A Closer Look at Functional Assessments in Duchenne Muscular Dystrophy

DMD is caused by an absence of functional dystrophin protein[1-4]

Duchenne muscular dystrophy (DMD) is a degenerative, neuromuscular disease characterized by variable, but progressive sequential loss of important milestones related to ambulation, upper limb function, and cardiopulmonary function. A range of functional scales are used to monitor and anticipate disease progression.

North Star Ambulatory Assessment (NSAA)[5]

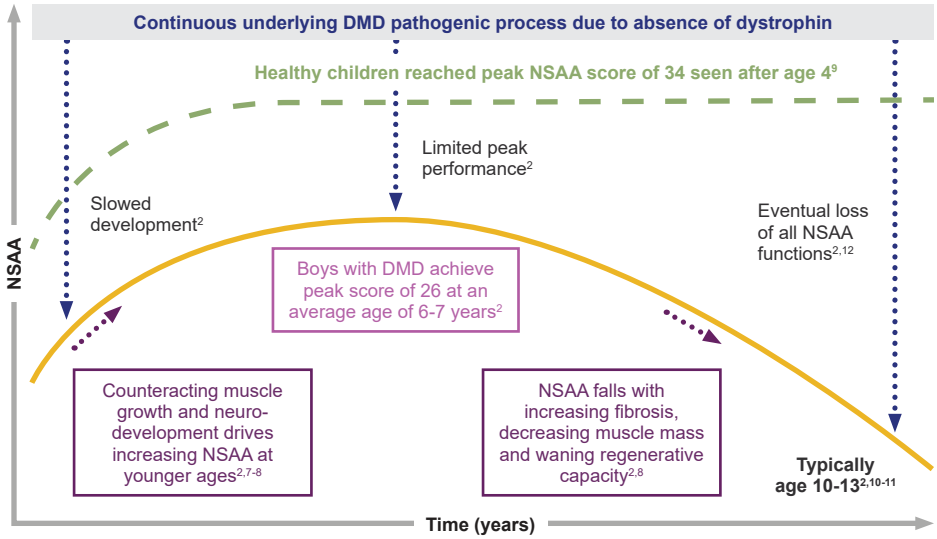
The NSAA is a validated scale developed to measure motor function in DMD. The score is a count of ability to perform 17 skills that are important for everyday mobility, with a total possible score of 34. It is useful to monitor progression over the ambulant phase of the disease and is recognized by the FDA as an endpoint in clinical trials.

- Stand
- Walk
- Rise from chair
- Get to sitting
- Stand on L&R legs
- Climb step L&R legs
- Descend step L&R legs
- Lift head
- Jump
- Run
- Rise from floor
- Stand on heels
- Hop L&R legs

NSAA SCORING PER ITEM[6]

Perform | Perform with compensatory movements | Unable to perform

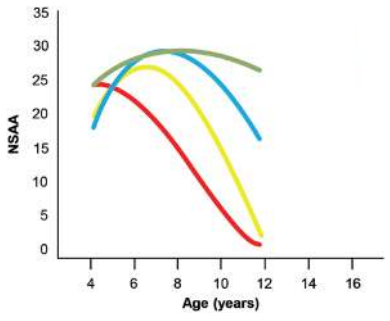
DMD natural history



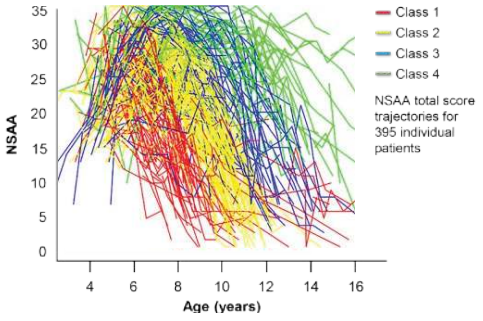
Prognostic value of NSAA[2]

At the population level, the NSAA is useful for predicting disease progression. Studies of natural history have shown that patients can be grouped into 1 of 4 general classes.

Fitted mean trajectories of NSAA total score by latent class*



Individual patient trajectories of NSAA total score by latent class*



At the individual level, there is a wide variation in disease trajectories. Therefore, detection of treatment effect in clinical trials may be facilitated by limiting the heterogeneity of the study populations and including an appropriate sample size to determine mean outcomes. It is also important that treatment and placebo groups are well-matched.[2,13]

***CLASS 1 (27% of patients):** NSAA total scores falling to ≤5 around 10 years of age **CLASS 2 (34% of patients):** NSAA total scores falling to ≤5 around 12 years of age **CLASS 3 (20% of patients):** NSAA total scores falling to ≤5 around 14 years of age **CLASS 4 (19% of patients):** NSAA total scores remaining >5 to at least 15 years of age

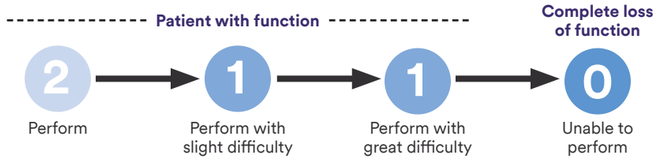
1. Birnkrant DJ, et al. Lancet Neurol. 2018; 17(3):251-67; **2.** Muntoni F, et al. PLoS One. 2019;14(9):e0221097; **3.** Bushby K and Connor E. Clin Invest (Lond). 2011;1(9):1217-35; **4.** Arora H, et al. Muscle Nerve. 2018;58(5):631-38; **5.** Zambon AA, et al. Dev Med Child Neurol. 2022;64(8):979–88; **6.** Lowes L, et al. Poster presented at: 27th International Congress of the World Muscle Society; October 11-15, 2022. [Halifax, Canada]; **7.** McDonald CM, et al. Lancet. 2018;391(10119):451–61; **8.** Rooney WD, et al. Neurology. 2020;94(15):e1622–33; **9.** Mercuri E, et al. PLoS One. 2016;11(8):e160195; **10.** Emery AEH. Lancet. 2002;359(9307):687–95; **11.** Niks EH and Aartsma-Rus A. Expert Opin Biol Ther. 2017;17(2):225–36; **12.** Stimpson J, et al. Neuromuscular Dis. 2024;11:153-166. **13.** Goemans N, et al. PLoS One. 2020;15(6):e0232870.

Sensitivity of NSAA and Timed Function Tests (TFTs)

NSAA provides a broad assessment of physical function[1-7]

NSAA scoring levels are designed to capture significant, step-wise alterations in muscular functions important for daily living. **The "1 score" for an NSAA skill encompasses a wide range of quality of movement from performing with slight difficulty to barely able to perform.** This aspect of NSAA may limit its sensitivity to changes over shorter time spans. TFTs may detect changes in skills sooner than changes within NSAA scoring as shown in the example below.

NSAA[4,6]
Ordinal Qualitative Data
NSAA SCORING PER ITEM



EVALUATION OF TIME TO RISE (TTR) ACROSS NSAA SCORES[8,*]	3.1 Seconds	4.7 Seconds	7.3 Seconds

Other measures of motor function[9-12]

A variety of TFTs and wearable devices are used to assessed motor function status. The NSAA includes timed items (e.g. TTR and 10-meter walk/run (10MWR)) that can be used to measure function independently of NSAA. The actual time taken to complete these tasks are not captured in the NSAA score but provides a potentially more continuous quantitative measure of abilities that can be monitored over time.

Part of NSAA assessment

TTR[10]
Time required to stand in an upright position starting from the supine position

10MWR[10]
Time required to run or walk 10 meters

ASCEND 4 STEPS[13]
Time required to ascend 4 standard steps

100MWR[14]
Time required to run or walk 100 meters

SV95C[15]
Highest stride velocity the participant reaches 5% of the time

Most assessments used in DMD were originally designed to capture loss of clinical milestones over natural DMD progression.[6,9,16-18] Clinical trials use these assessments to elucidate short-term (e.g. 1-year) impact of various intervention modalities and to detect changes in disease trajectory.[19]

TFTs may be more sensitive to functional changes than NSAA[5-6,12,20]

Timed function tests yield continuous quantitative data, which provide different information than categorical data (as measured in NSAA) and may allow for greater sensitivity to detect differences among patients in clinical trials.

The TFTs, including 10MWR, TTR, and time to ascend 4 steps, are common endpoints in DMD clinical trials, used to track gross motor abilities.[13]

Timed Function Tests[20]
Continuous Quantitative Data
INDIVIDUAL TIMED FUNCTION TEST

Continuous in seconds

*Hypothetical case; not based on actual patient data

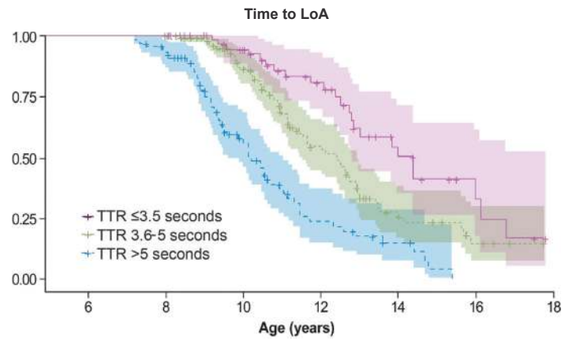
1. Straub V, et al. Neuromuscul Disord. 2018;28(8):690-701; **2.** Lowes L, et al. Poster presented at: 27th International Congress of the World Muscle Society; October 11-15, 2022. [Halifax, Canada]; **3.** Mercuri E, et al. PLoS One. 2016;11(8):e160195 **4.** Mayhew AG, et al. Dev Med Child Neurol. 2013;55(11):1046–52; **5.** Verhulst B and Neale MC. Behav Genet. 2021;51(3):204–14; **6.** Mazzone ES, et al. Neuromuscul Disord. 2009;19(7):458–61; **7.** Muscular Dystrophy UK. North Star Ambulatory Assessment Manual. **8.** Zambon AA, et al. Dev Med Child Neurol. 2022;64(8):979–88; **9.** Birnkrant DJ, et al. Lancet Neurol. 2018;17(3):251-67; **10.** Connolly AM, et al. Neuromuscul Disord. 2013;23(7):529-39; **11.** Ricci G, et al. Neurol Sci. 2022;43(Suppl. 2):625-33; **12.** Stimpson J, et al. Neuromuscular Dis. 2024;11:153-166. **13.** McDonald CM, et al. Muscle Nerve. 2013;48(3):343– 56; **14.** Miller NF, et al. Pediatr Neurol. 2020;113:15–20; **15.** European Medicines Agency (2023). Quantification Opinion for Stride Velocity 95th Centile as Primary Endpoint in Studies in Ambulatory Duchenne Muscular Dystrophy Studies. Available at: 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 January 2024; **16.** McDonald CM, et al. Lancet. 2018;391(10119):451-461. **17.** Muntoni F, et al. PLoS One. 2019;14(9):e0221097. **18.** Alfano LN, et al. Neuromuscul Disord. 2017;27(5):452-457. **19.** Duchenne muscular dystrophy and related dystrophinopathies: developing drugs for treatment. Guidance for industry. US Food and Drug Administration. https://www.fda .gov/regulatory-information /search-fda-guidance-documents /duchenne-muscular-dystrophy-and-related-dystrophinopathies-developing-drugs-treatment-guidance. Published February 2018. Accessed February 2024; **20.** Arora H, et al. Muscle Nerve. 2018;58(5):631–38.

Prognostic Value of Timed Function Tests

TFTs are useful in observing decline in performance prior to loss of skills[1-6]

TTR, 10MWR, time to ascend 4 steps, 100MWR, and SV95C are common endpoints used in DMD clinical trials. **Ability to perform TFTs is lost in a predictable and sequential manner.** There are certain time thresholds in TFTs that are predictive of an acceleration of disease progression leading to loss of ambulation (LoA). Decline in NSAA, TTRs, and 10MWR are prognostic for loss of ambulation.

TTR at baseline is predictive of time to loss of ambulation[7]

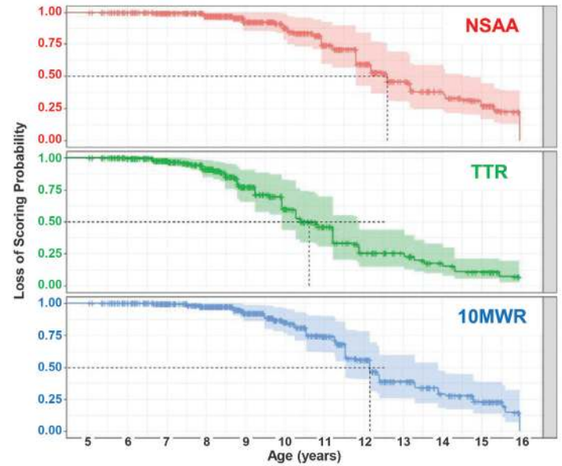


Different TTR durations predict markedly altered trajectories in time to loss of ambulation according to natural history data. A faster TTR at baseline was significantly associated with an older age at LoA.[7]

The median (IQR) age at LoA for TTR no more than 3.5 seconds, from 3.6 to 5 seconds, and more than 5 seconds was 14 years 5 months (12 years 5 months–16 years 1 month), 12 years 5 months (10 years 8 months –14 years 1 month), and 10 years 2 months (9 years–11 years 11 months) respectively.[7]

TTR greater than 5 seconds is predictive of functional decline.[7] Ten seconds or longer in 10MWR is similarly linked to progression of loss of ambulation within two years.[8]

Pattern of decline in NSAA, TTR, and 10MWR[9]



Data from UK Northstar registry presented centiles for NSAA, 10MWR,10MWR velocity, TTR and TTR velocity created from a cohort of glucocorticoid treated DMD boys between the ages of 5-16.[9]

The median age of loss of NSAA in this cohort is 12.6 years (95% CI: 11.8,14.7 years). The median age of loss of TTR is 10.6 years (95% CI: 9.9, 11.9 years). The median age at loss of 10MWR is 12.2 years (95% CI:11.5, 13.9 years).[9]

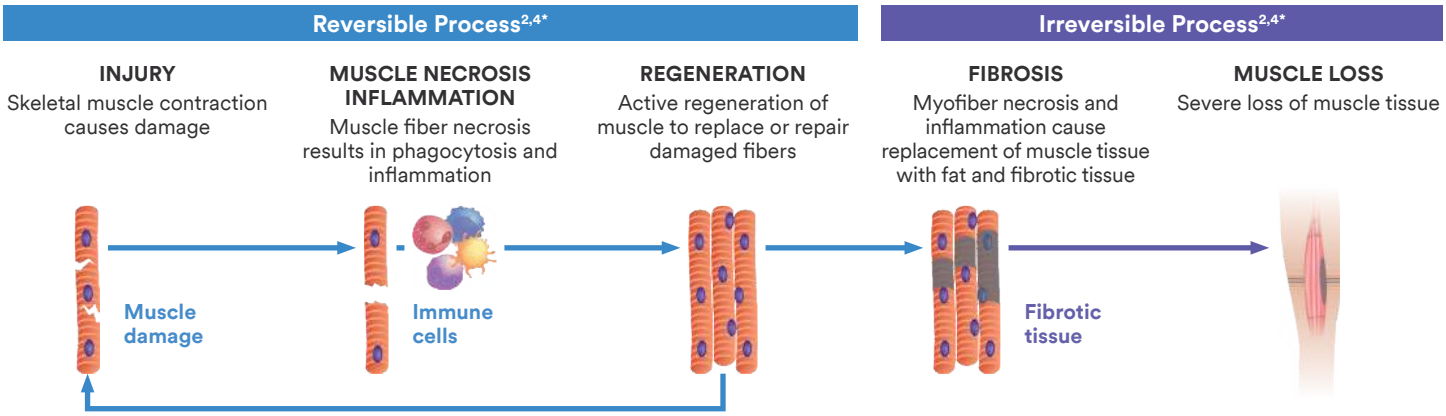
TTR is a sensitive marker of disease progression in earlier stages of the disease and has been used as the primary endpoint in a registrational trial.[6,10]

1. Birnkrant DJ, et al. Lancet Neurol. 2018; 17(3):251-67; **2.** McDonald CM, et al. Muscle Nerve. 2013;48(3):343– 56; **3.** Miller NF, et al. Pediatr Neurol. 2020;113:15–20; **4.** European Medicines Agency (2023). Quantification Opinion for Stride Velocity 95th Centile as Primary Endpoint in Studies in Ambulatory Duchenne Muscular Dystrophy Studies. Available at: 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 January 2024; **5.** Arora H, et al. Muscle Nerve. 2018;58(5):631–38; **6.** McDonald CM. Muscle Nerve. 2018;58(5):614–7; **7.** Zambon AA, et al. Dev Med Child Neurol. 2022;64(8):979-88; **8.** Muntoni F, et al. Neurology. 2023;100(15):e1540-54; **9.** Stimpson J, et al. Neuromuscular Dis. 2024;11:153-166; **10.** Clinicaltrials.gov. Accessed November 27, 2023. https://clinicaltrials.gov/study/NCT03167255.

Understanding Intervention Aims in DMD

DMD is a progressive and irreversible disease[1-3]

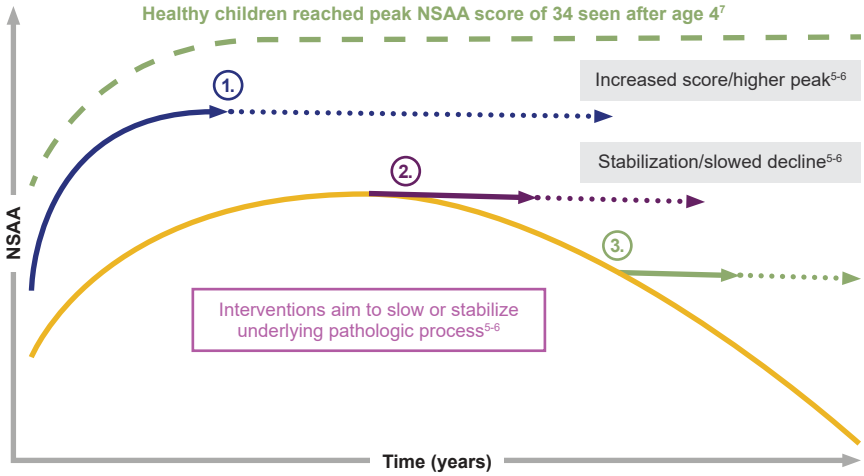
As boys with DMD age, increased fibrosis and loss of muscle become irreversible. Due to the continuous and irreversible decline in function, a proactive approach to intervention is needed.



Intervention aim[5-6]

Interventions aim to slow or stabilize disease progression. In the **1.) skill gaining phase** of DMD, early intervention aims to support achievement of higher peak function; whereas in the **2.) plateau phase**, an intervention that aims to stabilize may not produce a measurable divergence in the short term. Intervention during the **3.) losing skills phase** may present as stabilization or slowing decline at a time when greater/quicker loss of function is expected.

Assessing for intervention effectiveness in individuals is challenging. Change from baseline may not be an appropriate method to assess treatment outcomes as individual patient trajectories are difficult to predict.



Summary

Functional assessments provide essential information for estimating patient prognosis, but the ability of each test to accurately determine the effect of an intervention has yet to be fully understood.[5,8-11]

The emergence of treatment-related data for patients with Duchenne may provide insight on how functional test results can be used to appropriately assess treatment effect.[10,12-13]

There is no established consensus for a single primary endpoint for use in clinical trials in DMD. The appropriate measures may depend highly on specific populations studied and duration of study.[14]

* Image adapted from infographic on https://medhub.ptcbio.com/neuromuscular/dmd/. Last accessed: February 2024.
1. Scaglioni D, et al. Acta Neuropathol Commun. 2020;8(1):53; **2.** Klingler W, et al. Acta Myol. 2012;31(3):184-95; **3.** Miller NF, et al. Pediatr Neurol. 2020;113:15–20; **4.** Muscular Dystrophy Association (2023). DMD Muscular Dystrophy (DMD): Causes/Inheritance. Available at: https://www.mda.org/disease/duchenne-muscular-dystrophy/causes-inheritance. Last accessed: February 2024; **5.** Muntoni F, et al. PLoS One. 2019;14(9):e0221097; **6.** McDonald CM, et al. Lancet. 2018;391(10119):451-461; **7.** Mercuri E, et al. PLoS One. 2016;11(8):e160195; **8.** Zambon AA, et al. Dev Med Child Neurol. 2022;64(8):979-88; **9.** Markati T, et al. Front Pharmacol. 2021;12:735912; **10.** Nelson LL, et al. Neuromuscul Disord. 2021;31(10):1028–37; **11.** Goemans N, et al. PLoS One. 2020;15(6):e0232870; **12.** Senesac CR, et al. J Neuromuscul Dis. 2019;6(1):75–83; **13.** McDonald CM, et al. Muscle Nerve. 2013;48(3):357–68; **14.** Domingos J and Muntoni F. Dev Med Child Neurol. 2018;60(2):117.

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