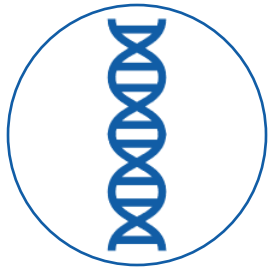
Module 4
How does Duchenne muscular dystrophy (DMD) progress over time?

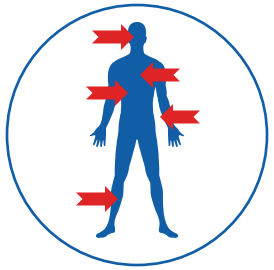
Dyne | Medical Central

Module summary



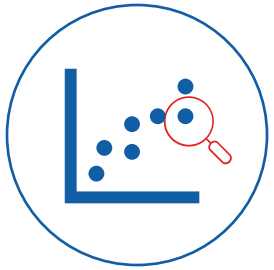
Variability in DMD and BMD phenotypic expression (severity) relates mainly to the type of mutation and how it affects dystrophin production[1]

A goal for disease-modifying treatment in DMD is to enable production of functional dystrophin[2]



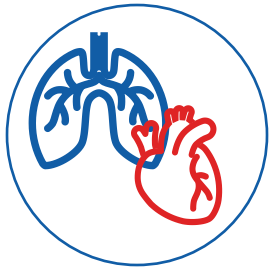
DMD affects skeletal, pulmonary, and cardiac muscle, and the CNS[3]

While DMD is characterized by progressive muscle damage, cognitive and behavioral abnormalities can also manifest[3]



Several prognostic indicators of disease progression in DMD have been identified[4]

These include DMD mutation type, DMD genetic modifiers, age at symptom onset, height, weight, and baseline functional tests[4–6]



Cardiorespiratory complications are a leading cause of death amongst individuals with DMD[7]

Loss of respiratory muscle strength leads to ineffective cough, need for ventilatory support, and ultimately respiratory failure[7]

Dystrophin deficiency in cardiac muscle manifests as cardiomyopathy, progressing to arrythmias and heart failure over time[7]

Approximately half of individuals with DMD experience neuropsychiatric symptoms[8]

Four of the six dystrophin isoforms are expressed in the CNS, and they have diverse functions in the brain[8,9]

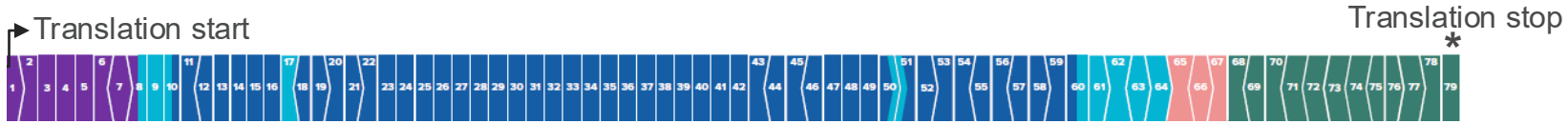
BMD, Becker muscular dystrophy; CNS, central nervous system; DMD, Duchenne muscular dystrophy.

1. Aartsma-Rus A, et al. *J Med Genet*. 2016;53:145–151; 2. Kole R, et al. *Nat Rev Drug Discov*. 2012;11:125–140; 3. Ohlendieck K, Swandulla D. *Pflügers Arch*. 2022;473:1813–1839; 4. Ferizovic N, et al. *PLoS One*. 2022;17:e0265879; 5. McDonald CM, et al. *Muscle Nerve*. 2013;48:343–56; 6. Zambon AA, et al. *Dev Med Child Neurol*. 2022;64:979–988; 7. Birnkrant DJ, et al. *Lancet Neurol*. 2018;17:347–361; 8. Vaillend C, et al. *Nat Commun*. 2025;16:1298; 9. Maresh K, et al. *Brain*. 2023;146:252–265.

How does the reading frame rule impact disease severity and symptoms?

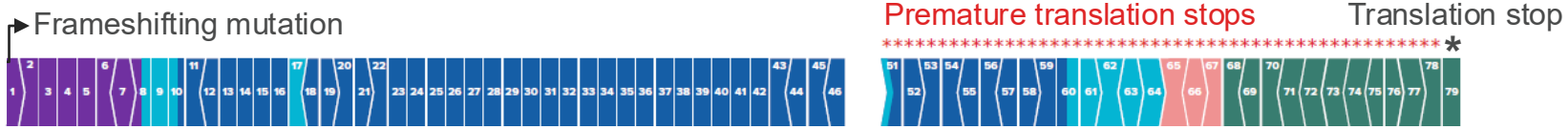
The variability in DMD and BMD phenotypic expression relates mainly to the type of mutation and how it affects production of dystrophin[1,2]

Non-diseased individuals[2–4]

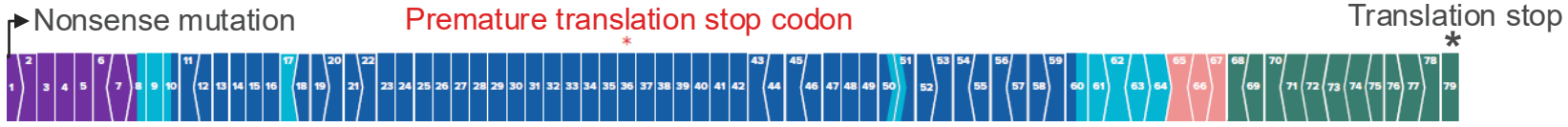


DMD transcript is translated into full-length dystrophin protein

DMD[2–4]
Severe clinical presentation

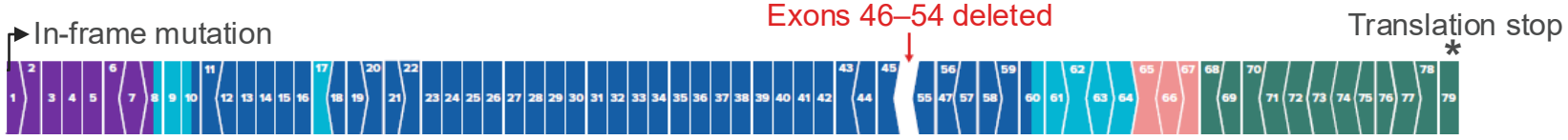


Reading frame disrupted resulting in premature termination of translation



Premature termination of translation without reading frame disruption

BMD[2–4]
Mild clinical presentation



Translation of a shorter, partially functional dystrophin

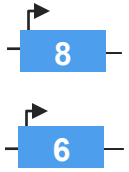
A goal for disease-modifying treatment in DMD is to enable production of high-quality dystrophin in all affected tissues[2,5,6]

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

1. Monaco AP, et al. *Genomics*. 1988;2:90–95; 2. Aartsma-Rus A, et al. *J Med Genet*. 2016;53:145–151; 3. Roberts RG, et al. *Genomics*. 1993;16:536–538; 4. Zhang Y, et al. *Physiol Rev*. 2018;98:1205–1240; 5. Kole R, et al. *Nat Rev Drug Discov*. 2012;11:125–140; 6. Ohlendieck K, Swandulla D. *Pflügers Arch*. 2022;473:1813–1839.

How can exceptions to the reading frame rule lead to variable phenotypes?

There are three instances in which a frameshift mutation results in BMD or a milder DMD* phenotype:[1]



Frameshifting or nonsense mutations before exon 8 due to the presence of alternative translation initiation sites in exons 6 or 8 that are activated by some mutations (eg, deletion of exon 2)[1]

Nonsense mutations in in-frame exons leading to exon skipping that maintains the reading frame[1,2]

Exon 44 skip-amenable mutations due to low levels of exon skipping*[1]

In-frame mutations that abolish the extracellular matrix-binding domain (exons 64–70) or all actin-binding domains (exons 2–10 and exons 32–45) result in DMD[1]

~10% of mutations in the *DMD* gene do not follow the reading frame rule[3]

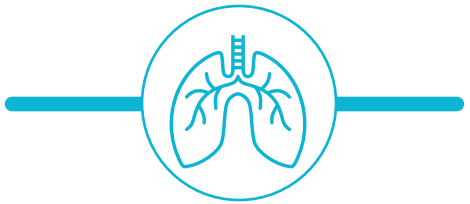
**DMD* mutations amenable to exon 44 skipping result in a milder DMD phenotype.*
BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy.
1. Aartsma-Rus A, et al. *J Med Genet.* 2016;53:145–151; 2. Waldrop MA, et al. *J Neuromuscul Dis.* 2020;7:217–229; 3. Bladen CL, et al. *Hum Mutat.* 2015;36:395–402.

How does DMD affect skeletal, pulmonary, and cardiac muscle, and the central nervous system?

Skeletal muscle

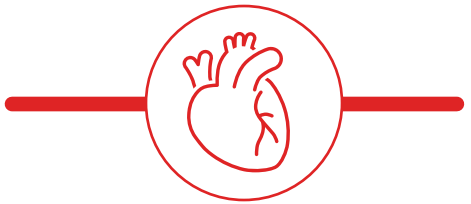
- Motor development delays[1]
- Progressive muscle weakness[1]
- Muscle fibrosis and fatty infiltration[2]
- Loss of ambulation[1]

Pulmonary



- Loss of dystrophin induces respiratory muscle failure and restrictive lung disease[3]
- Decrease in lung volume[3]
- Loss of ability to ventilate[3]
- Need for mechanical ventilation[3]

Cardiac



- Dystrophin deficiency manifests as cardiomyopathy[4]
- Myocardial fibrosis[4]
- Risk of arrhythmias[4]
- Development of clinical heart failure[4]

Central nervous system

- Learning and behavioral issues can be identified early in infancy but are not progressive[5,6]
- Intellectual disability in 19–35% of individuals[6]
- Depression and anxiety in 17–27% and 24–29% of individuals, respectively[6]

DMD is characterized by progressive skeletal, pulmonary, and cardiac muscle damage; cognitive and behavioral abnormalities can manifest due to a lack of CNS-localized dystrophin isoforms[1–6]*

*CNS manifestations dependent on *DMD* gene mutation.[6]

CNS, central nervous system; DMD, Duchenne muscular dystrophy.

1. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:251–267; 2. McDonald CM, et al. *Lancet.* 2018; 391:451–461; 3. Mayer OH, et al. *Pediatric Pulmonology.* 2015;50:487–494; 4. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:347–361; 5. Sayed MM, et al. *Middle East Current Psychiatry.* 2022;29:76; 6. Naidoo M, Anthony K. *Molecular Neurobiology.* 2020;57:1748–1767.

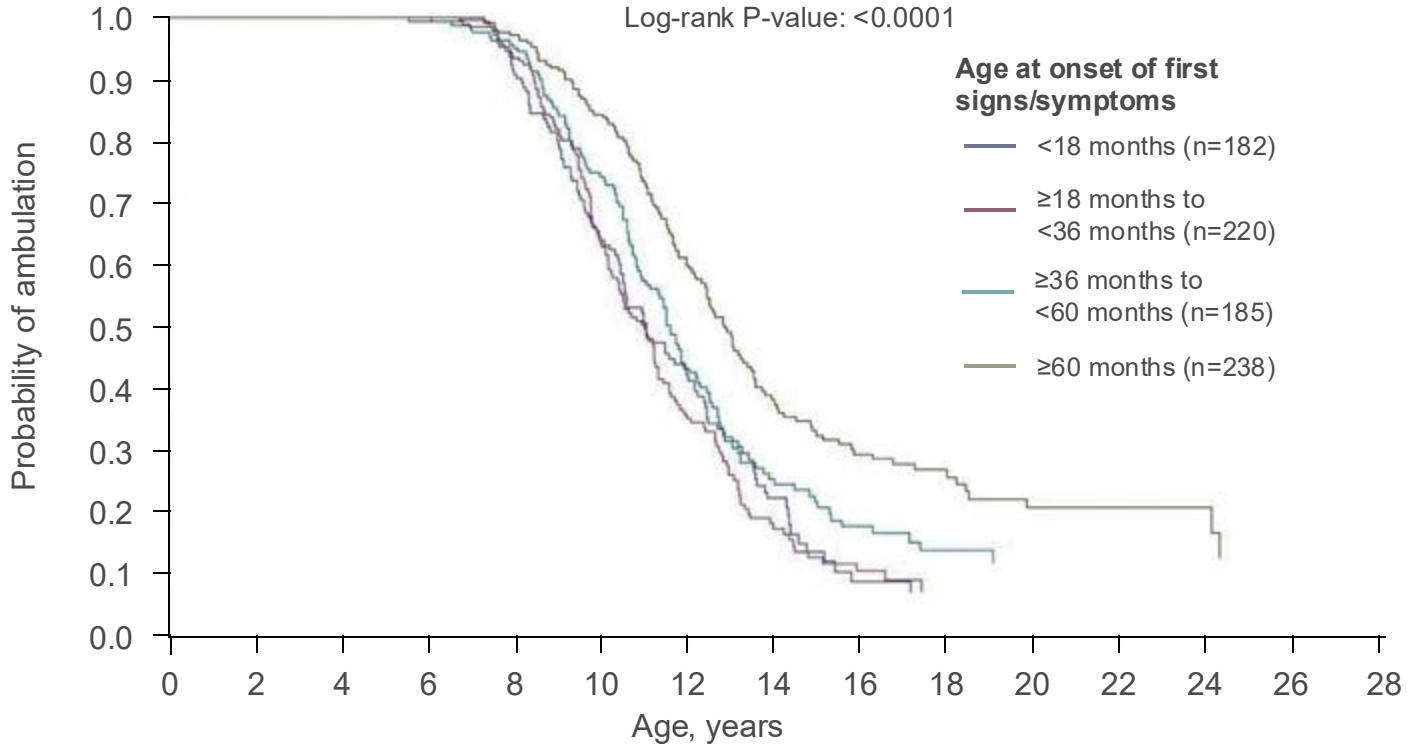
What are prognostic indicators of disease progression in DMD?

- A recent literature review found 35 studies presenting evidence of prognostic indicators of disease progression in DMD (measured as loss of independent ambulation)[1]
  - Loss of ambulation is a clinically meaningful natural history milestone and age at LoA is an indicator of the severity of disease progression in individuals with DMD[2–4]

Prognostic indicator	Effect on disease progression	LoE
Age at onset of symptoms[1]	Later onset → later LoA	2
DMD genetic modifiers[1]	Dependent on modifier	2 and 4
DMD mutation type[1]	Dependent on mutation	2 and 4
Glucocorticoid exposure[1]	Prolonged independent ambulation	2
Disease-modifying treatment[*1]	Prolonged independent ambulation	2
Baseline functional tests[4–6]	Worse baseline values → faster progression	3‡
Height[1]	Lower height → later LoA†	4
Weight[1]	Greater weight → later LoA†	4

*Includes exon-skipping therapies and ataluren. †In corticosteroid-treated individuals. ‡This study was not included in the literature review; LoE 3 has been assigned based on the observational nature of this study.
Levels of evidence: (1) systematic review of randomized trials or n-of-1 trials, (2) randomised trial or observational study with dramatic effect, (3) non-randomised controlled cohort/follow-up study, (4) case-series, case-control studies, or historically controlled studies, and (5) mechanism-based reasoning.[1]
DMD, Duchenne muscular dystrophy; LoA, loss of ambulation; LoE, level of evidence.
1. Ferizovic N, et al. *PLoS One.* 2022;17:e0265879; 2. Humbertclaude V, et al. *Eur J Paediatr Neurol.* 2012;16:149–160; 3. Henricson EK, et al. *Muscle Nerve.* 2013;48:55–67; 4. McDonald CM, et al. *Muscle Nerve.* 2013;48:343–356;
5. Muntoni F, et al. *PLoS One.* 2019;14:e0221097; 6. Mazzone ES, et al. *PLoS One.* 2016;11:e0151445.

How does age at sign or symptom onset predict disease progression in DMD?



The earlier the onset age at first sign/symptom, the higher the annual risk of LoA, except in those with onset at <18 months of age (p=0.001).

Age at onset of first signs/symptoms	HR (95% CI)
<18 months	1.52 (1.14–2.02)
≥18 months to <3 years	1.72 (1.31–2.26)
≥3 to <5 years	1.36 (1.02–1.81)
≥5 years	1.00 [reference group]

DMD disease progresses more rapidly in individuals with earlier onset of signs/symptoms

CI, confidence interval; DMD, Duchenne muscular dystrophy; HR, hazard ratio; LoA, loss of ambulation.

Ciafaloni E, et al. *J Pediatr Rehabil Med.* 2016;9:5–11.

How can genetic modifiers impact the phenotype of the primary disease-causing mutation?

Genetic modifier	Function	Marker	Effect
LTBP4	Regulates TGFβ activation[1]	Homozygous IAAM haplotype	Potential for prolonged ambulation compared to homozygous VTTT *LTBP4* haplotype[2]
SPP1 (osteopontin)	Involved in attachment of osteoclasts to bone matrix; upregulates expression of IFN-gamma and IL-12[3]	GT/GG genotype	Potential for reduced limb strength and earlier LoA; biomarker of corticosteroid response[4,5]
CD40	Encodes for a co-stimulatory molecule for T-cell polarization[6]	rs1883832 genotype	Earlier LoA[6]
ACTN3	Binding and crosslinking of actin thin filaments[7]	R577X (rs1815739) genotype	Reduced muscle strength, poor 10MWR performance[7]

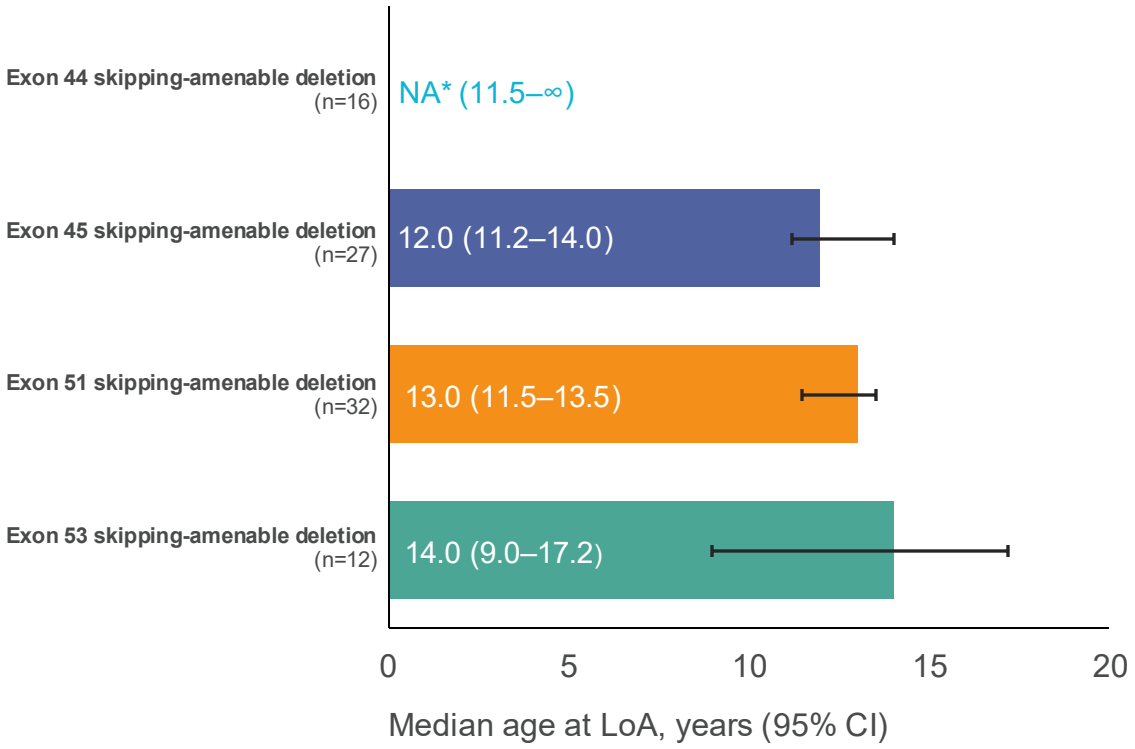
Genetic modifiers, in addition to the mutations in the *DMD* gene itself, may influence DMD disease severity and prognosis[2,4,6,7]

10MWR, 10-meter walk/run test; DMD, Duchenne muscular dystrophy. IFN, interferon; IL, interleukin; LoA, loss of ambulation; LTBP4, latent transforming growth factor-β binding protein 4; SPP1, secreted phosphoprotein; TGFβ, transforming growth factor-β.

1. National Center for Biotechnology Information Gene Library. https://www.ncbi.nlm.nih.gov/gene/8425#summary. Accessed September 24, 2025; 2. Flanigan KM, et al. *Ann Neurol.* 2013;73:481–488; 3. National Center for Biotechnology Information Gene Library. https://www.ncbi.nlm.nih.gov/gene/6696. Accessed September 24, 2025; 4. Pegoraro E, et al. *Neurology* 2011; 76:219–226; 5. Bello L, et al. *Ann Neurol.* 2015;77:684–696; 6. Bello L, et al. *Am J Hum Genet.* 2016;99:1163–1171; 7. Hogarth MW, et al. *Nature Communications.* 2017;8:14143.

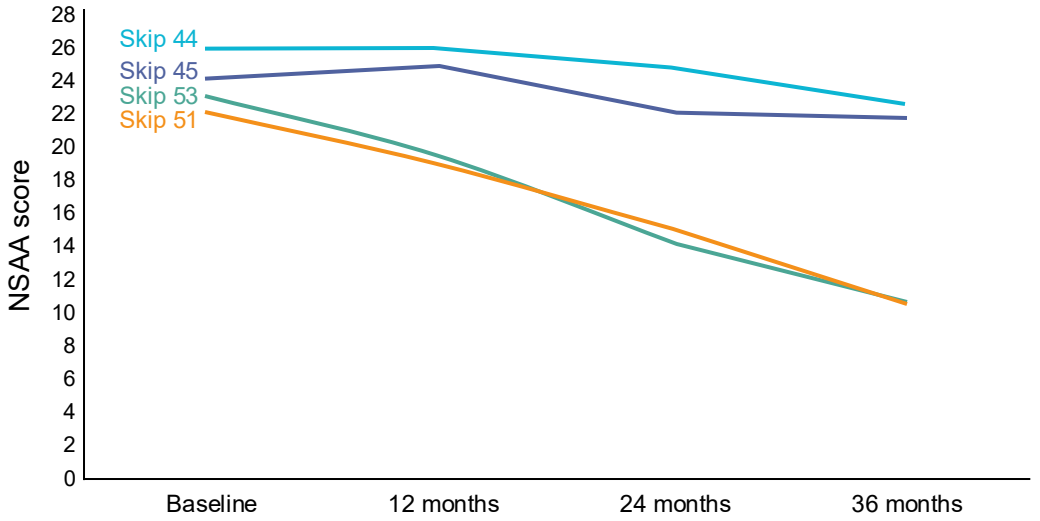
How do genetic mutations affect disease progression in DMD (1 of 2)

Age at loss of ambulation by mutation in GC-treated individuals[1]



∞, Upper confidence interval undetermined because of low N.
*Median not calculable as only 4/16 (<50%) had lost ambulation at last follow-up.

Change in NSAA score over 36 months by mutation[2*]



	Change from baseline, mean (SD)		
	12 months	24 months	36 months
Skip 44	0.1 (+4.3)	–1.8 (+7.7)	–3.3 (+7.3)
Skip 45	–1.3 (+6.9)	–2.9 (+7.9)	–2.3 (+9)
Skip 51	–3.5 (+5.0)	–7.9 (+7.8)	–12.6 (+7.9)
Skip 53	–3.2 (+4.9)	–7.8 (+7.4)	–11.4 (+8.9)

Individuals with mutations amenable to exon skip 44 (n=34), skip 45 (n=25), skip 51 (n=19), and skip 53 (n=28).

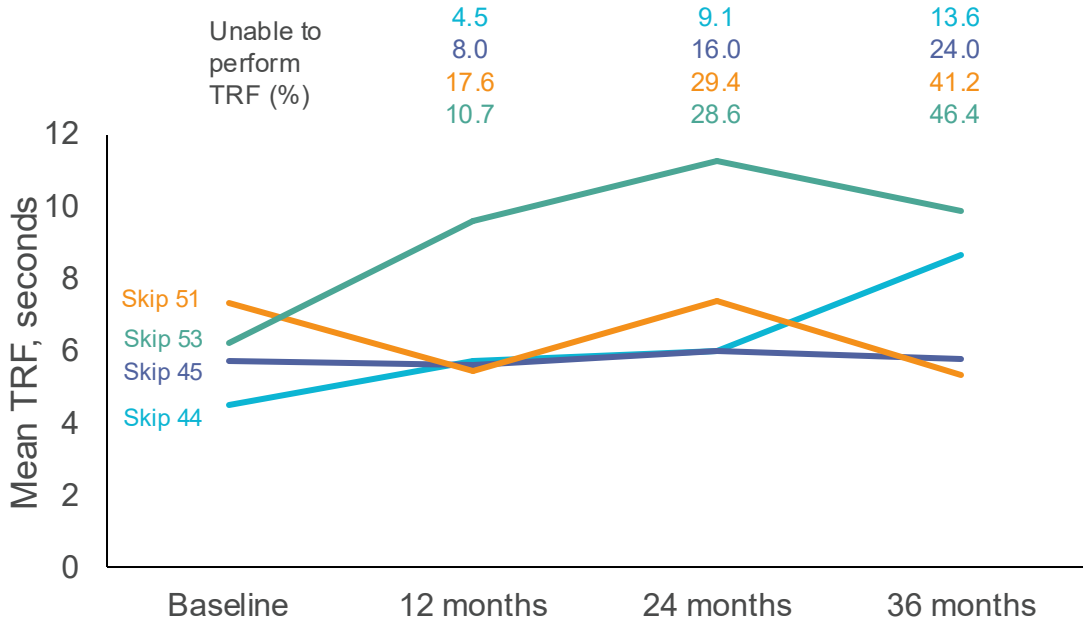
The type of *DMD* mutation affects the trajectory of decline of motor function, with exon 44 skip-amenable deletions predictive of slower disease progression[1,2]

CI, confidence interval; DMD, Duchenne muscular dystrophy; GC, glucocorticosteroid; LoA, loss of ambulation; NA, not available; NSAA, North Star Ambulatory Assessment; SD, standard deviation.

1. Bello L, et al. *Neurology*. 2016;87:401–409; 2. Coratti G, et al. *PLoS One*. 2021;16:e0253882.

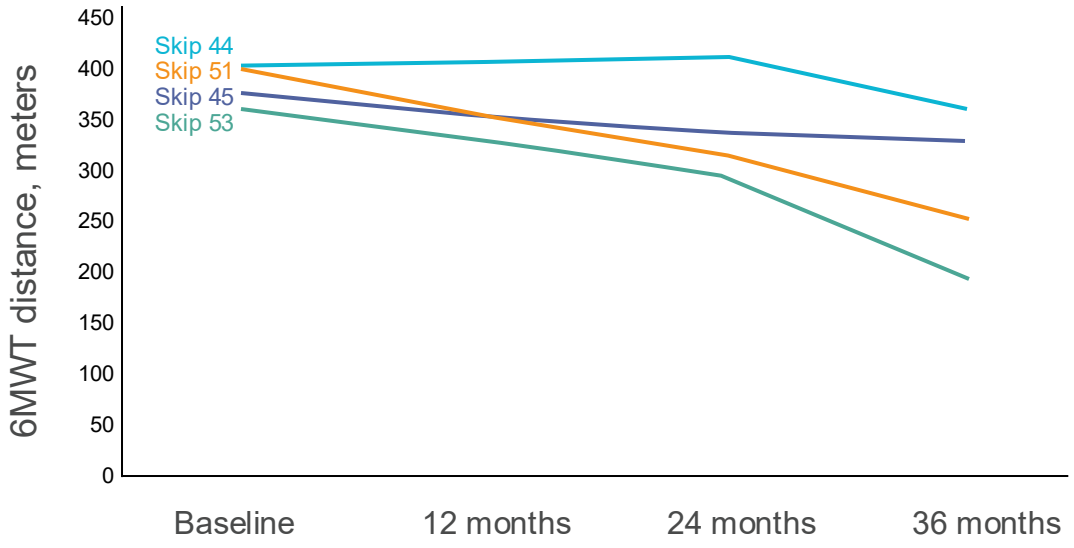
How do genetic mutations affect disease progression in DMD (2 of 2)

Mean TRF over 36 months by mutation



Individuals with mutations amenable to exon skip 44 (n=22), 45 (n=25), 51 (n=17), or 53 (n=28); all on steroid treatment.

Change in 6MWT distance over 36 months by mutation



Individuals with mutations amenable to exon skip 44 (n=24), skip 45 (n=27), skip 51 (n=18), and skip 53 (n=28), all on steroid treatment.

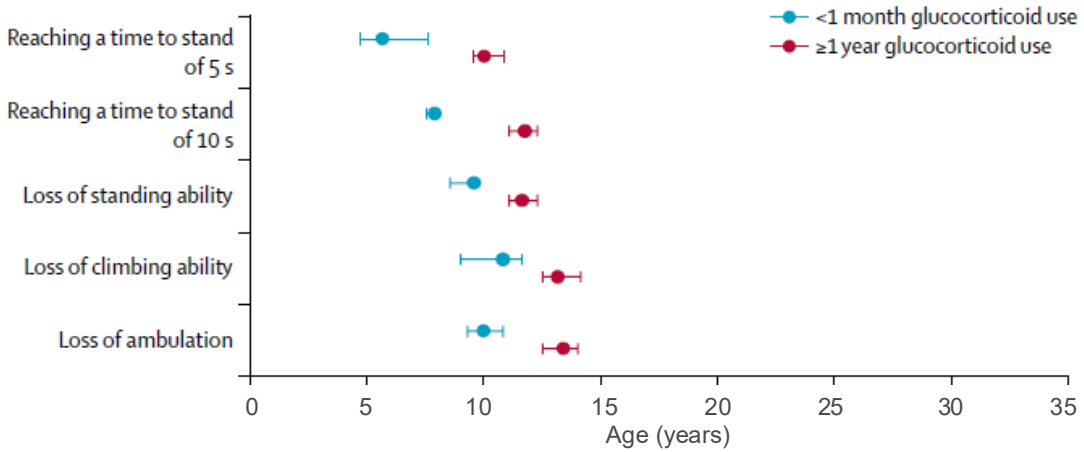
The type of *DMD* mutation affects the trajectory of decline of motor function, with exon 44 skip-amenable deletions predictive of slower disease progression

6MWT, 6-minute walking test; DMD, Duchenne muscular dystrophy; TRF, time to rise from the floor.

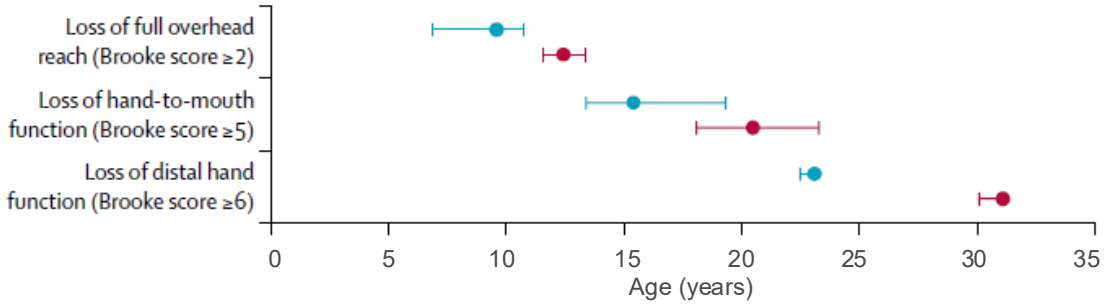
Brogna C, et al. *PLoS One*. 2019;14:e0218683.

How do corticosteroids (a mainstay of DMD treatment) impact disease progression?

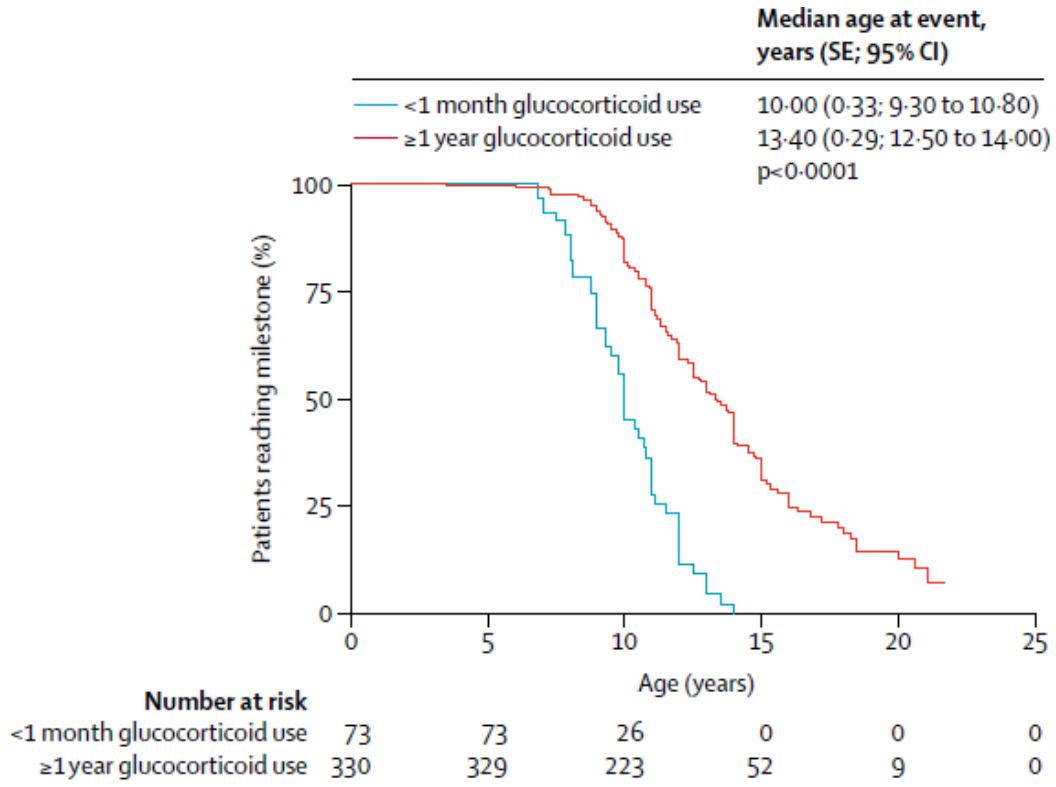
Age at LoA milestones[1]



Age at loss of upper limb function milestones[1]



Age at LoA[1]



Corticosteroids delay LoA, improve muscle function, preserve upper limb and respiratory function, and prolong survival in individuals with DMD[1–3]

CI, confidence interval; DMD, Duchenne muscular dystrophy; LoA, loss of ambulation; SE, standard error.

1. McDonald CM, et al. *Lancet*. 2018;391:451–461; 2. Birnkrant DJ, et al. *Lancet Neurol*. 2018;17:251–267; 3 McDonald CM, et al. *Neuromuscular Disorders*. 2018;28:897–909.

Beyond corticosteroids, what therapeutic approaches are approved for the treatment of DMD?

Dystrophin-producing therapeutic approaches

Exon-skipping therapies (naked PMOs)

- **Eteplirsen*** – US: for treatment of individuals with mutations amenable to exon 51 skipping[1]

- **Golodirsen* and viltolarsen*** – US: for treatment of individuals with mutations amenable to exon 53 skipping[2,3]

- **Casimersen*** – US: for treatment of individuals with mutations amenable to exon 45 skipping[4]

**US approval based on an increase in dystrophin production in skeletal muscle observed in some patients. Additional studies ongoing to verify clinical benefit*[1–4]

AAV-mediated micro-dystrophin gene therapy

Delandistrogene moxeparvovec – US: for treatment of individuals with DMD aged 4 years and older with no deletion in exon 8 and/or exon 9:[5]

- Who are ambulatory and have a confirmed mutation in the *DMD* gene
- Who are non-ambulatory and have a confirmed mutation in the *DMD* gene. *Approval in non-ambulatory patients was based on expression of micro-dystrophin protein in muscle biopsies. Additional studies are ongoing to verify clinical benefit**

Histone deacetylase inhibitor

Givinostat – US: for treatment of individuals with DMD aged 6 years and older[6]

EU: for treatment of ambulant individuals with DMD aged 6 years and older, and with concomitant corticosteroids
Conditional approval has been granted in Europe; further evidence on this medicine is awaited, and new information will be reviewed at least every year[7]

*At the time of approval of this module, Sarepta is supplying delandistrogene moxeparvovec only for ambulatory, but not non-ambulatory, patients;[8] contact your local regulator for further information.

AAV, adeno-associated virus; DMD, Duchenne muscular dystrophy; EU, European Union; PMO, phosphorodiamidate morpholino oligomer; US, United States.

1. EXONDYS 51 Prescribing Information. https://www.exondys51.com/pi; 2. VYONDYS 53 Prescribing Information. https://www.vyondys53.com/PI; 3. VILTEPSO Prescribing Information. https://www.viltepso.com/prescribing-information;
4. AMONDYS 45 Prescribing Information. https://www.amondys45.com/pi; 5. ELEVIDYS Prescribing Information. www.elevidys.com/pi; 6. DUVYZAT Prescribing Information. https://itftherapeutics.com/documents/PI.pdf;
7. DUVYZAT Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/duvyzat-epar-product-information_en.pdf. All last accessed August 1, 2025; 8. Sarepta Therapeutics. https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-second-quarter-2025-financial. Accessed September 24, 2025.

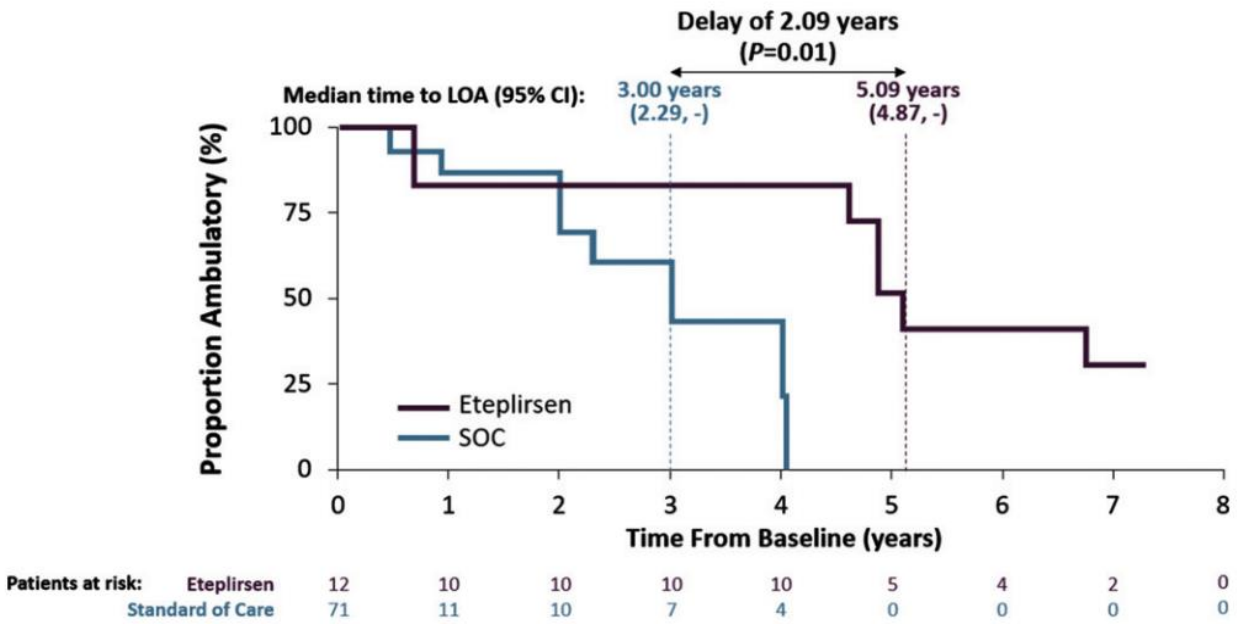
How do exon-skipping therapies (approved in the US) impact ambulation? (1/2)

Phase 4 EVOLVE study (NCT06606340)[1]

- Interim analyses of the EVOLVE study comparing eteplirsen-treated individuals (N=33) to corticosteroid-treated external controls (N=75) suggest that eteplirsen reduced LoA risk by 62% (95% CI, 20–82, p=0.011)
- Median age at LoA was 15.3 (95% CI, 11.4–15.8) years for eteplirsen-treated individuals, and 11.3 (95% CI, 8.0–12.8) years for controls

Under US Accelerated Approval, based on an increase in dystrophin production in skeletal muscle observed in some patients. Additional studies ongoing to verify clinical benefit.[2]

Exon 51-skipping therapy – eteplirsen[2,3]



CI, confidence interval; LoA, loss of ambulation; SOC, standard of care; US, United States.

Image used with permission of The Authors, from Mitelman O, et al. *J Neuromuscul Dis.* 2022;9:39–52; permission conveyed through Copyright Clearance Center, Inc.

1. Mathews K, et al. Poster abstract presented at: Muscular Dystrophy Association Clinical and Scientific Conference; March 16–19, 2025; Dallas, TX, USA (Poster P103); 2. EXONDYS 51 Prescribing Information. https://www.exondys51.com/sites/default/files/2023-06/EXONDYS51PI.pdf. Accessed May 13, 2025; 3. Mitelman O, et al. *J Neuromuscul Dis.* 2022;9:39–52.

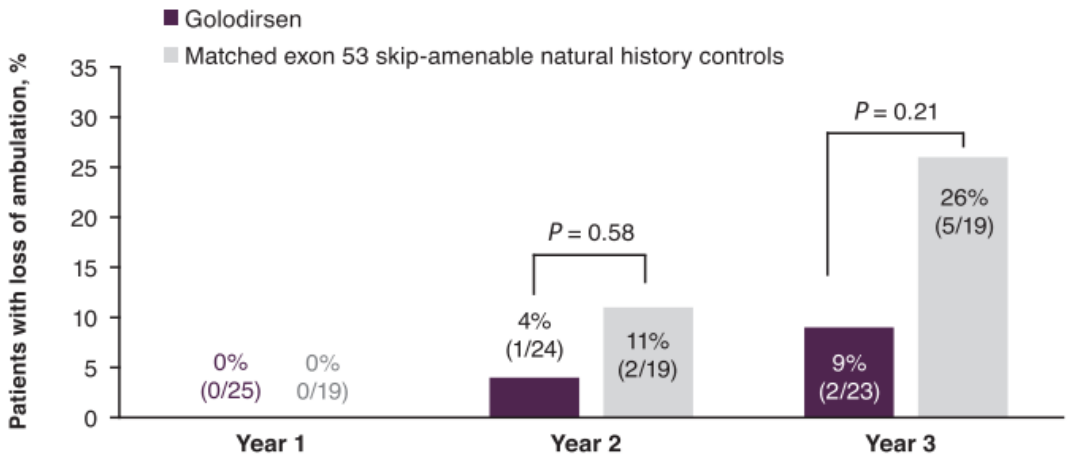
How do exon-skipping therapies (approved in the US) impact ambulation? (2/2)

Study 4053-101 (NCT02310906) and 4045-302 (NCT03532542)*[1]

- Over 6 years of treatment, median delay in time to LoA was ~2.4 years for those treated with golodirsen compared to age- and mutation-matched external controls
- This delay represents a 47.4% risk reduction (HR 0.526, p=0.149)

Under US Accelerated Approval, based on an increase in dystrophin production in skeletal muscle observed in some patients. Additional studies ongoing to verify clinical benefit.[2]

Exon 53-skipping therapy – golodirsen[2,3]

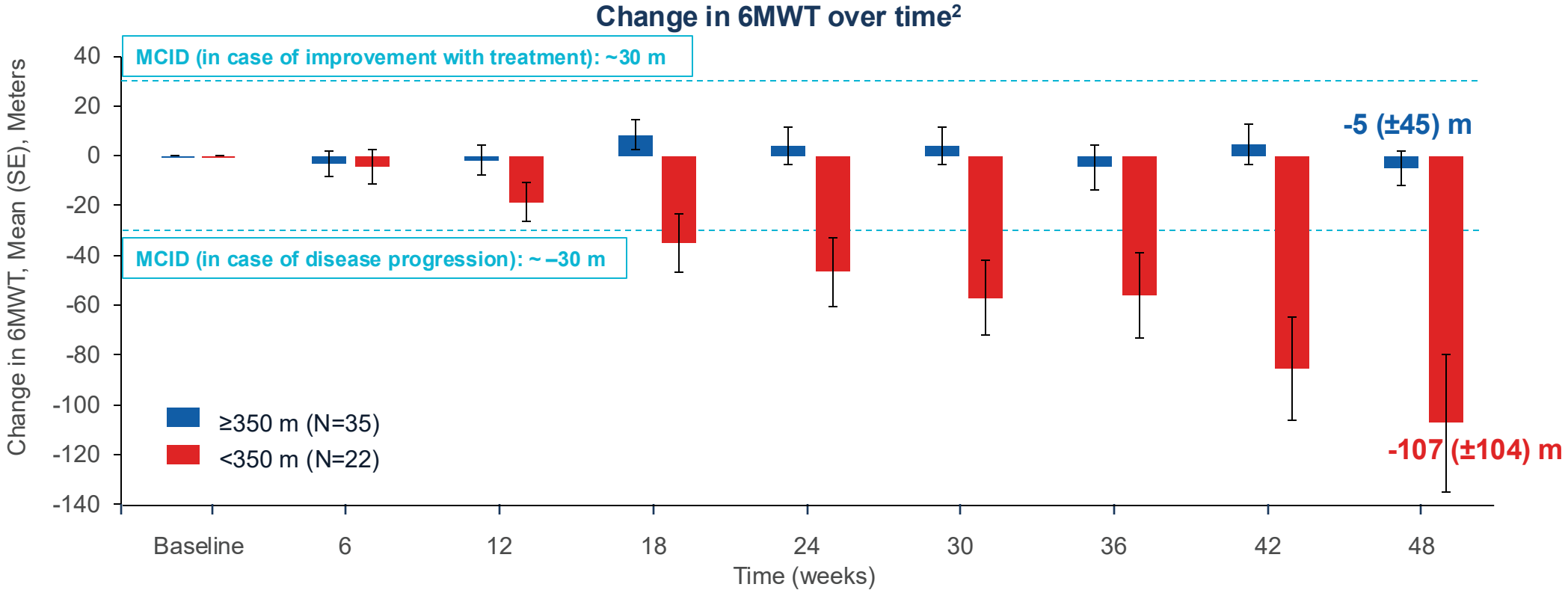


*A total of 25 patients completed the open-label extension study, 4045-302.[1]
DMD, Duchenne muscular dystrophy; HR, hazard ratio; LoA, loss of ambulation; US, United States.

1. Mercuri EM, et al. Abstract presented at: Muscular Dystrophy Association Clinical and Scientific Conference; March 16–19, 2025; Dallas, TX, USA (Abstract M162); 2. VYONDYS 53 Prescribing Information. https://www.vyondys53.com/sites/vyondys53/files/2022-10/PI.pdf. Accessed May 13, 2025; 3. Servais L, et al. *Nucleic Acid Ther.* 2022;32:29–39.

Do baseline functional tests predict disease progression? 6MWT

6-minute walk test (6MWT): The distance an individual can walk in 6 minutes.[1]



Inability to walk 350 m in 6 minutes is predictive of ambulatory decline[2]

6MWT, 6-minute walk test; MCID, minimum clinically important difference; SE, standard error.

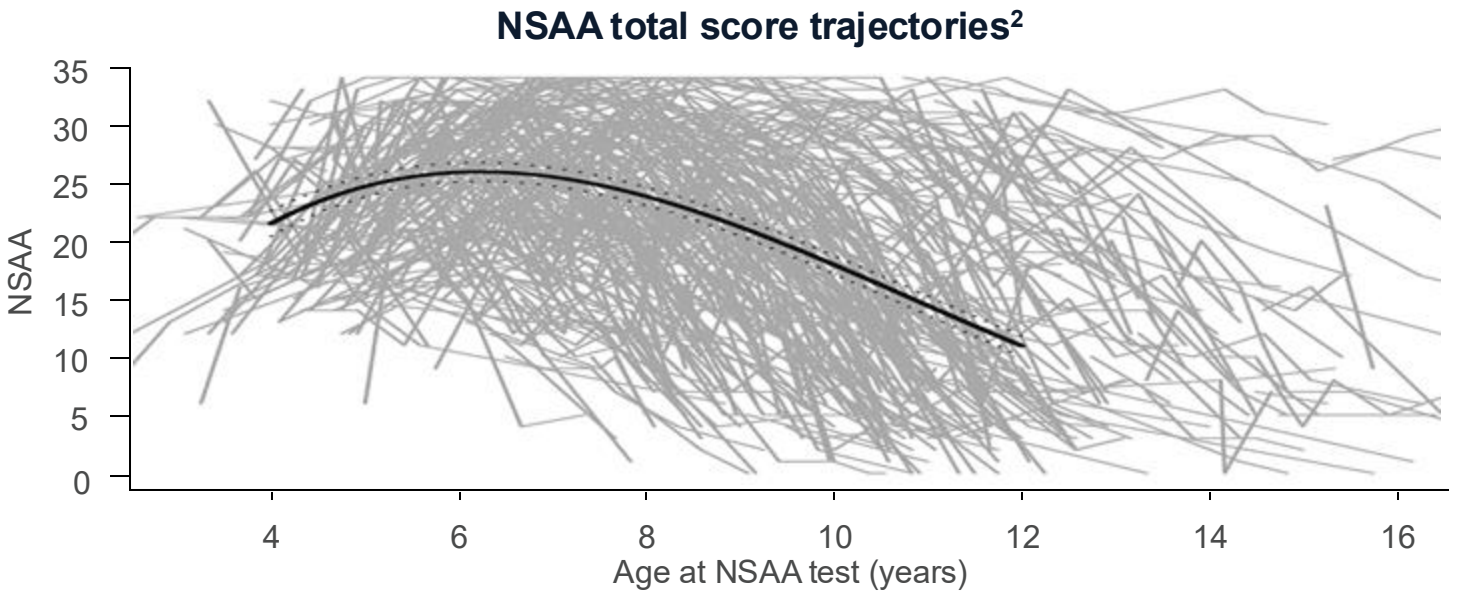
1. Arora H, et al. *Muscle Nerve*. 2018;58:631–638; 2. McDonald CM, et al. *Muscle Nerve*. 2013;48:343–356.

Do baseline functional tests predict disease progression? NSAA total score

North Star Ambulatory Assessment (NSAA): The sum of scores on 17 ordinal tasks, each scored as:
0 = inability to perform task,
1 = modified method of completing task, or
2 = normal activity with no obvious modification.[1]

Tasks mostly involve the lower limbs, and do not assess upper limb function.[1]

Younger and older individuals may sometimes have the same NSAA total score but are likely to have different care needs, so total score should be interpreted within a trend of decline (eg, loss of ≥3 points in the last 14 months) or stability/improvement.[1] Longitudinal changes in NSAA can be biased by effort.[4]



NSAA total score trajectories for individual patients by age (in grey) and the fitted mean and 95% confidence interval (in black). Each grey line represents NSAA total scores from an individual person with DMD plotted versus age; the population mean, and its 95% confidence bands are shown in black.

MCID for annual change in NSAA: ~3.5 points[3*]

Improvements in NSAA total score are observed up to 6.3 years of age in individuals with DMD, after which a steady decline occurs at an average of 3 points per year[2]

*MCID derived using an anchor-based approach using data from the iMDEX natural history study; an annual decline of 30 m in the 6MWT was used as the anchor.
6MWT, 6-minute walk test; DMD, Duchenne muscular dystrophy; MCID, minimum clinically important difference; NSAA, North Star Ambulatory Assessment.
Image adapted from Muntoni F, et al. *PLoS One*. 2019;14:e0221097, licensed under a CC-BY 4.0 Creative Commons license; doi.org/10.1371/journal.pone.0221097.
1. Stimpson G, et al. *Eur J Paediatr Neurol*. 2024:53:123–130; 2. Muntoni F, et al. *PLoS One*. 2019;14:e0221097; 3. Ayyar Gupta V, et al. *PLoS One*. 2023;18:e0283669; 4. Cantor Fitzgerald Research. Industry Report - Muscling Up: Deep Dive Into DMD - Part 2. May 28, 2025.

What ordinal tasks are included in NSAA?

North Star Ambulatory Assessment (NSAA) tasks:

Stand
Stand barefoot for as long and still as possible (no external support)

Walk
Walk forward barefoot (long enough to observe gait)

Rise from chair
Stand up from a seated position in a chair with arms crossed

Ascend step (right and left sides)
Step onto a box (≥15 cm high)

Descend from step (right and left sides)
Step down from the box (≥15 cm high) facing forwards

Sit up from lying down
Lie flat on the floor with arms by side and move to a sitting position (without turning towards the floor or using both hands)

Run
Run as fast as possible for about 10 meters

Stand on leg (right and left sides)
Stand on one leg with arms down for as long as possible

Jump
Jump as high as possible from standing with both feet together

Stand on heels
Lean back onto heels while barefoot (both feet lifted off ground towards shin)

Rise from floor
Lay flat on back and stand up as quickly as possible (without Gower's maneuver)

Lift head
Lay flat on the floor with arms crossed across the chest and lift head, touching chin to chest, while keeping arms folded

Hop (right and left legs)
Stand on one leg and hop one-legged while barefoot

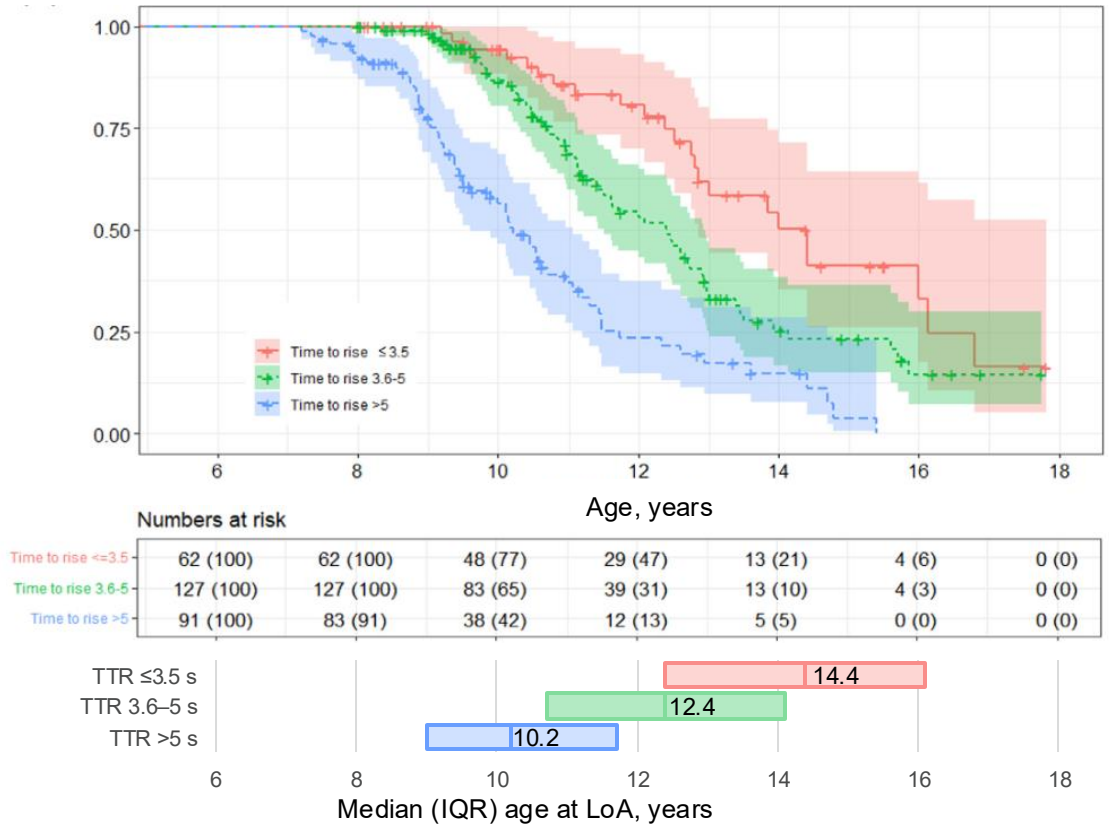
NSAA, North Star Ambulatory Assessment.

touchNEUROLOGY. North Star Ambulatory Assessment. https://www.touchneurology.com/wp-content/uploads/sites/3/2018/03/www.musculardystrophyuk.org_assets_0000_6388_NorthStar.pdf. Accessed September 24, 2025.

Do baseline functional tests predict disease progression? TTR

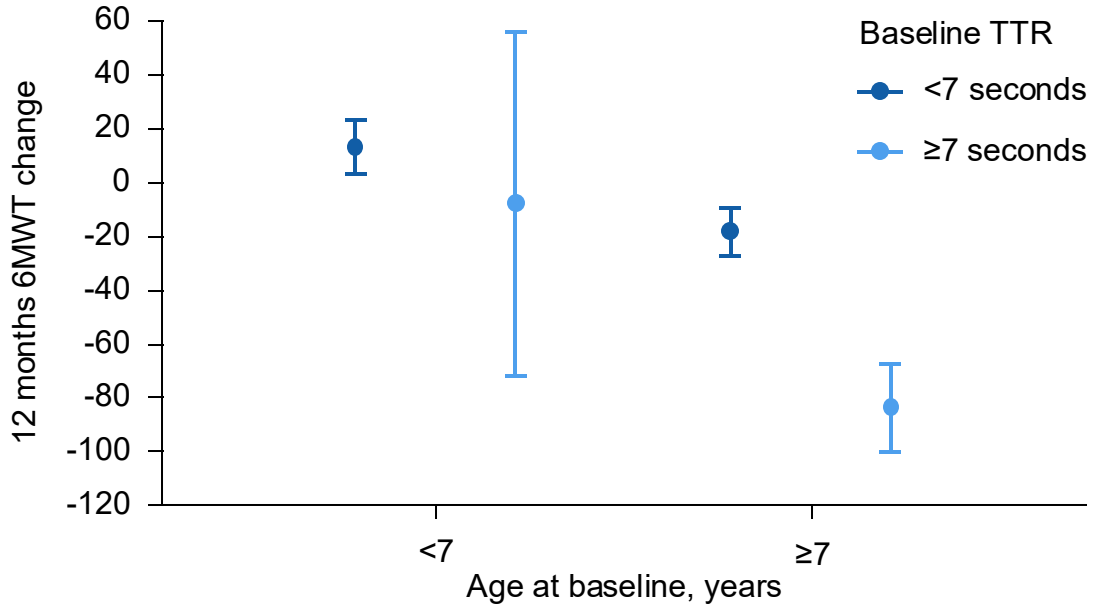
Time to rise (TTR): The time taken to stand from lying face up on the ground[1]

Time to LoA[2*]



MCID in TTR velocity over 12 months: 0.023 rise per second[3]

6MWT change[1†]



MCID in 6MWT: ~30 m[4]

Prolonged time to rise from floor at baseline suggests an increased risk of earlier LoA[2]

6MWT, 6-minute walk test; IQR, interquartile range; LoA, loss of ambulation; MCID, minimum clinically important difference; TTR, time to rise.

*Image reproduced from Zambon AA, et al. *Dev Med Child Neurol.* 2022;64:979–988, licensed under a CC-BY 4.0 Creative Commons license; doi: 10.1111/dmcn.15176.

†Image adapted from Mazzone ES, et al. *PLoS One.* 2016;11:e0151445, licensed under a CC-BY 4.0 Creative Commons license; doi: 10.1371/journal.pone.0151445.

1. Mazzone ES, et al. *PLoS One.* 2016;11:e0151445; 2. Zambon AA, et al. *Dev Med Child Neurol.* 2022;64:979–988; 3. Duong T, et al. *J Neuromuscul Dis.* 2021;8:939–948; 4. McDonald CM, et al. *Muscle Nerve.* 2013;48:343–356.

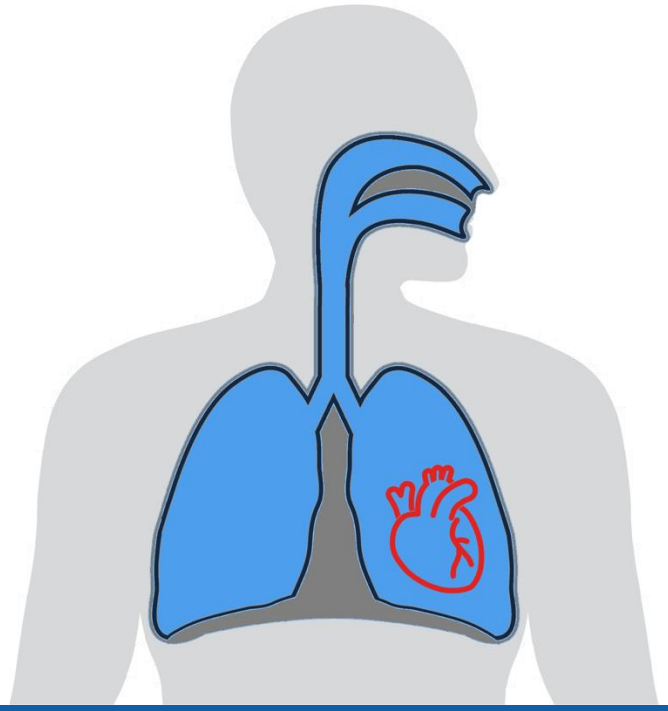
How do cardiopulmonary complications drive outcomes in DMD?

Pulmonary

Progressive loss of muscle strength leads to complications such as ineffective cough, need for nocturnal hypoventilation, sleep disordered breathing, and ultimately, daytime respiratory failure[1]

Non-invasive and invasive ventilation are eventually required[1,2]

Respiratory muscle weakness tends to occur gradually over time in individuals with DMD, and compromised respiratory function (FVC <1 L) is a reliable prognostic indicator of mortality[1,3]



Cardiac

Lack of dystrophin in the heart manifests as cardiomyopathy characterized by widespread fibrosis of the left ventricular wall.[1,4] Cardiomyopathy is evident in approximately 60% of individuals with DMD aged 10 years, and nearly all individuals over 18 years of age[5]

As the disease progresses, arrhythmias develop, and end-stage heart failure typically occurs in the 3rd or 4th decade of life.[6,7] LVEF decreases 1–3% per year, and reductions ≥3% correlate with increased risk of cardiac mortality[8]

Early detection of cardiomyopathy is challenging, due to a long subclinical phase of ventricular dysfunction and difficulties in performing cardiovascular assessment in non-ambulatory individuals[7,9]

The severity of cardiomyopathy does not appear to correlate with the severity of skeletal muscle symptoms[8]

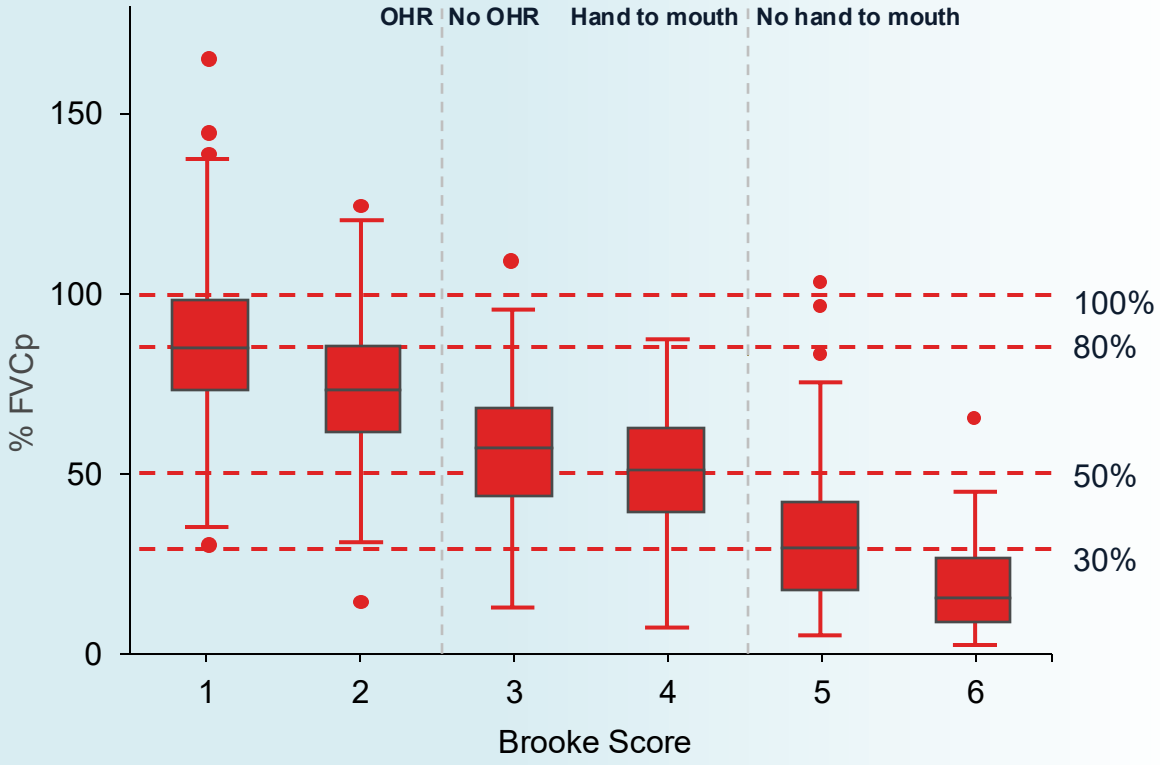
Cardiorespiratory complications are a leading cause of death amongst individuals with DMD[1]

DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; LVEF, left ventricular ejection fraction.

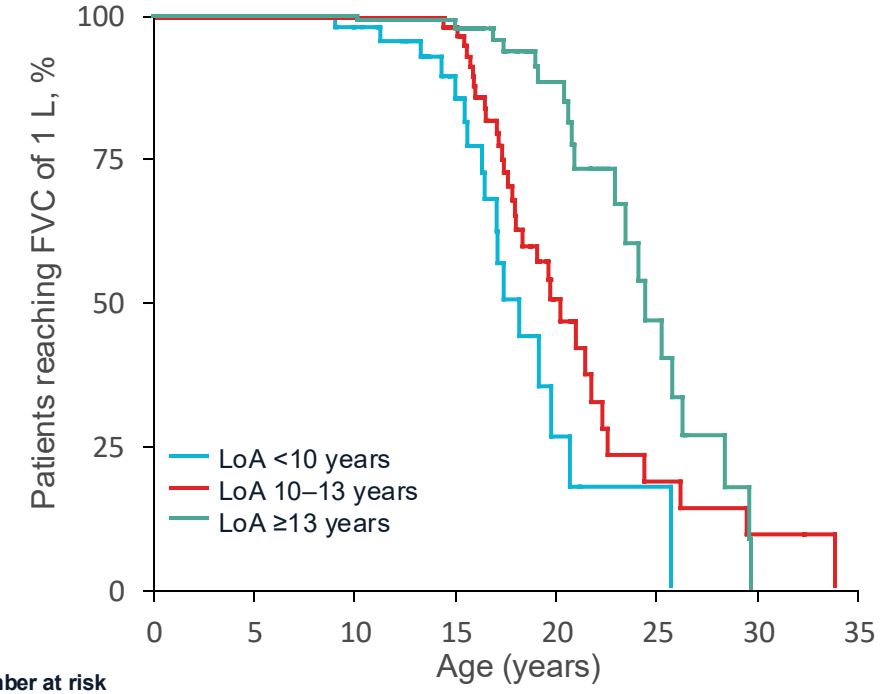
1. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:347–361; 2. Finder JD, et al. *Am J Resp Crit Care Med. 2004;*170:456–465; 3. Phillips MF, et al. *Am J Respir Crit Care Med.* 2001;164:2191–2194; 4. Sanyal SK, et al. *Circulation.* 1978;57:1122–1129; 5. Nigro G, et al. *Int J Cardiol.* 1990;26:271–277; 6. Chenard AA, et al. *Neuromuscul Disord.* 1993;3:201–206; 7. D'Amario D, et al. *Heart.* 2017;103:1770–1779; 8. Cantor Fitzgerald Research. Industry Report – Muscling Up: Deep Dive Into DMD – Part 2. May 28, 2025; 9. Spurney C, et al. *Muscle Nerve.* 2014;50:250–256.

Does loss of pulmonary function correlate with functional decline in DMD?

%FVCp correlates with Brooke upper extremity function score[1*]



Age at FVC <1 L correlates with LoA (P<0.0001)[2†]



Number at risk								
LoA <10 years	53	53	46	22	3	1	0	0
LoA 10–13 years	87	87	86	60	13	4	2	0
LoA ≥13 years	208	208	132	71	27	7	0	0

Pulmonary function loss correlates with general disease state in DMD[1]

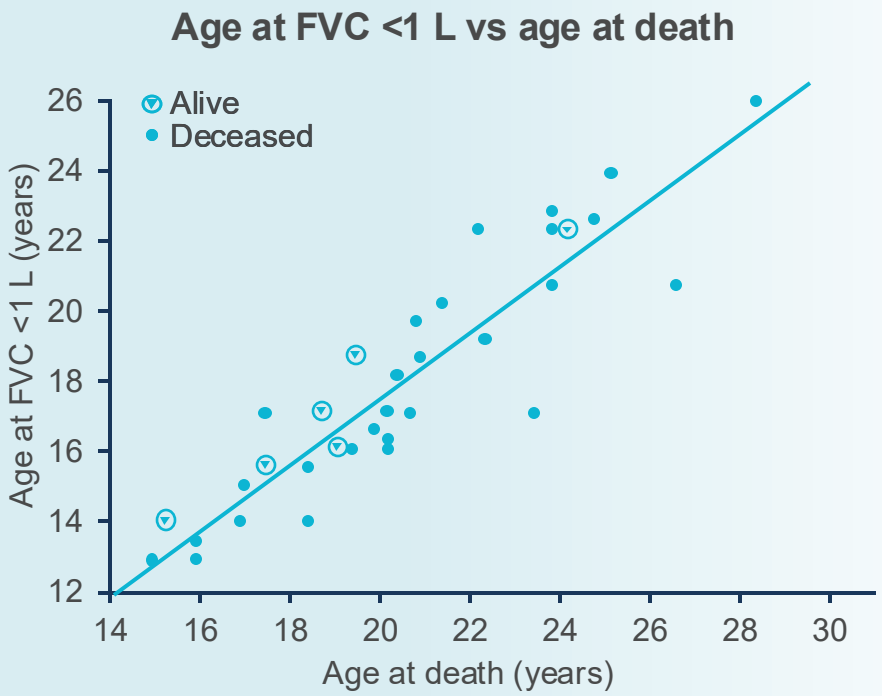
DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; FVC%p, forced vital capacity percent predicted; LoA, loss of ambulation; OHR, overhead reach.

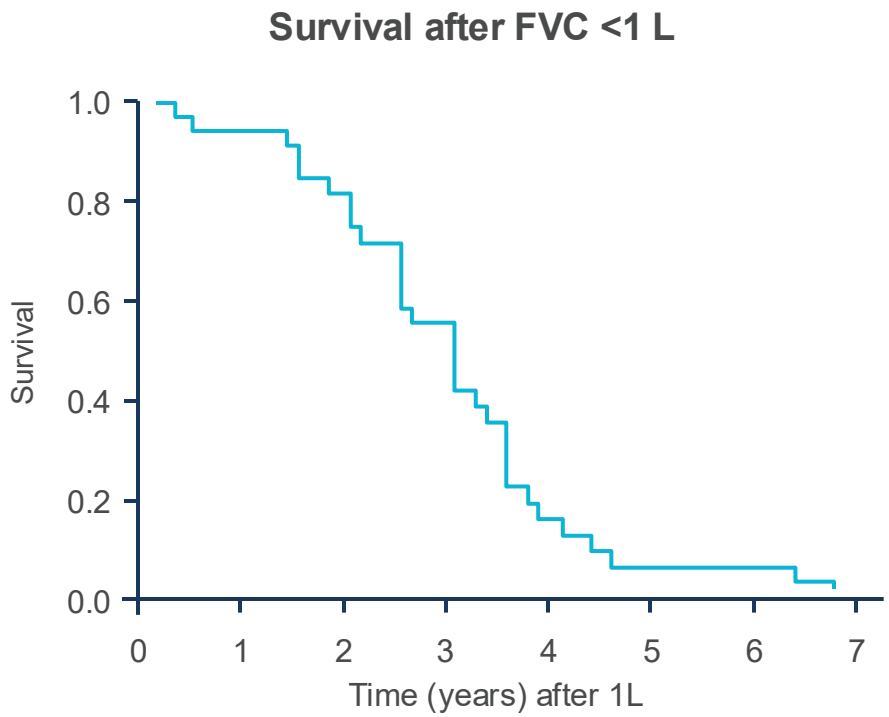
*Image used with permission of Touch Medical Media, from Mayer OH, et al. *US Neurol.* 2017;13:35–41; permission conveyed through Copyright Clearance Center, Inc.

†Image used with permission of Elsevier Ltd, from McDonald CM, et al. *Lancet.* 2018;391:451–461; permission conveyed through Copyright Clearance Center, Inc.

1. Mayer OH, et al. *US Neurol.* 2017;13:35–41; 2. McDonald CM, et al. *Lancet.* 2018;391:451–461.

Is FVC <1 L a prognostic indicator of mortality?





The median survival of individuals who have reached FVC <1 L is 3.1 years; the 5-year survival rate is 8%

FVC, forced vital capacity.

Phillips MF, et al. *Am J Respir Crit Care Med.* 2001;164:2191–2194.

What is the natural course of cardiovascular dysfunction in patients with DMD?

Early signs of cardiovascular dysfunction in DMD are not clinically apparent[1,2]

Disease stage	Subclinical	Clinical	Detectable cardiac involvement
Age	First decade	Second decade	Third decade
Symptoms of heart failure present?	No classic symptoms of heart failure	Heart failure symptoms in minority of individuals	Symptoms of heart failure, palpitations, syncope in ~60% of individuals
Cardiovascular symptoms	• ECG abnormalities and conduction defects • Cardiomyocyte hypertrophy • Diastolic dysfunction • Wall motion abnormalities	• Progressive heart chamber dilation • Apoptosis of cardiomyocytes • Subendocardial fibrosis	• Systolic dysfunction (dilated cardiomyopathy) • Symptomatic conduction abnormalities • Arrhythmic complications • Detectable signs of cardiac dysfunction in 80–100% of individuals • Sudden death

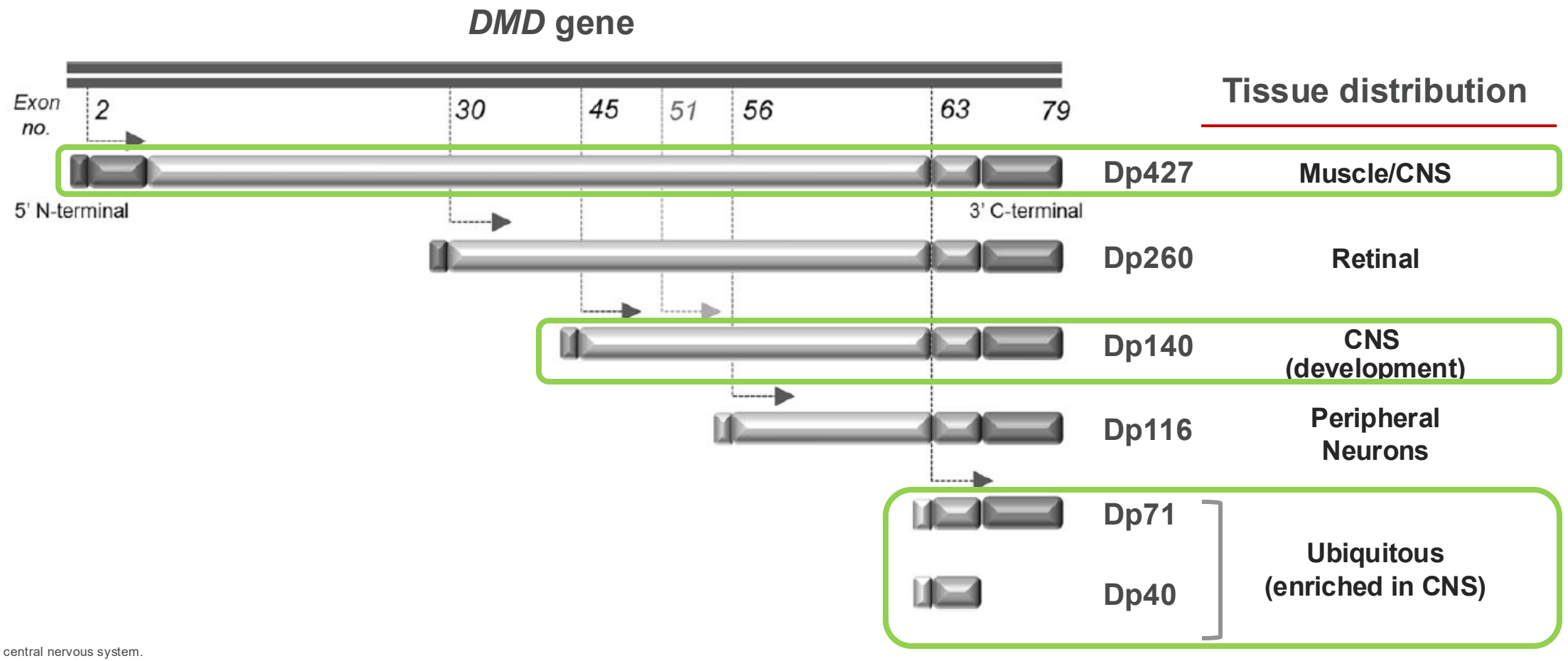
The optimal window for initiation of treatment is prior to the development of clinical heart failure[1]

DMD, Duchenne muscular dystrophy; ECG, electrocardiogram.

1. D'Amario D, et al. *Heart* 2017;103:1770–1779; 2. D'Amario D, et al. *J Clin Med.* 2018;7:291.

Which dystrophin isoforms are expressed in the CNS?

The *DMD* gene has multiple isoforms with varying tissue expression patterns that are believed to play unique roles during embryogenesis and in adulthood[1]



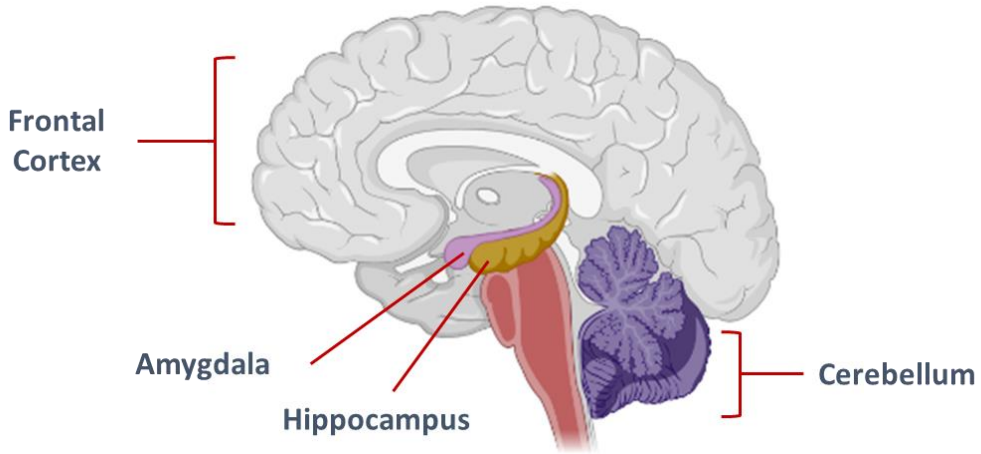
CNS, central nervous system.

Image adapted from Maresh K, et al. *Brain* 2023;146:252–265, licensed under a CC-BY 4.0 Creative Commons license; doi.org/10.1093/brain/awac048.

1. Hildyard JCW, et al. *Wellcome Open Res.* 2020;5:76.

What diverse functions do dystrophin isoforms perform in the brain?

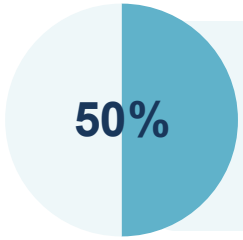
- Dystrophin is enriched in the cortex, amygdala, hippocampus, and cerebellum[1]
  - **Dp427** is involved in recruitment of $GABA_A$ receptors in inhibitory neurons[1–3]
  - **Dp140** is particularly expressed during fetal development and may play a role in cognitive functioning, as well as coordination and motor performance[1–4]
    - In a retrospective analysis of 459 individuals with DMD, those who lack Dp140 had lower grip strength and pinch strength, and reduced respiratory function (FVC) than those with Dp140 present, across all age groups[5]
  - **Dp71** plays key roles in neuronal and glial cell function[1,2]



Dysregulation of excitatory/inhibitory signaling in these regions via lack of dystrophin isoforms correlates with neuropsychiatric manifestations of DMD[1,3]

FVC, forced vital capacity; GABA, gamma-aminobutyric acid.
Image created with BioRender.
1. Maresh K, et al. *Brain*. 2023;146:252–265; 2. Hendriksen RGF, et al. *Front Cell Neurosci*. 2016;10:174; 3. Vaillend C, et al. *Nat Commun*. 2025;16:1298; 4. Chesshyre M, et al. *J Cachexia Sarcopenia Muscle*. 2022;13:1360–1372;
5. Chesshyre M, et al. *Dev Med Child Neurol*. 2025;67:e115.

What neuropsychiatric symptoms might be observed in DMD?



Approximately 50% of individuals with DMD experience neuropsychiatric symptoms[1,2]

Neuropsychiatric symptoms of DMD are not secondary to muscle disease[1]

Neuropsychiatric comorbidities in individuals with DMD[3]

Comorbidity	Approximate Prevalence (%)
Intellectual disability	19–35
Epilepsy	2–12
Autism	20
Internalizing problems	24–34
Depression	17–27
Anxiety	24–29
OCD	5–14
Externalizing problems	15
ADHD	12–32
Reading disability	40–50

Location of the mutation in the *DMD* gene influences the likelihood and severity of neuropsychiatric symptoms, depending on the impact on the different dystrophin isoforms[1,3]

- **Intellectual function** is linked to the integrity of the Dp140 and Dp71 dystrophin isoforms[1]
- **Neuropsychiatric manifestations** such as ASD are seen across the spectrum of DMD mutations, suggesting that the full-length Dp427 isoform is implicated[1]
- **Anxiety** may be related to a lack of the Dp427 isoforms, exacerbated by a loss of Dp140[1]
- **ADHD** may be associated with a lack of all three CNS isoforms: Dp427, Dp140 and, Dp71[1]

Neuropsychiatric manifestations of DMD are not thought to be progressive, unlike those seen in muscle[3–5]

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CNS, central nervous system; DMD, Duchenne muscular dystrophy; OCD, obsessive compulsive disorder.

1. Vaillend C, et al. *Nat Commun*. 2025;16:1298; 2. Maresh K, et al. *Brain*. 2023;146:252–265; 3. Naidoo M, Anthony K. *Molecular Neurobiology*. 2020;57:1748–1767; 4. Hendriksen RGF, et al. *Front Cell Neurosci*. 2016;10:174; 5. Chamova T, et al. *Balkan J Med Genet*. 2013;16:21–30.