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

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Module summary

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

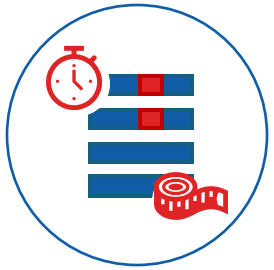
Fatty infiltration of thigh muscle tissue begins as early as 1–2 years of age[2]

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]

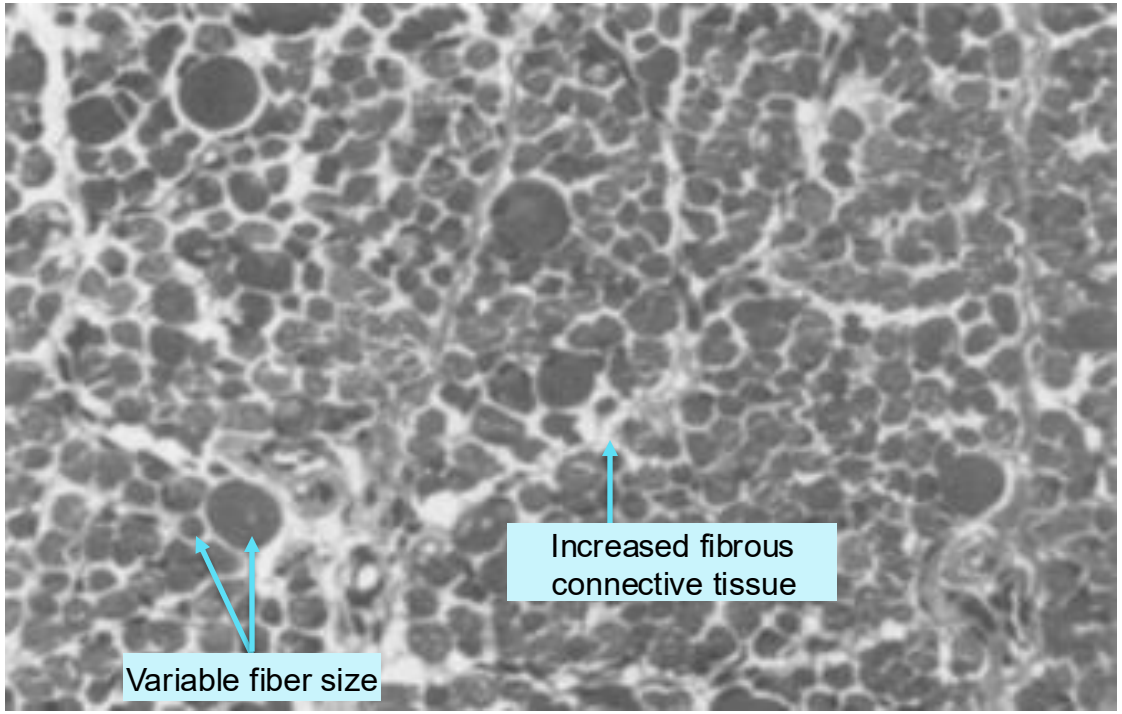
4SC, 4 Stair Climb; 6MWT, 6-Minute Walk Test; 10MRW, 10-Meter Walk/Run; CK, creatine kinase; DMD, Duchenne muscular dystrophy; EMA, European Medical Association; NSAA, North Star Ambulatory Assessment; SV95C, Stride Velocity 95th Centile; TTR, Time to Rise.

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.

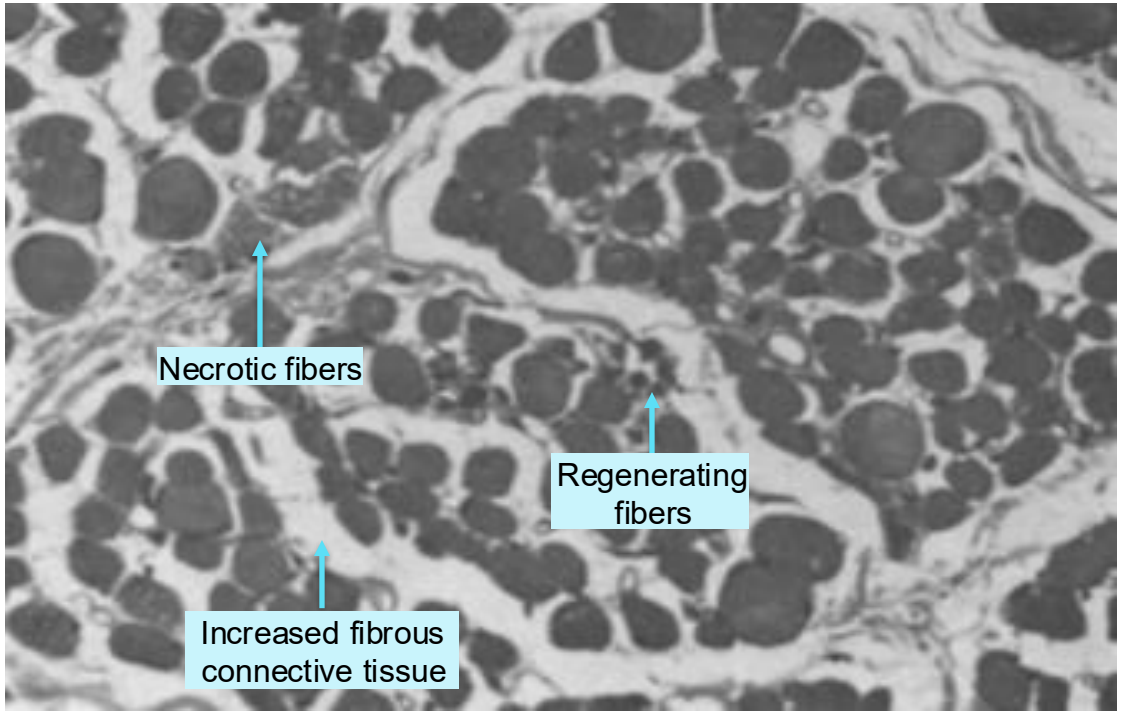
What structural changes might be seen in early stages of DMD?

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†



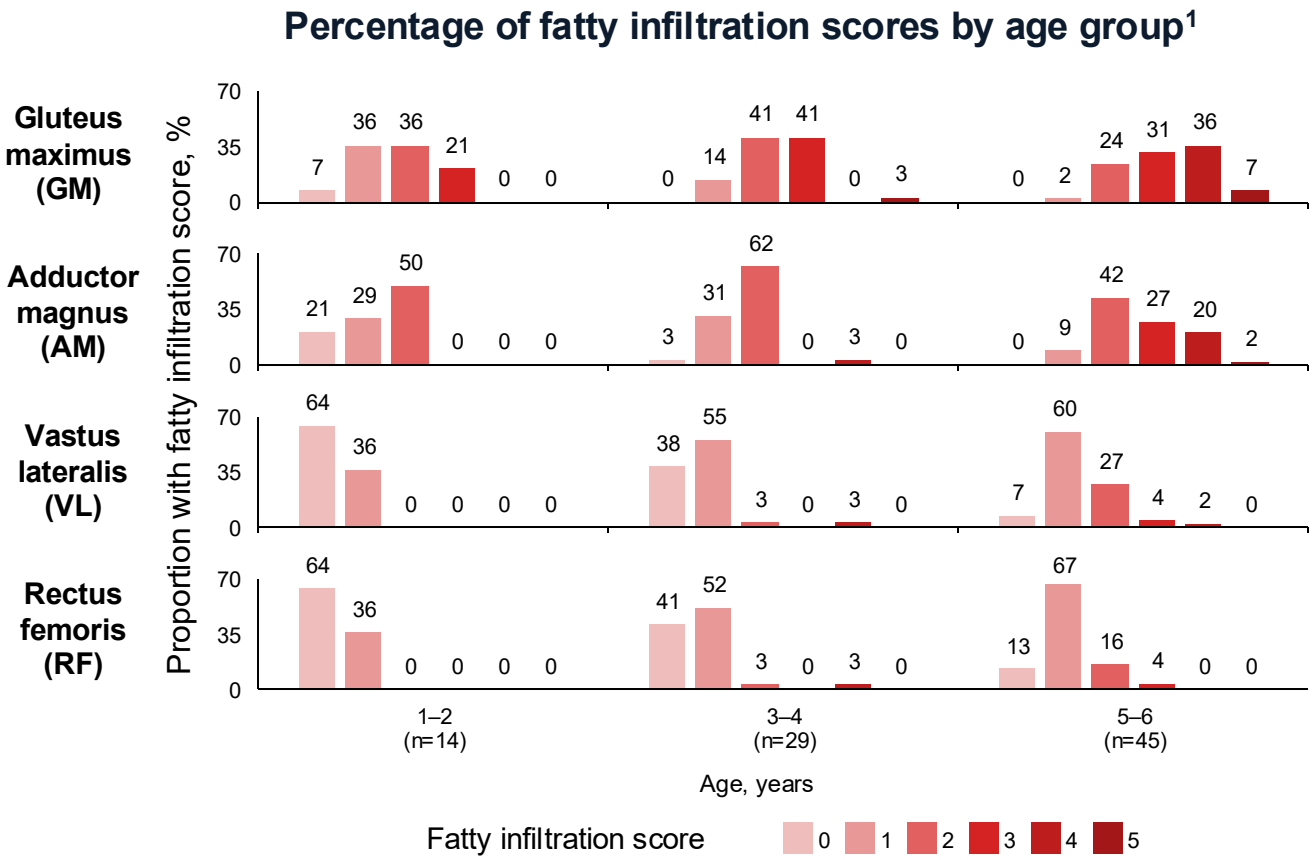
Muscle damage in DMD precedes appearance of clinical symptoms

*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.

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]

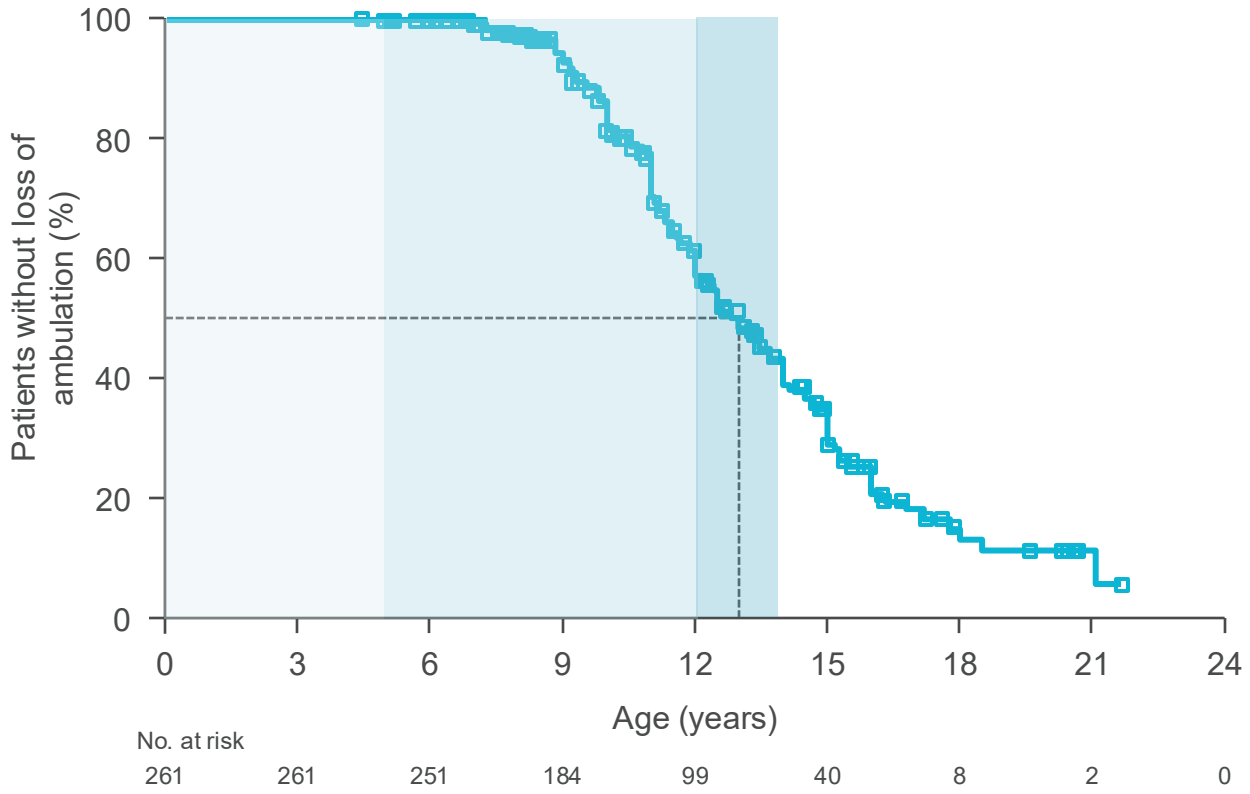
Effects initially include toe walking, difficulty with physical activity, waddling gait, and Gower's sign[1,2,4]

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.

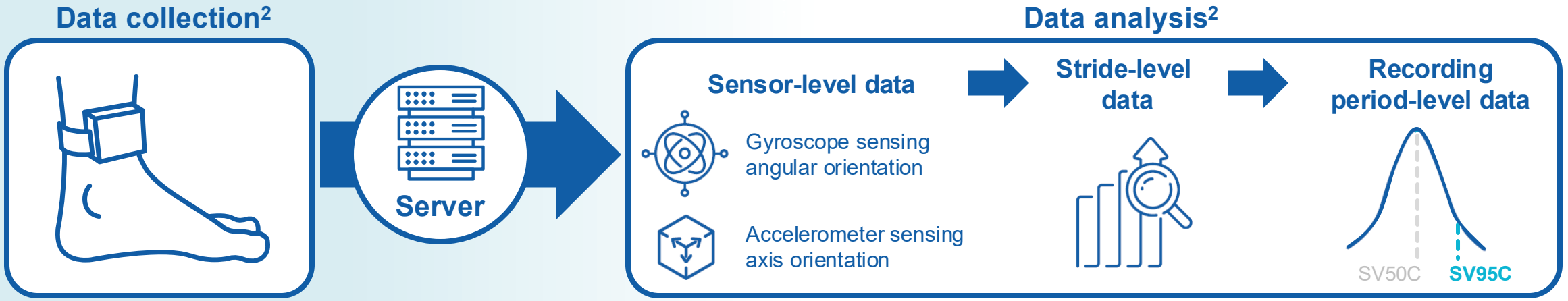
Timed tests are generally sensitive to age, function at baseline, effort, and background steroid use[9]

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.