OPINION PAPER ON:

Outcome Measures for Patients With Duchenne Muscular Dystrophy

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INTRODUCTION

The purpose of this paper is to provide a rational and feasible approach to monitoring patients with Duchenne muscular dystrophy (DMD) in a clinical setting to better assist providers and insurers in assessing response to treatment compared to the natural history of DMD. Patient groups with different genetic mutations vary in their expected rates of decline, so genotype-specific natural history should inform evaluations when available.[1,2]

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DUCHENNE MUSCULAR DYSTROPHY

DMD is a severe form of muscular dystrophy, impacting up to 1 in 3500 live births. It is caused by a mutation in the DMD gene that codes for the protein dystrophin. *DMD* is one of the largest known genes with more than 4700 mutations causing DMD or the milder form, Becker muscular dystrophy.[3] Dystrophin links the muscle cell membrane and extracellular matrix, acting like a "shock absorber" to protect muscle from damage during contraction. The lack of dystrophin causes muscle cell membranes to be unstable, which leads to muscle damage and loss of muscle tissue. Dystrophin is not only present in skeletal muscle tissues, but also expressed in cardiac and diaphragm muscle and brain tissue. As a result, DMD is associated with cardiomyopathy, respiratory failure, and intellectual disability making it a multi-organ system disease.[4,5]

Muscle weakness typically begins between ages 3-5 years, with loss of ambulation usually occurring by 12 years of age. Death typically occurs before 30 years generally from respiratory and/or cardiac muscle involvement.[5-8]

Patients with DMD typically follow a predictable course of decline that has been studied by multisite collaborations such as the Cooperative International Neuromuscular Research Group (CINRG). These studies suggest that in general, children will lose function in the following progression:

Loss of clinically meaningful milestones occurs in a predictable order in DMD[9]

Ambulatory Milestones

- Unable to jump, hop, and run
- Gowers sign with standing
- Loss of standing from the floor
- Loss of lie to sit
- Loss of stair climbing
- Loss of ability to stand from a chair
- Loss of ability to walk independently (10-meter walk/run; 6-Minute Walk Distance (6MWD))
- Loss of standing in place

Non-ambulatory Milestones

- Loss of ability to reach overhead
- Loss of ability to reach the scalp
- 50% Forced Vital Capacity (FVC) (Cough Assistance; monitoring required)
- Loss of ability to self-feed without adaptations (hand to mouth)
- Loss of ability to place hands to tabletop
- Inability to sustain adequate overnight ventilation without support (>30% FVC)
- Loss of ability to use a computer (distal hand function)

From: CINRG Natural History Study.

Duchenne progressively weakens skeletal, pulmonary, and cardiac tissue

	Pre-diagnosis	Early-stage disease	Mid-stage disease	Late-stage disease
Skeletal muscle	• Delayed developmental milestones[10] • Waddling gait[7] • Falls easily + difficulty climbing stairs[7]	• Unable to rise from seated position without use of arms[7] • Gowers maneuver[7] • Toe walking[7]	• Lumbar lordosis becomes pronounced[7] • Wheelchair typically needed	• Decline in upper limb function[11] • Inability to self-feed[11]
Pulmonary	• Diminished chest wall movement • Linear decline in pulmonary function	• Decline in measurable pulmonary function begins[14]	• Pulmonary function decline becomes more rapid[13]	• Risk of nocturnal hypoventilation once forced vital capacity percent predicted (FVC) is <50%[14]
Cardiac	• Persistent sinus tachycardia[7] • Abnormal QRS complex visible on electrocardiogram[7]	• Reduced circumferential strain detected • 30% of patients have signs of cardiomyopathy[16]	• Myocardial fibrosis detectable • Left ventricular ejection fraction dysfunction can occur in early teen years • Dilated cardiomyopathy evident by mid-adolescence[19]	• Left ventricular dysfunction can result in presence of chronic arrhythmias and heart failure[20,21]

This table is based on the recommendations and clinical experience of the authors and is not a comprehensive list of care considerations, nor is it a diagnostic tool.

FUNCTIONAL ASSESSMENTS

Ideal outcome measures for tracking disease progression should be readily available, easy to administer, and reliably able to measure meaningful change.

Measures used in clinical research may be useful in proving efficacy of a treatment but may not be as suitable for use in a clinical practice setting. Therefore, we reviewed the evidence supporting various outcome measurements and assessed not only their ability to measure change, but also their appropriateness to be performed in an average clinical practice setting. Furthermore, the gathering of Real-World Data and Patient-Reported Outcome measures are being utilized in clinical practice as these are increasingly important to providers, patients, and the payer community. Real-World Data can come from a variety of sources, including EHRs, product and disease registries, and patient-generated data including in home-use settings.

An additional consideration in functional assessments is the patient's specific mutation of DMD. Mutation subgroup variability may impact the rate of ambulatory decline. Shown below is the trajectory of the traditional 6-minute walking distance (6MWD) in meters by DMD mutation subgroup.

6-Minute Walking Distance (meters) by DMD Mutation Subgroup[1]

Patient group by exon skipping	Baseline	12-month change	24-month change	36-month change	% change at 36 months
Exon 44 (n=24)	402.25	3.85	9.75	-43.04	11% decrease
Exon 45 (n=27)	377.27	-27.28	-39.79	-50.85	13% decrease
Exon 51 (n=18)	400.46	-46.90	-86.73	-147.34	37% decrease
Exon 53 (n=28)	359.46	-28.97	-65.15	-168.54	47% decrease

Because the disease impacts patients differently over the course of their lifetime, different outcome measures are needed at different ages and stages of the disease.

AMBULATORY BOYS

For ambulatory boys, we recommend using the North Star Ambulatory Assessment (NSAA) and timed testing including timed supine to stand, timed up and go, timed 4 stair climb, and timed 10-meter walk/run as well as pulmonary function tests (PFTs), of which the FVC% predicted is the most sensitive.

10-Meter Walk Test (10MWT)[10,22,23]

Appropriate Disease Stage: Ambulatory to early nonambulatory
Timing: Every 6 months at routine clinic appointments
Description: Assesses walking speed in meters per second over a short distance. The time to walk the middle 6 meters, the level of assistance, and type of assistive device and/or bracing used are documented

4-stair climb[22]

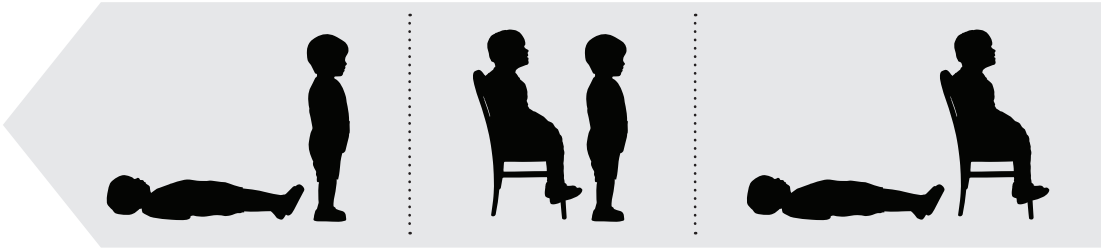
Appropriate Disease Stage: Ambulatory to early nonambulatory
Timing: Every 6 months at routine clinic appointments
Description: Measures the time to climb 4 stairs

Supine to stand, sit to stand, supine to sit[10,22]

Appropriate Disease Stage: Ambulatory to early nonambulatory

Timing: Every 6 months at routine clinic appointments

Description: These tests assess the speed that a patient switches between sitting, standing, or supine positions



NON-AMBULATORY BOYS

As children begin to lose ambulation, it is more important to monitor changes in respiratory, cardiac, and upper extremity function. At this point we recommend ongoing Pulmonary Function Tests (PFTs), echocardiogram (specifically left ventricular ejection fraction), Brooke scale, Egen Klassifikation scale, and optionally the Muscular Dystrophy Functional Rating Scale (MDFRS) and PUL 2.0. The Egen Klassifikation scale together with the percent predicted FVC has shown good predictive correlation with time to need for assisted ventilation.[24]

HALLMARKS FOR DISEASE PROGRESSION

Outcome measures are used to monitor clinical progression and functional motor changes. These measures can be used to predict disease progression. Some predictors of disease progression are age, prolonged time to rise off the floor, and the age of onset of loss of ambulation (LOA). The order of loss is usually time to rise off floor, followed by ability to climb stairs, and then LOA. Minimum clinically important differences (MCID) are associated with greater functional decline in ambulation over time:

For example, for the timed 10-meter walk/run it has been found that a time of under 6 seconds is predictive of ongoing ambulation for the next 12 months, while a score of over 12 seconds is predictive of loss of ambulation in the next 12 months.[25] We also encourage use of the NSAA, which is a 17-item test that assesses multiple domains of mobility. This measure has shown good correlation with the 6-minute walk test, which is difficult for most nontertiary centers to perform reliably.[26] A score of over 30 correlates best with a 6MWT of at least 400 meters, while a score of less than 16 correlates with a 6MWT of under 300 meters.[26] It is also helpful to use at least one upper extremity function scale such as the Brooke scale or the Performance of Upper Limb module (PUL), which can detect changes in upper extremity function before loss of ambulation. We feel it adds value to use measures such as the MDFRS to capture functional items not always measurable on other tests.

Signals of Progression in DMD[10,25]

- 6MWT <325 m after age 7 or 10% decline over a year
- Time to stand >30 sec
- Time to climb 4 stairs >8 sec
- 10-min walk or run time >12 sec
- NSAA raw score of 9

Appropriate and Recommended outcome measures by disease stage:

	6 and under	7–9	10–12	13–18*
Recommended outcome measures	• Timed testing —Supine to stand —Up and Go —4 stair climb —10-m walk/run • Revised NSAA (if age 3-5) • %Predicted FVC (once) • LVEF (baseline and at least every 2 years)	• Timed testing —Supine to stand —Up and Go —4 stair climb —10-m walk/run • NSAA or 6MWT • %Predicted FVC (once) • LVEF (baseline and at least every 2 years)	• Timed testing —Supine to stand —Up and Go —4 stair climb —10-m walk/run • NSAA or 6MWT • %Predicted FVC (annually) • LVEF (1-2 times a year)	• Timed testing —4 stair climb —10-m walk/run • Brooke scale • %Predicted FVC (once a year or every 6 months in non-ambulatory) • LVEF (1 or more times a year) • Egen Klassification scale
Optional outcome measures	• Bayley III Developmental Scales and Adaptive Behavior Scale (ABS)	• MDFRS • Vignos • Brooke	• MDFRS • Vignos • Brooke	• MDFRS • PUL 2.0

***For boys over the age of 18, we recommend using the Brooke Scale and maintenance would be score of 5 or less.**

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CONCLUSIONS

In this new era of rapid advances in therapies for DMD, it becomes more important than ever that we have a clear method of tracking response to treatment using validated outcome measures. Functional tests used in clinical trials, many which were designed over 5 years ago, may not be generally used in clinical practice, and the types of functional tests being used may vary by institution (or clinical practice setting). The functional tests in research trials are evolving and we recommend payers consider various assessments in their decision-making process.

We recommend using tools that are reliable, readily available, and feasible in a typical clinical setting. These measures are also designed to capture important functional outcomes at different stages of the disease based on known natural history. However, insurers are frequently requiring use of the outcome measures collected during clinical trials as criteria for approval of treatment. These studies have not included the full age spectrum in DMD, and other measures are more appropriate for assessing individual efficacy in older and non-ambulatory patients. In addition, how we measure response to treatment should reflect expected disease trajectory. For example, a slowing of disease progression should be considered a positive response to treatment. Implementing appropriate outcome measures into coverage policies will promote responsible stewardship of new therapies, set reasonable expectations for providers, payers, and families, and help actualize the promise of new therapies in this debilitating disease.

SUMMARY OF FUNCTIONAL MEASURES/TESTS OVERVIEW

Functional Assessment	Description	Outcome(s)	Disease Stage
Six-minute walk test (6MWT)[25]	• The 6MWT assesses function and endurance • The 6MWT is a robust assessment tool for use in clinical trials given its ability to quantitatively evaluate ambulation in a controlled environment	• Six-minute walk distance (6MWD) • Loss of ambulation (LOA)	Ambulatory
North Star Ambulatory Assessment (NSAA)[27]	• A 17-item rating scale that is used to measure functional motor abilities in ambulant children with Duchenne —Stand —Walk —Run —Stand from chair —Stand on one leg (right/left) —Climb box step (right/left) —Descend box step —Sit from supine —Rise from supine —Lift head from floor —Stand on heels —Jump —Hop on one leg (right/left) —10-m walk/run	• Ability to perform activities of daily living • Each item can be scored on a 3-point scale: —2- Normal – Achieves goal without any assistance —1- Modified method but achieves goal —0- Unable to achieve independently	Ambulatory

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Functional Assessment	Description	Outcome(s)	Disease Stage
Timed Function Tests (TFTs)[22,28]	• TFTs provide a measure of functional capability in ambulatory patients • Complementary to the 6MWT • Reproducible and easy to administer Includes: —Time to rise from floor* —Time to climb 4 stairs* —Time to run/walk 10m* —Timed up and go (TUG)	• Functional motor abilities	Ambulatory
Manual muscle testing/quantitative muscle testing[29]	• Manual and quantitative methods have been used to quantify and summarize muscle strength • The strength of individual muscle groups is assessed, and data is also summarized to characterize the overall rate of disease progression	• Muscle strength	Ambulatory & Non-ambulatory
Upper limb function tests (eg, Performance of upper limb [PUL], Brooke upper extremity grade, Egen Klassification Scale, Nine-hole peg test, etc.)[10,11,30]	• Assessments of upper limb function have been used to capture functional changes across different stages of the disease • A number of these assessments have explored the effect of progressive weakness on upper limb and manual abilities and dexterity	• Upper limb function	Ambulatory & Non-ambulatory
Spirometry[31]	• Decline of pulmonary function is a key contributor to morbidity and mortality in patients with Duchenne	• Pulmonary function testing (eg, forced vital capacity [FVC], maximal inspiratory pressure [MIP], maximal expiratory pressure, etc.)	Ambulatory & Non-ambulatory

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Functional Assessment	Description	Outcome(s)	Disease Stage
Respiratory Intervention[31]	• Progressive pulmonary decline requires the use of cough assistance, deep lung inflation, and finally noninvasive and invasive ventilation and is a key milestone in the progression of Duchenne, significantly impacting quality of life • Ventilation is the main intervention affecting survival in Duchenne muscular dystrophy	• Need for cough assist • Need for deep lung inflation • No ventilator use • Nocturnal ventilator use • Full-time ventilator dependence	Ambulatory & Non-ambulatory
Cardiac function tests, such as electrocardiogram, echocardiogram, cardiovascular MRI and others[31]	• Cardiovascular complications are a leading cause of disease-related morbidity and mortality among individuals with Duchenne	• Cardiac function	Ambulatory & Non-ambulatory
Patient reported outcomes (PROs) Pediatric Outcomes Data Collection Instrument (PODCI) Pediatric Quality of Life Inventory (PedsQL) Neuromuscular module of the PedsQL (NMM)[28]	• PROs, including those measuring activities of daily living, can be designed to assess the abilities and experiences of patients across a spectrum of disease stages and severities • PROs can be useful to assess the clinical meaningfulness of an objective finding of a relatively small magnitude and to contribute to assessments of benefit and risk	• Physical functioning • Psychosocial functioning	Ambulatory & Non-ambulatory

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