PCR28

Characterization of Patients with Duchenne Muscular Dystrophy Across Previously Developed Health States

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Introduction

- Duchenne Muscular Dystrophy (DMD) is a rare, progressive genetic disorder that causes muscle degeneration and weakness, starting in early childhood and leading to a deterioration of mobility, independence, and ultimately, life expectancy[1]
- In order to better understand the progression of DMD and inform decision-making in healthcare, a model of disease progression across eight health states has been developed based on the input from clinicians, patients, and caregivers by Project HERCULES[2]
- The model seeks to provide a comprehensive understanding of the disease trajectory and capture the natural progression of the disease from early ambulatory health states though non-ambulatory health states and eventual mortality

Objective

- To characterize the ages, steroid treatments and functional profiles of patients with DMD classified into health states consistent with those of the HERCULES model

Methods

Data Sources and Sample Selection

- Placebo arm data from phase 3 clinical trials:
  - The PTC Therapeutics phase 3 trial of ataluren (Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy [ACT DMD]; NCT01826487)
  - The Eli Lilly phase 3 trial of tadalafil (NCT01865084)
  - The GlaxoSmithKline phase 3 trial of drisapersen (DEMAND III; NCT01254019; provided by CureDuchenne)
- Real-world/natural history data sources:
  - Universitaire Ziekenhuizen Leuven (provided by the Leuven Neuromuscular Reference Center in Leuven, Belgium)
  - BioMarin natural history study (PRO-DMD-01; NCT01753804; provided by CureDuchenne)
  - North Star Clinical Network (NSUK; http://www.northstardmd.com)
  - ImagingDMD (iDMD; NCT01484678)
  - iMDEX/French Muscular Dystrophy Association (iMDEX; NCT02780492)
- To maximize use of the available data, the selected study sample consisted of all patient visits that could be classified into one of the health states of interest and had data on outcomes of interest

Health States

- Patient visits were classified into health states with definitions derived to match those of project HERCULES as closely as possible based on available data elements[2] (see **Figure 1**)

Analysis

- Summary statistics for demographic characteristics, steroid use, motor, pulmonary and cardiac functions, were calculated based on visits for each health state among patient with non-missing data
- If a patient had multiple visits in a particular health state, all of their visits were included in the summaries
- Means and standard errors for continuous measures were computed using generalized estimating equations (GEEs) with an exchangeable covariance structure to account for use of multiple visits from individual patients

Figure 1. Definition of Health States

	Ambulatory		Transfer
	State 1: Early ambulatory	**State 2:** Late ambulatory	**State 3:** Transfer
	– Able to rise from supine – Able to walk 10 meters	– Not able to rise from supine – Able to walk 10 meters	– Not able to rise from supine – Not able to walk 10 meter – Able to remain standing
Supine (NSAA item 11 > 0)	☑	☒	☒
Walk 10m	☑	☑	☒
Stand (NSAA item 1 > 0)	☑*	☑*	☑

* Condition not enforced in the data since ability to walk 10m presumes the ability to stand.

	Non-Ambulatory				
	State 4: – HTMF – No ventilation	**State 5:** – No HTMF – No ventilation	**State 6:** – HTMF – Night-time ventilation	**State 7:** – No HTMF – Night-time ventilation	**State 8:** – Full-time ventilation
	– PUL entry item ≥ 2 – FVC%p ≥ 50%	– PUL entry item < 2 – FVC%p ≥ 50%	– PUL entry item ≥ 2 – 30% ≤ FVC%p < 50%	– PUL entry item < 2 – 30% ≤ FVC%p < 50%	– PUL entry item < 2 – FVC%p < 30%
HTMF	☑	☒	☑	☒	☒
Night-time ventilation	☒	☒	☑	☑	☒
Full-time ventilation	☒	☒	☒	☒	☑

Abbreviations: HTMF: Hand-to-mouth function. PUL: Performance of the upper limb. FVC%p: Forced vital capacity percent predicted.

Results

- The study included a total of N=5,296 ambulatory and non-ambulatory visits distributed across all eight states, representing 1,175 boys with DMD (see **Table 1**)
- Sample sizes for all non-ambulatory groups, except for the first group (HTMF, No Ventilator), were relatively small
- Ages increased on average across increasingly progressed health states, despite overlapping distributions and broad heterogeneity within health states (see **Figure 2**)
- Compared to non-ambulatory states, patients in ambulatory and transfer states
  - Were younger
  - Had better pulmonary function (i.e., higher FVC %predicted)
  - Had better cardiac function in general (i.e., higher left ventricular ejection fraction, see **Figure 3**)
  - Used more steroids in general (especially in transfer state), with 67%, 71%, and 40% of the boys on daily steroids for health state 1 (early ambulatory), 2 (late ambulatory), and 3 (transfer), respectively
- Patients in earlier non-ambulatory states had better outcomes in PUL total score than patients in later non-ambulatory states

Table 1. Summary of Characteristics Across Health States

	Early Ambulatory N = 3,925 (953 patients)	Late Ambulatory N = 1,025 (406 patients)	Transfer N = 39 (37 patients)	HTMF, No Ventilator N = 208 (82 patients)	No HTMF, No Ventilator N = 24 (15 patients)	HTMF, Night Ventilator N = 31 (17 patients)	No HTMF, Night Ventilator N = 24 (9 patients)	Full Ventilation N = 20 (10 patients)
DEMOGRAPHICS & MEDICATIONS								
Age (years)	8.47 ± 0.07	10.85 ± 0.13	11.70 ± 0.42	13.17 ± 0.32	14.33 ± 0.62	14.94 ± 0.68	16.44 ± 0.59	16.84 ± 0.37
Height (cm)	121.06 ± 0.35	131.45 ± 0.58	142.58 ± 3.16	143.56 ± 1.64	153.24 ± 4.29	151.03 ± 4.20	157.50 ± 3.79	164.62 ± 2.10
Weight (kg)	28.02 ± 0.30	36.70 ± 0.69	49.30 ± 3.13	48.76 ± 1.78	51.15 ± 3.85	56.24 ± 5.00	63.89 ± 4.83	60.88 ± 6.11
Race								
White	1,545 (85.55%)	586 (78.98%)	7 (100.00%)	177 (88.06%)	24 (100.00%)	30 (96.77%)	24 (100.00%)	17 (100.00%)
Asian	142 (7.86%)	42 (5.66%)	0 (0.00%)	6 (2.99%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Black or African American	19 (1.05%)	23 (3.10%)	0 (0.00%)	1 (0.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Other	100 (5.54%)	91 (12.26%)	0 (0.00%)	17 (8.46%)	0 (0.00%)	1 (3.23%)	0 (0.00%)	0 (0.00%)
Ethnicity								
Hispanic or Latino	219 (20.02%)	80 (18.78%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	–	–	–
Not Hispanic or Latino	875 (79.98%)	346 (81.22%)	5 (100.00%)	3 (60.00%)	1 (100.00%)	–	–	–
Steroid use								
Deflazacort or Prednisone	3,221 (92.98%)	940 (97.71%)	30 (100.00%)	191 (91.83%)	19 (79.17%)	26 (83.87%)	16 (66.67%)	2 (10.00%)
On daily regimen	1,980 (66.67%)	632 (71.49%)	10 (40.00%)	134 (70.16%)	12 (63.16%)	17 (65.38%)	14 (87.50%)	2 (100.00%)
Not on steroid	243 (7.02%)	22 (2.29%)	0 (0.00%)	17 (8.17%)	5 (20.83%)	5 (16.13%)	8 (33.33%)	18 (90.00%)
DMD MEASURES								
NSAA total score	23.69 ± 0.19	12.68 ± 0.23	3.76 ± 0.31					
Timed 4 stair climb (seconds)	4.50 ± 0.13	13.18 ± 0.54	18.30 ± –					
Health utility index	0.83 ± 0.02	0.77 ± 0.04	0.48 ± –					
PUL								
Total score				61.30 ± 0.73	38.00 ± 1.85	53.58 ± 2.73	30.99 ± 3.02	21.91 ± 3.93
Entry question				4.55 ± 0.12	0.96 ± 0.04	3.43 ± 0.27	1.00 ± -	1.00 ± 0.00
Hands-to-mouth				2.79 ± 0.05	0.89 ± 0.19	2.28 ± 0.18	0.31 ± 0.12	0.24 ± 0.06
Remove lid from container				0.93 ± 0.02	0.74 ± 0.11	0.90 ± 0.05	0.52 ± 0.13	0.13 ± 0.09
Push on the light				2.61 ± 0.05	2.10 ± 0.20	2.30 ± 0.17	1.50 ± 0.23	0.89 ± 0.27
FVC %-predicted (%)	94.47 ± 0.77	89.13 ± 1.33	76.75 ± 3.09	77.20 ± 1.69	69.34 ± 4.55	42.34 ± 1.19	39.19 ± 1.27	20.57 ± 1.63
Left ventricular ejection fraction (%)	63.91 ± 0.37	61.73 ± 0.90	64.06 ± –	56.87 ± 1.36	55.10 ± 4.55	59.07 ± 48.69	46.77 ± 4.91	47.70 ± 2.81

Notes:
[1] To account for correlations to multiple observations per patient, means and standard errors are estimated using generalized estimating equations (GEE).
[2] Two outliers, one with height ≤ 11.8 cm and one with weight ≤ 3.3 kg, were removed from the calculations.
[3] Percentages were calculated among non-missing data.
[4] Gray cells represent unavailable data corresponding to a given health state.

Figure 2. Distributions of Patient Ages and Levels of Pulmonary Function Across Health States

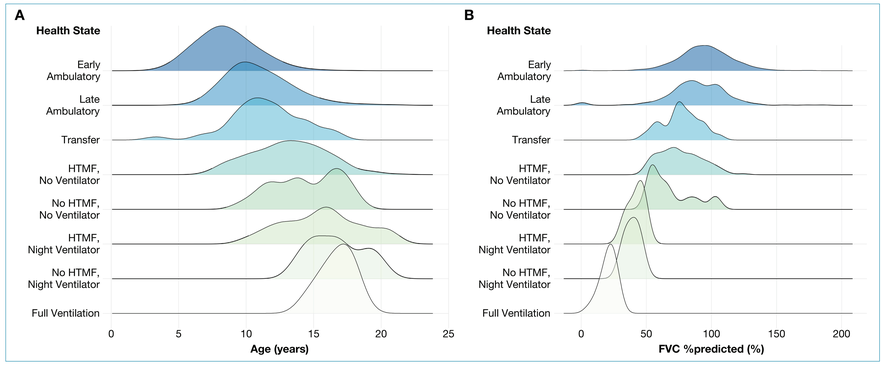
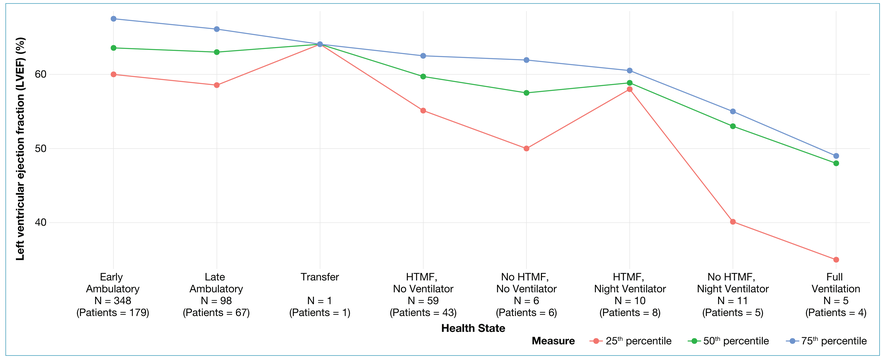


Figure 3. Left Ventricular Ejection Fraction



Notes:
[1] Sample sizes and patient counts reported per health state represents the observations with available data for left ventricular ejection fraction.
[2] Percentiles are based on the visits in each respective health state.

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Disclosures

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3. Research has shown that key DMD outcomes in RWD-NHD and CTPA are consistent with one another, justifying analyses that combine patients from both types of sources. See, e.g., Mercuri, E., N. Goemans, G. Sajeev, Z. Yao, E. McDonnell, S. Ward, and J. Signorovitch. (2017) "Consistency between natural history and clinical trial placebo arms for 48-week changes in six-minute walk distance (6MWD) in patients with Duchenne muscular dystrophy (DMD)." Neuromuscular Disorders 27: S232, and Goemans, N., B. Wong, F. Muntoni, C. McDonald, E. Mercuri, A. Mazur, J. Signorovitch et al. (2019) "P. 150 Consistency of 48-week changes in North Star Ambulatory Assessment (NSAA) between Duchenne muscular dystrophy natural history data and clinical trial placebo arms, after adjustment for prognostic factors." Neuromuscular Disorders 29: S92.

Limitations

- Data sources have varying contributions of patients across different disease health states, which may impact patterns of steroid use and other factors
- Sample sizes were limited in the "transfer state." Many clinics and data sources do not assess NSAA scores when patients cannot stand, and thus patients with documented NSAA stand scores equal to 0 may be underrepresented
- Sample sizes were also limited in the later ages (>18 years) from the available data sources

Conclusions

- Health states proposed for DMD disease progression showed concordantly worsened average levels of function for later health states across different domains, including ambulatory motor, pulmonary, upper-limb and cardiac function.
- Use of steroids declined among the later health states
- These findings further characterize health states and their interpretation in economic modeling and decision-making

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