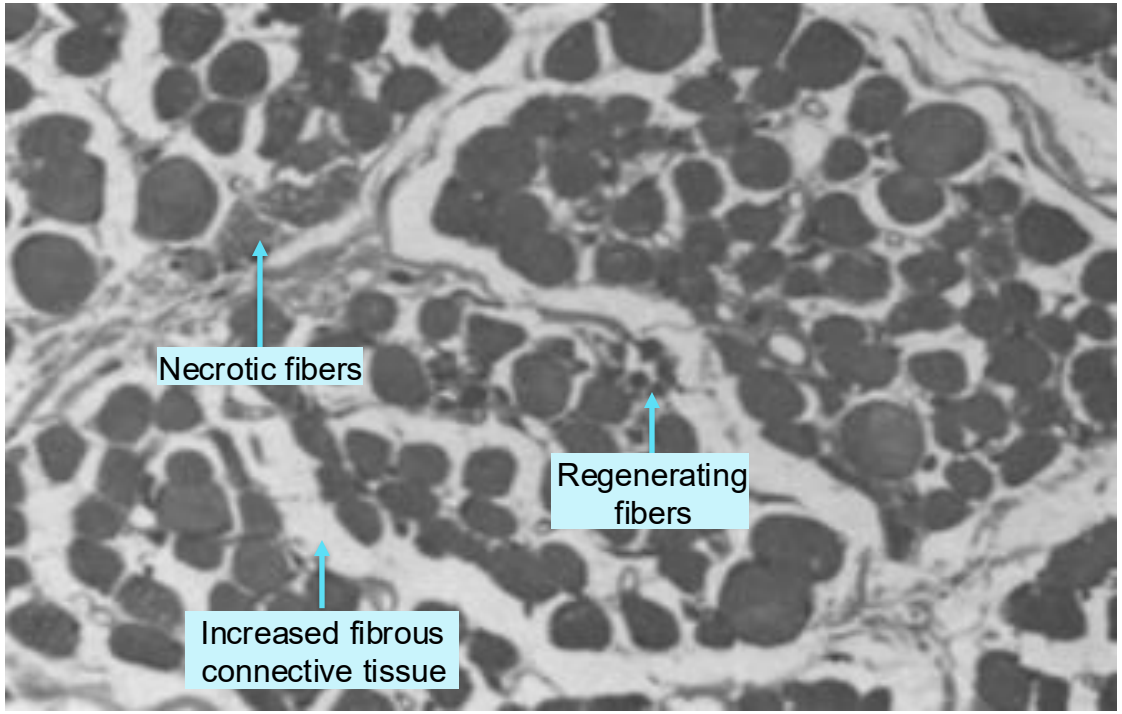
What structural changes might be seen in early stages of DMD?

Two muscle biopsy samples from the same boy with DMD at two separate timepoints

2.5 weeks of age*



3 years, 2 months of age†

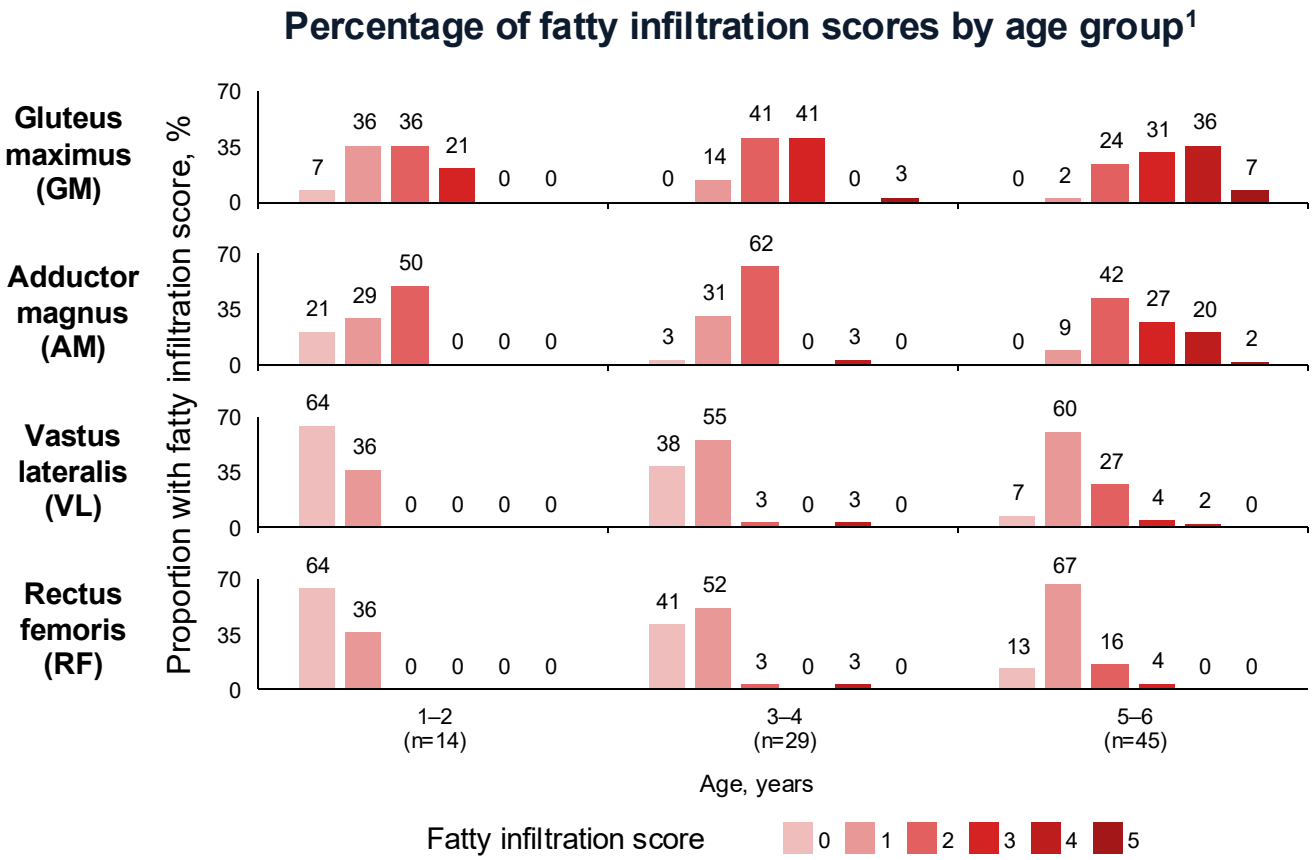


Muscle damage in DMD precedes appearance of clinical symptoms

*Section showed abnormal variability of fiber size, moderate number of hyaline fibers, and a slight increase of fibrous connective tissue;
†Section showed hyaline, necrotic, and regenerating fibers with increased endomysial fibrosis. The boy showed the florid pathologic changes of preclinical DMD.
DMD, Duchenne muscular dystrophy.
Images used with permission of The Author(s), from Bradley WG, et al. *J Neurol Neurosurg Psychiatry.* 1972;35:451–455; permission conveyed through Copyright Clearance Center, Inc.
Bradley WG, et al. *J Neurol Neurosurg Psychiatry.* 1972;35:451–455.

When does fatty infiltration of muscle become evident in boys with DMD?

- Fatty infiltration of the thigh muscle begins at a very early age, but individual muscles are affected at different ages[1]
- Fatty infiltration of the GM and AM occurred before 2 years of age, and these muscles had the highest fat content and greatest fatty infiltration at all ages[1]
- VL and RF were affected by 3–4 years of age; quadriceps and hamstrings were affected by 5–6 years of age (data not shown)[1]
- Severe fatty infiltration of all thigh muscles started after 7 years of age[1]
- Baseline VL fat fraction is suggested to be a predictor of motor function over the following 12–24 months[2]



Replacement of thigh muscle tissue with fat begins as early as 1–2 years of age[1]

AM, adductor magnus; DMD, Duchenne muscular dystrophy; GM, gluteus maximus, RF, rectus femoris; VL, vastus lateralis.

1. Li W, et al. *Neuromuscul Disord*. 2015;25:375–380; 2. Barnard AM, et al. *Neurology* 2020; 94:e897–e909.

How do the muscle-deteriorating effects of DMD manifest over time?

The muscle-deteriorating effects of DMD often first become evident at <5 years of age[1–3]

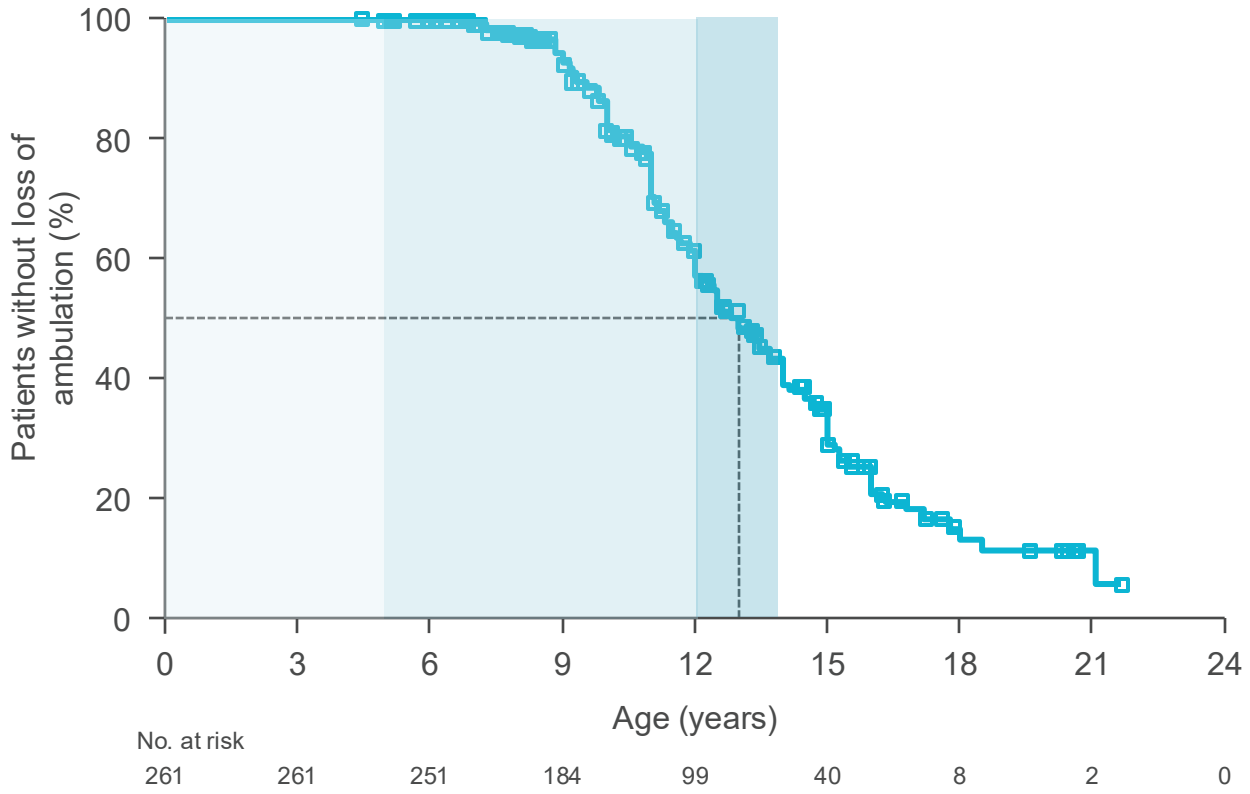
Effects initially include toe walking, difficulty with physical activity, waddling gait, and Gower's sign[1,2,4]

Over time, this progressively worsens to include contractures, loss of motor skills, and weakness in the arms[1,4–6]

Wheelchair dependence and loss of ambulation occurs around 12 to 13 years of age[4,5,7–10]

Around the time of LoA, there is an increased need for respiratory and cardiac interventions[11]

Age at loss of ambulation for patients in CINRG DNHS



LoA is a clinically meaningful natural history milestone and age at LoA is an indicator of the severity of disease progression in individuals with DMD[4,5,12]

CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; DMD, Duchenne muscular dystrophy; LoA, loss of ambulation.

Image adapted from Mercuri E, et al. *J Neurol.* 2023, licensed under a CC-BY 4.0 Creative Commons license; doi: 10.1007/s00415-023-11687-1.

1. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:251–267; 2. Crossnohere NL, et al. *Am J Med Genet C Semin Med Genet.* 2022;190:169–177; 3. van Dommelen P, et al. *Dev Med Child Neurol.* 2020;62:1198–1204; 4. Bushby K, et al. *Lancet Neurol.* 2010;9:77–93; 5. Humbertclaude V, et al. *Eur J Paediatr Neurol.* 2012;16:149–160; 6. McDonald CM, et al. *Am J Phys Med Rehabil.* 1995;74:S70–S92; 7. Bello D, et al. *Neurology.* 2016;87:401–409; 8. Mendell JR, et al. *J Neuromuscul Dis.* 2021;8:469–479; 9. McDonald CM, et al. *J Comp Eff Res.* 2022;11:139–155; 10. Mercuri E, et al. *J Neurol.* 2023;270:3896–3913 11; Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:347–361; 12. Henricson EK, et al. *Muscle Nerve.* 2013;48:55–67.

What measures are used to monitor progressive loss of motor function in DMD?

Measures of motor and functional ability used in DMD clinical trials and clinical practice	Summary
6-Minute Walk Test (6MWT)[1]	The distance an individual can walk in 6 minutes
10-Meter Walk/Run (10MWR)[1]	The time taken for an individual to run or walk 10 meters
4 Stair Climb (4SC)[1]	The time taken for an individual to climb four stairs
Time to Rise (TTR)[2]	The time taken to stand from lying face up on the ground
North Star Ambulatory Assessment (NSAA)[3,4]	17 ordinal tasks – including rising from the floor, moving from sitting to standing, jumping, running, and ascending or descending steps
Stride Velocity 95th Centile (SV95C)*[5]	A digital ambulation measure derived from a wearable device that allows the passive collection of continuous and objective data in real-world settings
Performance of Upper Limb (PUL)[6]	22 tasks engaging the upper limbs to assess motor performance relating to everyday life
Brooke Upper Extremity Scale[7]	6-point scale assessing shoulder and hand mobility
Motor Function Measure Scale (MFMS)[8]	32 tasks to assess motor function in three domains – standing position and transfers, axial and proximal, and distal

*Recognized as a study endpoint by EMA CHMP.[10] Not yet recognized by other regulatory authorities.

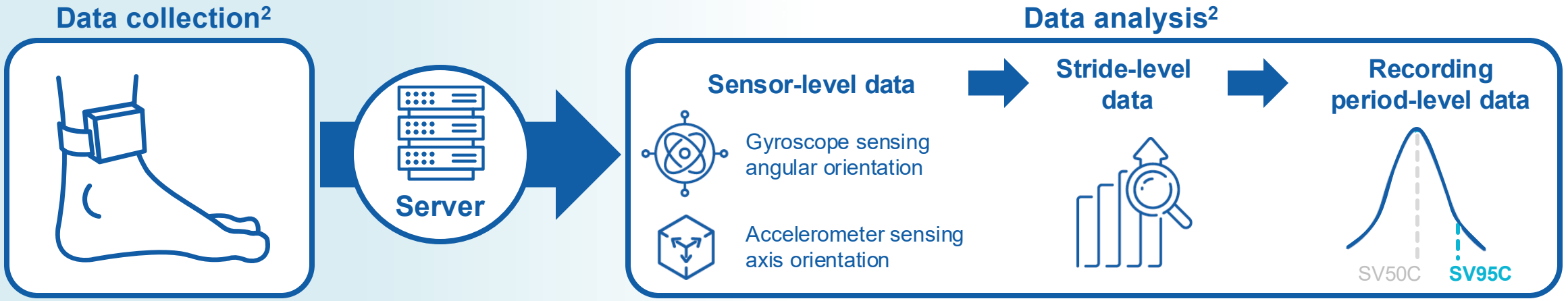
Timed tests are generally sensitive to age, function at baseline, effort, and background steroid use[9]

CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency.
1. Arora H, et al. *Muscle Nerve.* 2018;58:631–638; 2. McDonald CM, et al. *Lancet.* 2018;391:451–461; 3. Stimpson G, et al. *Eur J Paediatr Neurol.* 2024:53:123–130; 4. Muntoni F, et al. *PLoS One.* 2019;14(9):e0221097; 5. Servais L, et al. *Nat Med.* 2023;29:2391–2392; 6. Mayhew AG, et al. *Dev Med Child Neurol.* 2020;62:633–639; 7. Lu YM, Lue YJ. Strength and Functional Measurement for Patients with Muscular Dystrophy. In: Hegde M, Ankala A, eds. *Muscular Dystrophy* [Internet]. IntechOpen; 2012. https://www.intechopen.com/chapters/36741. Accessed September 24, 2025; 8. Bérard C, et al. *Neuromuscul Disord.* 2005;15:463–470; 9. Cantor Fitzgerald Research. Industry Report – Muscling Up: Deep Dive Into DMD – Part 2. May 28, 2025; 10. EMA. Opinion on SV95C. July 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-primary-endpoint-studies-ambulatory-duchenne-muscular-dystrophy-studies_en.pdf. Accessed September 24, 2025.

How is stride velocity 95th centile (SV95C) used to measure ambulatory performance in DMD?

SV95C is a digital objective endpoint of ambulatory performance in patients' normal daily environment, and is qualified as a primary endpoint by the EMA in studies in boys with DMD ≥4 years old[1,2]

- Correlated with traditional hospital-based clinical outcomes (6MWT, NSAA, 4SC)[1,2]
- Demonstrated sensitivity to detect change over time in natural history, steroid-treated individuals, and in clinical trials[1]
  - SV95C has greater sensitivity and responsiveness vs other function tests[1,3]
    - In an analysis of individuals with DMD on stable steroid regimens from three natural history studies and two clinical trials, SV95C demonstrated a progressive loss of maximal speed that could be observed as early as 3 months versus 9 months with 6MWT and NSAA[3]
- Proposed SV95C MCID = 0.1 m/s (36 m in 6 min) corresponds to 6MWT MCID = 30 m[1,4,5]
- Continuously collects data over a period of time; minimally impacted by social, familial, or environmental factors[1,5]
- Individuals with DMD show small improvements in SV95C until the age of 7 years, followed by a gradual decline[6]



EMA, European Medicines Agency; DMD, Duchenne muscular dystrophy; MCID, minimal clinically important difference; 6MWT, 6-minute walk test; NSAA, North Star Ambulatory Assessment; 4SC, 4-stair climb.

1. EMA. Opinion on SV95C. July 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-primary-endpoint-studies-ambulatory-duchenne-muscular-dystrophy-studies_en.pdf. Accessed September 24, 2025; 2. Servais L, et al. *Nat Med*. 2023;29:2391–2392; 3. Servais L, et al. *Sci Rep*. 2024;14:29681; 4. McDonald CM, et al. *Muscle Nerve*. 2013;48:357–368; 5. EMA. Opinion on SV95C. April 2019. https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular-dystrophy-measured-valid-and-suitable-wearable-device_en.pdf. Accessed September 24, 2025; 6. Cantor Fitzgerald Research. Industry Report – Musding Up: Deep Dive Into DMD – Part 2. May 28, 2025.

Can biomarkers of muscle damage be used to monitor disease progression in DMD?

CK

A marker of muscle damage used in initial detection of DMD and newborn screening, but **less suitable for monitoring progression and treatment response**[1,2]

- CK levels vary with age, environment, and phenotype:
  - CK levels peak between 1 and 6 years of age, then decline as disease progresses and muscle is replaced by fibrotic and adipose tissue[1]
  - CK levels are highly influenced by environmental factors such as metabolic changes, muscle trauma, and exercise[1]
  - CK levels vary with phenotype:[3]
    - >5× normal in BMD
    - >10× normal in DMD
- CK levels correlate poorly with NSAA progression in natural history or clinical trials[4,5]

Myoglobin

- Marker of muscle damage; myoglobin is released from damaged myofibres[6]
- Serum myoglobin levels are high in young individuals with DMD, then decline with age, likely due to muscle loss[7,8]

AST and ALT

- Elevated in individuals with DMD due to muscle damage, not liver dysfunction[9,10]
- Can be early indicators of DMD, before other clinical signs emerge[10,11]
- Levels are high in young individuals with DMD, then levels decline with age[12]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMD, Becker muscular dystrophy; CK, creatine kinase; DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment.

1. Fortunato F, Ferlini A. *J Neuromuscul Dis*. 2023;10:987–1002; 2. Timonen A, et al. *Int J Neonatal Screen*. 2019;5:27; 3. Darras BT. Dystrophinopathies. 2000 Sep 5 [Updated 2022 Jan 20]. In: Adam MP, Feldman J,Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2025; 4. Burch PM, et al. *J Neuromuscul Dis*. 2015;2:241–255; 5. Cantor Fitzgerald Research. Industry Report – Muscling Up: Deep Dive Into DMD – Part 2. May 28, 2025; 6. Khan FY. *Neth J Med*. 2009;67:272–837; 7. Hathout Y, et al. *Proc Natl Acad Sci USA*. 2015;112:7153–7158 (supplementary material); 8. Hathout Y, et al. *Proc Natl Acad Sci USA*. 2015;112:7153–7158; 9. Parent Project Muscular Dystrophy. Diagnosing Duchenne. https://www.parentprojectmd.org/care/for-healthcare-providers/diagnosing-duchenne/. Accessed September 24, 2025; 10. Wright MA, et al. *J Am Board Fam Med*. 2012;25:536–540; 11. Kansu A, et al. *Front Pediatr*. 2023;11:1272177; 12. Rodríguez-Cruz M, et al. *Am J Phys Med Rehabil*. 2020;99:1121–1128.