Poster # P.68

A Prognostic Score for Time to Loss of Ambulation in Duchenne Muscular Dystrophy

Craig McDonald[1], Heather Gordish-Dressman[2], James Signorovitch[3,4], Gautam Sajeev[3], Mirko Fillbrunn[3], Molly Frean[3], Susan Ward[4], Nathalie Goemans[5], Krista Vandenborne[6], Eugenio Mercuri[7], Francesco Muntoni[8,9], Investigators for CINRG-DNHS, the PRO-DMD-01 study, the Imaging DMD study, iMDEX, and the Collaborative Trajectory Analysis Project (cTAP)

[1] Department of Physical Medicine and Rehabilitation, University of California, Sacramento, California, USA [2] George Washington University School of Medicine and Health Sciences, Washington, DC, USA [3] Analysis Group, Inc., Boston, MA, USA [4] Collaborative Trajectory Analysis Project (cTAP), Cambridge, MA, USA [5] University Hospitals Leuven, Child Neurology, Leuven, Belgium [6] University of Florida, Gainesville, FL, USA [7] Department of Pediatric Neurology, Catholic University, Rome, Italy [8] Dubowitz Neuromuscular Centre, Great Ormond Street Institute of Child Health, London, UK [9] NIHR Great Ormond Street Hospital Biomedical Research Centre, London, UK

Introduction & Objective

- Loss of walking ability is an important milestone in the progression of DMD. Patients typically experience loss of ambulation (LoA) between the ages of 6 and 13 years, with variation linked to factors such as steroid use (Marden et al. 2019) or genotype (Bello et al. 2016), among others
- Across therapeutic areas in which patients have variable rates of disease progression, prognostic tools have long been used to better understand individual patients and to guide drug development efforts (Escudier et al. 2019)
- To this end, we developed and validated an easy-to-use prognostic tool for LoA in DMD

Methods

Data sources

- Patient data were included from four real world or natural history data (RWD/NHD) sources (Leuven, PRO-DMD-01, iMDEX, ImagingDMD) and three clinical trial placebo arms (Tadalafil DMD trial, PTC 007, PTC 020) and used as the development sample
- Patient data from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS) were used as the validation sample

Patients

- Patients with a visit satisfying the following criteria were included:
  1. Six-minute walk distance (6MWD) ≥ 75 m
  2. At least one subsequent visit with an outcome assessment that allowed identification of LoA
  3. Currently receiving steroids
  4. Available data on candidate prognostic factors: 10-meter walk/run (10MWR), climbing 4 stairs (4SC), rise from floor (RFF), age, height, and weight
- A patient's first visit satisfying the above criteria served as their index visit

Outcome

- Time to LoA was defined in the development and validation samples as follows:
  - Time from the index visit to the first visit at which the patient was unable to complete the 6MWD test (development sample)
  - Time from the index visit to wheelchair dependence, defined as participant- or caregiver-reported age at continuous wheelchair use (validation sample)

Candidate prognostic factors

- Candidate prognostic factors included age, performance on timed function tests (10MWR, 4SC, RFF), height, weight, and body mass index (BMI) at the index visit

Statistical methods

- A classification and regression tree (CART) model was estimated for time to LoA in the development sample
  - CART is a predictive machine learning technique that selects variables from a set of candidate predictors and recursively splits the population of patients based on thresholds of these predictors to create risk groups with increasingly homogeneous outcomes
  - The output from the CART model was simplified to arrive at an easy-to-use, final prognostic score
- Patient characteristics were summarized at the index visit overall and by risk group for both the development and validation samples
- The performance of the prognostic score with respect to differentiating LoA risk was assessed using Kaplan-Meier (KM) curves in both the development and validation samples

Results

- A total of 608 patients was included in the development sample. Patients were on average 9.1 years old at their index visit (range of 4.4 to 19.4) with an average 6MWD of 360 m (SD=79) (**Table 1**).
- Mean duration of follow-up was 2.0 years (0.2 to 9.2) and 116 out of 608 patients (19%) experienced LoA. Median time to LoA from index was 4.6 years and mean age at time of LoA was 12.2 years. In addition, 98.5%, 91.3%, and 80.7% of patients remained ambulatory at 6, 12, and 24 months, respectively.
- The CART model identified three prognostic factors (RFF, 10MWR, and 4SC) as relevant to determine 6 risk groups. Age was not selected as an important prognostic factor for time to LoA. The risk groups explained 35.7% of variation in LoA risk (max 69.6%), as judged by pseudo R-squared in a Cox model with the risk groups as covariates.
- A simplified model was explored by removing 4SC (to avoid requiring availability of the 4-stair apparatus for use of the score), rounding thresholds, and combining two categories with similar risk. The resulting model was based only on RFF and 10MWR and included 5 risk groups (**Figure 1**). This simplified model explained 33.3% of the variation in LoA risk.
- The prognostic score was presented in a tabular representation to facilitate use (**Figure 2**).
- KM curves for time to LoA in both the development and validation samples were well separated and showed that patients in the 5 risk groups differed in their times to LoA (**Figures 3A and 3B**).
  - Development sample: median times to LoA for risk groups 1 (longest time to LoA) through 5 (shortest time to LoA) were not reached (NR), 4.4, 3.0, 2.0, and 0.9 years, respectively [data not shown]
  - Validation sample: median times to LoA for risk groups 1-5 were NR, 7.7, 3.7, 2.2, and 0.6 years, respectively [data not shown]
- Steroid type was not included as a prognostic factor as it was thought that the choice of steroid could depend on both the current and predicted performance of the patient (i.e., steroid use may be endogenous). Sensitivity analyses indicated that patients in the intermediate risk groups experienced numerically longer times to LoA with deflazacort compared to prednisone, whereas times to LoA were similar by steroid type in the groups with highest and lowest LoA risk (**Figure 3C**).

Table 1. Patient Characteristics at the Index Visit, Overall and by Risk Group

	Total N = 608	Final CART Model Risk Group 1 N = 189	2 N = 170	3 N = 141	4 N = 73	5 N = 35	P-value
Demographics							
Age (years)	9.05 ± 2.40	7.83 ± 1.69	8.56 ± 2.08	9.71 ± 2.23	10.89 ± 2.42	11.53 ± 2.81	< 0.001 *
Age group							< 0.001 *
4-6	46 (7.84%)	24 (12.70%)	20 (11.98%)	2 (1.47%)	0 (0.00%)	0 (0.00%)	
6-8	182 (31.01%)	88 (46.56%)	54 (32.34%)	32 (23.53%)	6 (9.09%)	2 (6.90%)	
8-10	206 (35.09%)	59 (31.22%)	58 (34.73%)	51 (37.50%)	26 (39.39%)	12 (41.38%)	
10-12	105 (17.89%)	14 (7.41%)	28 (16.77%)	36 (26.47%)	20 (30.30%)	7 (24.14%)	
12-14	48 (8.18%)	4 (2.12%)	7 (4.19%)	15 (11.03%)	14 (21.21%)	8 (27.59%)	
Steroid Use							
Steroid Type							< 0.05 *
Prednisone	257 (42.27%)	67 (35.45%)	76 (44.71%)	73 (51.77%)	24 (32.88%)	17 (48.57%)	
Deflazacort	351 (57.73%)	122 (64.55%)	94 (55.29%)	68 (48.23%)	49 (67.12%)	18 (51.43%)	
Steroid Duration							< 0.05 *
0-12mo.	166 (27.53%)	58 (31.02%)	54 (32.14%)	36 (25.53%)	14 (19.44%)	4 (11.43%)	
12-24mo.	121 (20.07%)	43 (22.99%)	37 (22.02%)	24 (17.02%)	11 (15.28%)	6 (17.14%)	
≥24mo.	316 (52.40%)	86 (45.99%)	77 (45.83%)	81 (57.45%)	47 (65.28%)	25 (71.43%)	
Ambulatory Function							
6MWD (10 meters)	36.01 ± 7.89	40.96 ± 6.06	38.51 ± 6.23	33.36 ± 4.79	29.53 ± 6.14	21.34 ± 5.69	< 0.001 *
Timed 10MWR (seconds)	6.17 ± 2.56	4.34 ± 1.03	5.28 ± 1.06	7.05 ± 1.27	8.26 ± 1.76	12.52 ± 3.95	< 0.001 *
Timed RFF (seconds)	9.77 ± 9.01	3.05 ± 0.52	5.15 ± 0.81	11.07 ± 3.13	26.28 ± 5.92	28.80 ± 2.89	< 0.001 *
Timed 4SC (seconds)	5.60 ± 5.40	2.37 ± 0.78	3.75 ± 1.55	6.17 ± 2.24	10.87 ± 6.55	18.70 ± 9.00	< 0.001 *
NSAA total score	22.67 ± 7.00	28.72 ± 3.56	25.89 ± 4.69	19.14 ± 4.77	15.13 ± 3.61	10.38 ± 3.13	< 0.001 *
Vitals							
Height (cm)	123.28 ± 11.23	116.73 ± 8.48	121.16 ± 9.51	128.18 ± 10.85	131.60 ± 10.92	131.77 ± 9.18	< 0.001 *
Weight (kg)	29.69 ± 10.38	24.62 ± 6.11	27.57 ± 8.60	33.15 ± 11.32	37.40 ± 11.49	37.30 ± 11.91	< 0.001 *
BMI (kg/m^2)	19.06 ± 4.03	17.85 ± 2.61	18.44 ± 3.82	19.78 ± 4.54	21.23 ± 4.54	21.08 ± 4.98	< 0.001 *

Means and standard deviations are shown for continuous characteristics; counts and percentages are shown for categorical characteristics. P-values were calculated comparing across risk groups.

Figure 1. CART Results, Original and Final Prediction Model

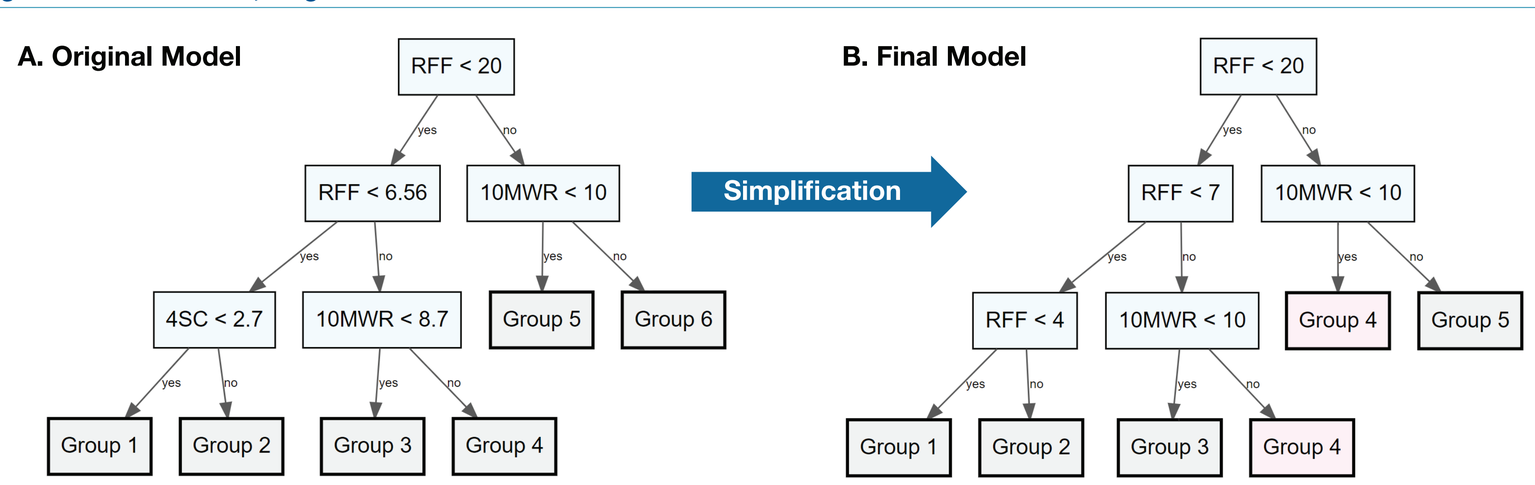
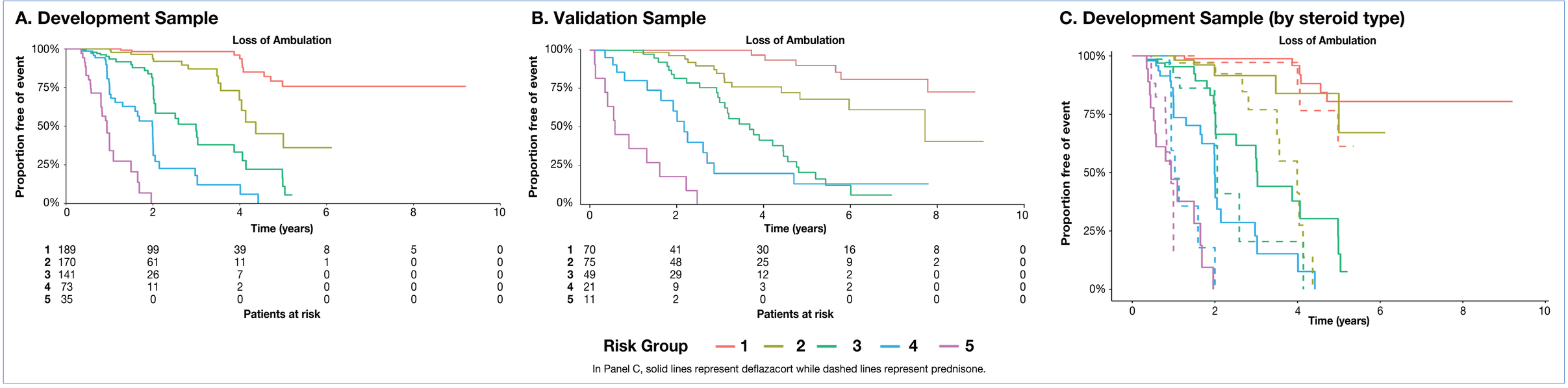


Figure 2. Tabular Representation of Prediction Model

Loss of ambulation risk score		Completion Times (seconds) RFF	10MWR
Lowest risk	1	< 4	Any
	2	4-7	
	3	7-20	< 10
	4		≥ 10
		≥ 20	< 10
Highest risk	5		≥ 10

Figure 3. KM Analysis of Prediction Model



In Panel C, solid lines represent deflazacort while dashed lines represent prednisone.

Limitations

- Data beyond 4 years of follow-up were limited in both the development and validation samples. Times to LoA beyond 4 years are therefore not precisely estimated. This may have contributed to the large numerical difference between the development and validation samples in median time to LoA in group 4
- While prognostic scores have informed treatment guidelines in multiple therapeutic areas, the present score was not evaluated for use in DMD clinical practice. Additional research would be required to assess potential use in DMD care including appropriate use and interpretation
- The prognostic score did not consider other patient characteristics, such as genetic or magnetic resonance imaging biomarkers, which could potentially improve prognostic accuracy

Conclusions

- A prognostic score was developed using machine learning based on data from multiple natural history databases and clinical trial placebo arms
- The score stratified patients into groups with meaningfully different times to LoA, and is easy to apply based on timed RFF and 10MWR tests
- The prognostic score performed well in a separate validation dataset

Disclosures

This study was conducted within the collaborative Trajectory Analysis Project (cTAP), a precompetitive coalition of academic clinicians, drug developers, and patient foundations formed in 2015 to overcome the challenges of high variation in clinical trials in DMD. cTAP has received sponsorship from Astellas (Mitobridge), Avidity Biosciences, BioMarin Pharmaceutical, Bristol Meyers Squibb, Catabasis, Daiichi Sankyo, Edgewise Therapeutics, Entrada Therapeutics, FibroGen, Italfarmaco SpA, Marathon Pharmaceuticals, NS Pharma, Pfizer, PTC Therapeutics, Roche, Sarepta Therapeutics, Shire, Solid Biosciences, Summit Therapeutics, Ultragenyx, Vertex Pharmaceuticals, Parent Project Muscular Dystrophy, Charley's Fund, and CureDuchenne, a founding patient advocacy partner and provider of initial seed funding to cTAP.

Acknowledgments

- The authors are grateful to the patients for participating in the clinical assessments and for agreeing to make their data available for research. Data from PRO-DMD-01 were provided to cTAP by CureDuchenne. The authors would like to thank investigators and research staff from all the data sources used in this study.

References

1. Marden JR, et al. J Comp Eff Res 2019;9.3:177-189.
2. Bello L, et al. Neurology 2016;87.4:401-409.
3. Escudier B, et al Ann Oncol 2019;30.5:706-720.

www.ctap-duchenne.org

Presented at the 27th International Hybrid Annual Congress of the World Muscle Society, October 11–15, 2022, Halifax, Nova Scotia, Canada