Predicting Trajectories of Ambulatory Function in Duchenne Muscular Dystrophy

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Disclosures and funding

- This study was conducted within the Collaborative Trajectory Analysis Project (cTAP), a pre-competitive 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, Daiich Sankyo, Edgewise Therapeutics, FibroGen, Italfarmaco SpA, Marathon Pharmaceuticals, NS Pharma, Pfizer, PTC Therapeutics, Roche, Sarepta Therapeutics, Shire, Solid Biosciences, Summit Therapeutics, Wave Life Sciences, Vertex Pharmaceuticals, Parent Project Muscular Dystrophy, Charley's Fund, and CureDuchenne, a founding patient advocacy partner and provider of initial seed funding to cTAP.

Background

- The North Star Ambulatory Assessment (NSAA) is a validated assessment that serves as an endpoint in multiple Duchenne muscular dystrophy (DMD) clinical trials
- Previous research has identified prognostic factors for short-term changes in motor function measures including NSAA, but prognostic models for longer-term trajectories of change have not yet been developed
- Validated prediction models for longer-term NSAA trajectories for patients based on real-world data/natural history data (RWD/NHD) are valuable for drug development via
  - Individualized predictions of reference trajectories for drug-treated patients
  - Knowledge of important prognostic factors to use for matching or adjustment in comparisons to long-term RWD/NHD external controls
- These steps will be necessary for understating the long-term efficacy of novel therapies in DMD, beyond the time periods addressable in randomized, placebo-controlled trials

Objectives

- Identify prognostic factors for longer-term changes in NSAA total score
- Develop and validate a multivariable prognostic model for longer-term change trajectories in NSAA total score

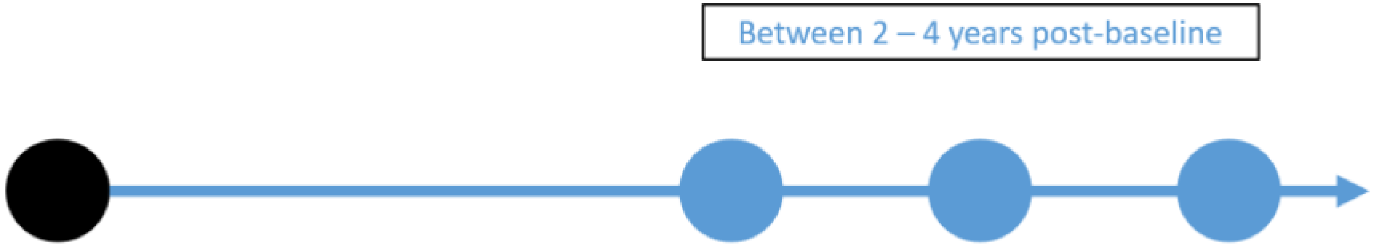
Methods - Data Sources

Source	Description
Leuven	Curated real-world data from routine clinical practice at the pediatric neurology clinic at the Leuven Neuromuscular Reference Center in Leuven, Belgium
iMDEX	A natural history study of DMD conducted in several tertiary care centers in Europe
North Star UK	Natural history data from a registry of 20+ clincial centers in the North Star Clinical Network in the United Kingdom
PRO-DMD-01	A natural history study of DMD conducted in 16 tertiary care centers worldwide

PRO-DMD-01 data provided by CureDuchenne

Methods – Patient eligibility and samples

- Patients were required to meet specific criteria at the baseline visit and have outcome visits with available NSAA data
- Eligible patients were randomly divided into training and validation sets



Baseline Visit

- Age between 4 and 10 years old
- NSAA Total Score > 12
- Non-missing data on candidate prognostic factors

Outcome Visits

- Non-missing data on NSAA total score

All eligible patients
(n = 261)

80%

Training set (n = 208)
Used to identify prognostic factors and build prediction model

20%

Validation set (n = 53)
Used to evaluate model's predictive performance

Methods – Statistical analysis

- **Model building**
  - Mixed effect models for change trajectory in NSAA total score including different sets of candidate predictors were fit in the training set
- **Model selection and validation**
  - Akaike information criterion (AIC) was used to identify the best fitting candidate models
  - Root mean squared error (RSME) was evaluated for the candidate models in the 20% validation set
  - For the final selected model, trajectories stratified by quartile of predicted 4-year change were plotted for each patient

Candidate predictors (at baseline)
Age
Steroid use (not on steroids, deflazacort/ prednisone)
NSAA total score
Rise from supine velocity
10-meter walk/run velocity
NSAA item scores (selected models)
Height
Weight
Body mass index (BMI)
Data source

Methods – Assessment of bias due to missingness

- NSAA score was assigned to equally spaced, 6-month time points based on the closest measured value available within ±3 months of each time point
- Imputation of missing follow-up NSAA values was performed using multiple imputation by chained equations (MICE) with predictive mean matching
  - 100 imputed datasets with 30 iterations were used
  - Convergence of predictions was assessed graphically across iterations
- Mean change from baseline trajectories were compared between the imputed and non-imputed datasets using generalized estimating equations (GEE) models with exchangeable covariance structure and quadratic effect of time

Results - Baseline statistics

	Total N = 261	Training Sample N = 208	Validation Sample N = 53
Data source, n (%)			
Leuven	19 (7.3%)	17 (8.2%)	2 (3.8%)
iMDEX	20 (7.7%)	17 (8.2%)	3 (5.7%)
NSUK	147 (56.3%)	112 (53.9%)	35 (66.0%)
PRO-DMD-01	75 (28.7%)	62 (29.8%)	13 (24.5%)
Age, mean ± SD (years)	6.8 ± 1.5	6.8 ± 1.5	6.9 ± 1.5
Steroid type, n (%)			
Not on steroids	63 (24.1%)	49 (23.6%)	14 (26.4%)
Prednisone	137 (52.5%)	107 (51.4%)	30 (56.6%)
Deflazacort	61 (23.4%)	52 (25.0%)	9 (17.0%)
NSAA total score, mean ± SD	25.6 ± 5.3	25.7 ± 5.3	25.2 ± 5.1
Timed rise from supine velocity, mean ± SD (1/s)	0.26 ± 0.15	0.27 ± 0.16	0.24 ± 0.11
Timed 10MWR velocity, mean ± SD (m/s)	1.9 ± 0.6	1.9 ± 0.6	1.8 ± 0.5
Follow-up duration after index, mean ± SD (years)	3.1 ± 0.6	3.1 ± 0.6	3.2 ± 0.6

Abbreviations: BMI: body mass index; NSAA: North Star Ambulatory Assessment; 10MWR: 10-meter walk/run; SD: standard deviation

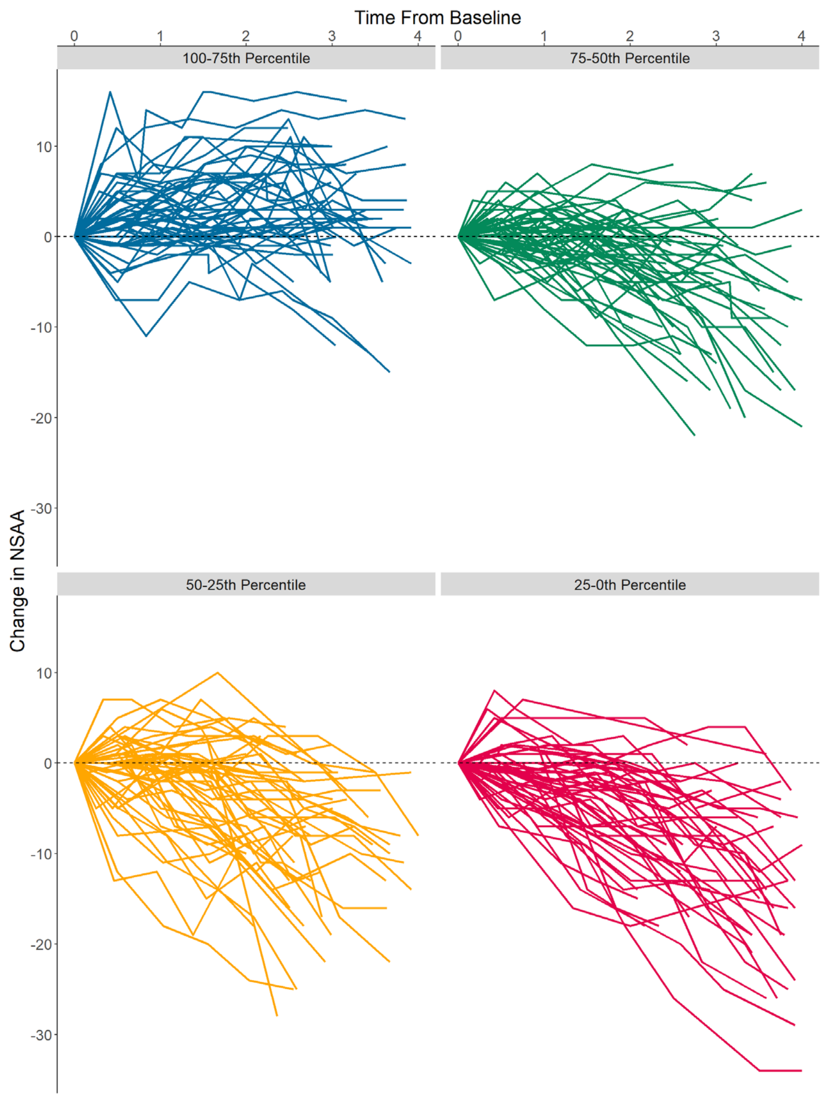
Results - Identified prognostic factors

- Important baseline predictors of greater decline in NSAA identified in the training sample included:
  - Older age
  - Longer rise-from-floor times
  - Higher NSAA (more room to decline)
  - Greater height
  - Greater body mass index
  - Data source
- Adding NSAA items did not further improve model performance in the training sample

Results - NSAA Trajectories by Prognostic Quartile

- Best-fitting model explained 27% of variation in post-baseline change in NSAA with average prediction errors of ±5.6 units in the validation sample.

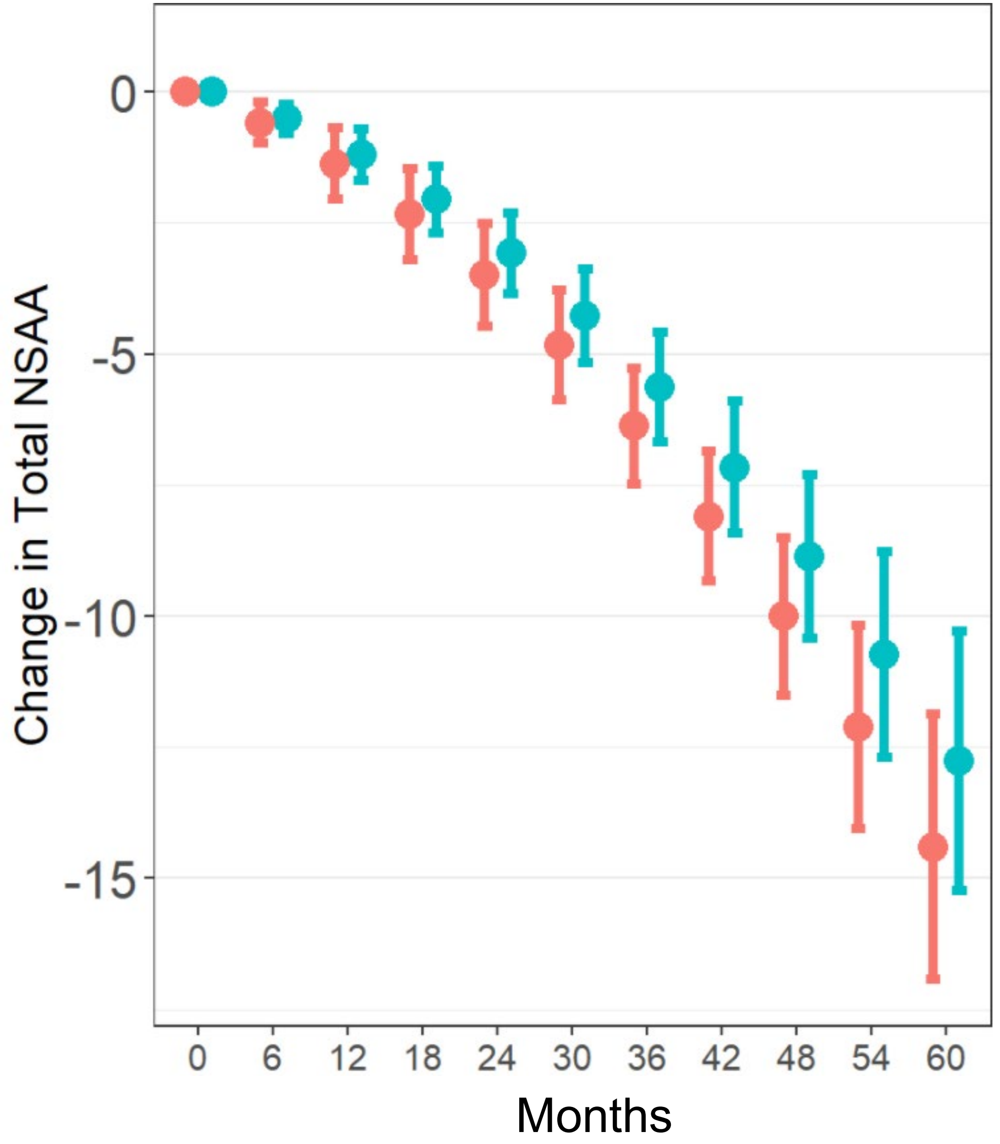
- Patients can be segmented into the following four groups based on quartiles of predicted change in NSAA



Results – Magnitude of Bias Due to NSAA Missingness

- Small (+0.2 units) bias at year 1
- Increasing bias up to +0.8 NSAA units at year 3 and +1.6 units by year 5
- Direction of bias is as expected: without imputation NSAA natural history looks better
- This would result in bias *against* treatment in a comparison to long-term natural history controls

	12 months	24 months	36 months	48 months	60 months
Observed only	-1.2 ± 0.2	-3.1 ± 0.4	-5.6 ± 0.5	-8.9 ± 0.8	-12.8 ± 1.3
Observed and imputed NSAA	-1.4 ± 0.3	-3.5 ± 0.5	-6.4 ± 0.6	-10.0 ± 0.8	-14.4 ± 1.3



Limitations

- The current model was developed among boys aged 4 to 10 years and should be extended to include older boys.
- Prognostic factors considered here are limited to those available across multiple data sources. Exploration of additional prognostic factors may help further improve prediction accuracy.
- Additional validation in larger external samples is recommended to further validate the model.
- Research is ongoing within cTAP to address these issues.

Conclusions

- Trajectories of ambulatory function in DMD can be well-predicted using baseline characteristics, including multiple measures of baseline function.
- Bias in NSAA predictions due to data missingness was generally low and towards better-than-actual outcomes, supporting the use of predicted values for externally controlled comparisons of new treatments.
- Additional validation analyses in larger samples are warranted.

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