Prediction of North Star Ambulatory Assessment Trajectories in Becker Muscular Dystrophy: Model Development and Validation

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1. Introduction & Objectives

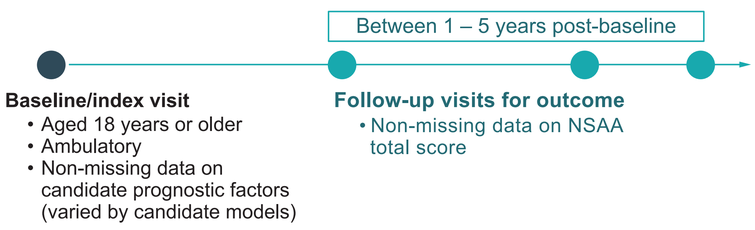
- Prediction models for natural history trajectories can provide important benchmarks for the outcomes of patients receiving novel therapies
- This is especially valuable over multi-year periods in Becker Muscular Dystrophy (BMD) for which placebo controls are not feasible
- To this end, we developed a prediction model for changes in the North Star Ambulatory Assessment (NSAA) total score in BMD patients based on longitudinal natural history data
- The model was then validated against published studies of independent BMD data

2. Methods

Patients

- From 37 adult male BMD subjects monitored at Leiden University Medical Center (LUMC), ambulatory patients with NSAA total score available at baseline and at least one follow-up visit were selected (**Figure 1**)

Figure 1: Sample selection



Abbreviations: NSAA, North Star Ambulatory Assessment

Primary outcome

- Changes from baseline in the NSAA total score (ΔNSAA) were studied over all available follow-up
- The NSAA assesses 17 activities, scoring each as 0 (unable to perform the activity independently), 1 (able to perform a modified activity independently), or 2 (able to perform the activity independently without modification). The NSAA total score, ranging from 0 to 34, reflects functional health, with higher scores indicating better motor function

External validation data

- A targeted literature review was conducted to identify publications reporting baseline characteristics and ΔNSAA at 9 to 18 months follow-up for patients with BMD
- Two published studies, Bello et al (2016)[1] and De Wel et al (2024)[2], were identified as suitable

Statistical methods

- A series of prediction models was evaluated to identify baseline characteristics that impact the trajectory of NSAA change
  - Candidate baseline predictors: age, NSAA total score, rise from supine (RFS) velocity, 10-meter walk/run (10MWR) velocity, 4-stair climb (4SC) velocity, and body mass index (BMI)
  - Trajectories of NSAA change: linear, quadratic, and piecewise linear
  - Longitudinal mixed-effects models were used
- Model performance was assessed using the corrected Akaike Information Criterion (AICc), marginal R^2, and marginal root mean square error (RMSE)
- External validation was performed by predicting ΔNSAA values at month 12 (Bello et al., 2016[1]) and at months 9 and 18 (De Wel et al., 2024[2]) using reported average baseline characteristics and comparing them to the reported observed ΔNSAA values

3. Results

Baseline characteristics

- A total of 24 ambulatory male patients with BMD were included, with mean (standard deviation) age of 39.4 (12.6) years and mean NSAA total score of 23.9 (10.6) units (**Table 1**)
- Median (range) follow-up was 37.0 months (11.7 to 60.7)

Table 1: Baseline patient characteristics of patients at LUMC

Patient characteristics, mean ± SD	LUMC Patients Ambulatory at Baseline N = 24[a]
Age, years	39.4 ± 12.6
NSAA total score	23.9 ± 10.6
10MWR velocity, meter/s	2.0 ± 1.2
RFS velocity, 1/s	0.2 ± 0.2
4SC velocity, task/s	0.3 ± 0.3

Abbreviations: NSAA, North Star Ambulatory Assessment; RFS, rise from supine; SD, standard deviation; s, seconds; 10MWR, 10-meter walk/run; 4SC, 4-stair climb.
Note:
[a] Baseline characteristics were summarized for the analytical sample (n=24) used in the final (best-fitting) prediction model including age, NSAA total score, 10MWR velocity, RFS velocity, and 4SC velocity with a linear time effect.

3. Results (Continued)

Model performance

- The best performing model included a linear trajectory, modified by baseline age, NSAA total score, RFS velocity, 10MWR velocity, and 4SC velocity (**Table 2**)
- The model achieved a marginal R^2 of 53%, more parsimonious with low AICc and RMSE compared to other models (**Table 2**)
- Statistically significant predictors included the linear time effect and baseline 10MWR velocity (**Table 3**)

External validation

- Compared to Bello et al. (2016), the predicted mean ΔNSAA at 12 months (-0.9 [95%CI: -1.3 to -0.5]) closely matched the observed value (-0.9) (**Figure 2**)
- Compared to De Wel et al. (2024), the predicted mean ΔNSAA showed slightly smaller declines of -0.9 [95%CI: -1.2 to -0.7] vs -1.3 at 9 months, and -1.9 [95%CI: -2.4 to -1.4] vs -2.5 at 18 months; however, absolute differences were within 1 unit (**Figure 2**)

Table 2: Model performance

Model specification	AICc	Marginal R^2	Marginal RMSE
Predictor set 1: Age, 10MWR, 4SC, RFS, NSAA N= 24[a]			
Piecewise linear time effect	336.70	0.53	2.05
Quadratic time effect	354.24	0.51	2.04
Linear time effect (best-fitting)	***328.31***	***0.53***	***2.05***
Predictor set 2: Age, 10MWR, NSAA N= 26[a]			
Piecewise linear time effect	381.99	0.42	2.43
Quadratic time effect	394.20	0.40	2.47
Linear time effect	373.16	0.44	2.43

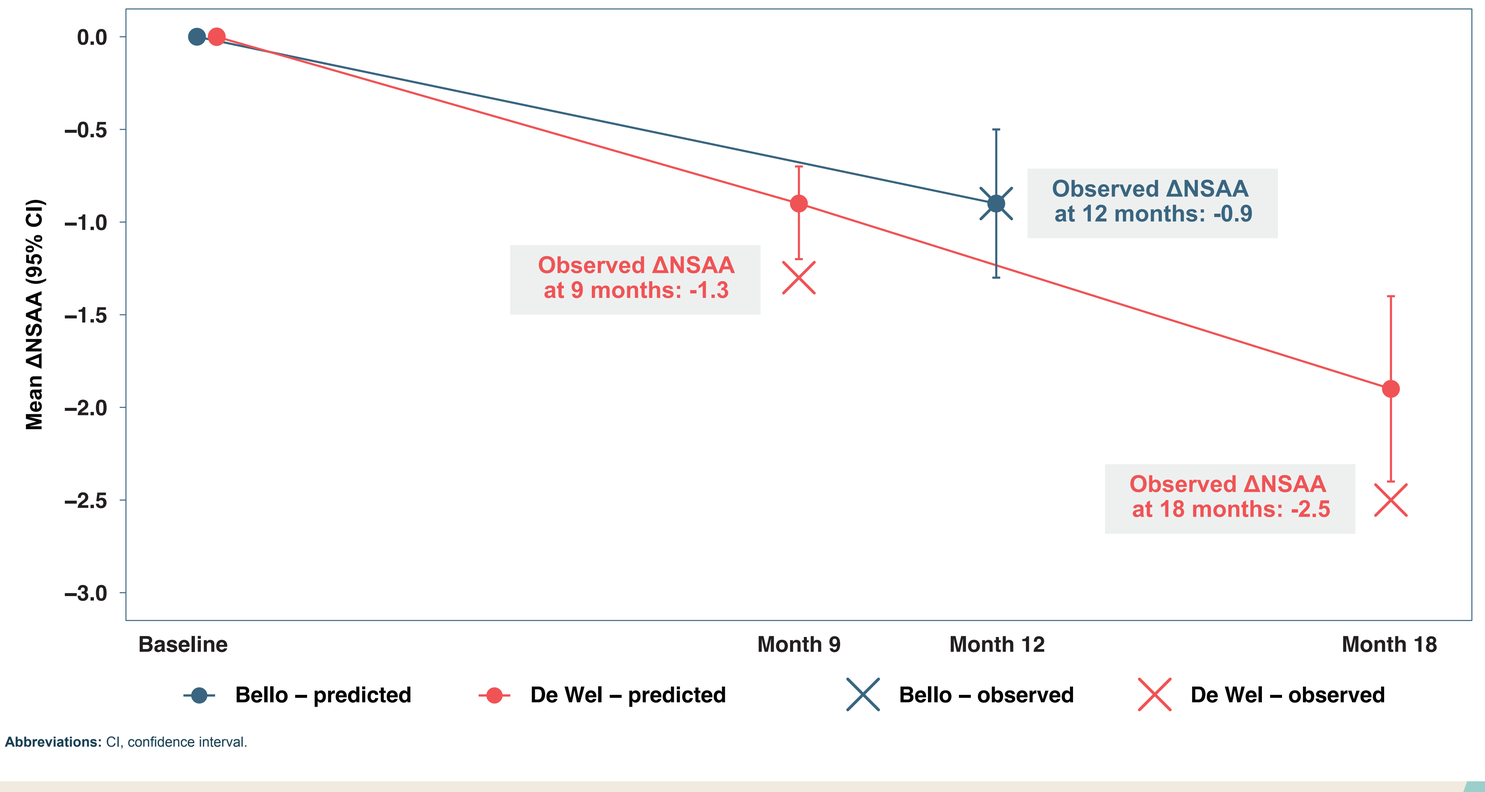
Abbreviations: AICc, corrected Akaike Information Criterion; NSAA, North Star Ambulatory Assessment; RFS, rise from supine; RMSE, root mean square error; 10MWR, 10-meter walk/run; 4SC, 4-stair climb
Note:
[a] The sample size varied across candidate models depending on the availability of baseline predictors. Therefore, comparisons of model fit parameters should be interpreted with caution due to differences in sample sizes.

Table 3: Best-fitting prediction model for annual NSAA slope

Parameter	Coefficient (per year)	S.E.	P-value
Time from baseline (years)	-2.59	0.94	0.015*
Age (years)	0.02	0.02	0.133
NSAA total score	-0.06	0.05	0.228
10MWR velocity (meter/s)	0.76	0.33	0.033*
RFS velocity (rise/s)	2.99	2.09	0.173
4SC velocity (task/s)	-0.71	0.93	0.456

Abbreviations: NSAA, North Star Ambulatory Assessment; RFS, rise from supine; S.E., standard error; 10MWR, 10-meter walk/run; 4SC, 4-stair climb.
Note: * *p-value* < 0.05

Figure 2: Predicted ΔNSAA over time with 95% confidence interval



Abbreviations: CI, confidence interval.

4. Conclusions

- While the selected prediction model was trained on a relatively small number of subjects, its performance on external data sources shows adequate predictive performance to benchmark and contextualize NSAA treatment outcomes over 2+ years in ambulatory BMD
- Incorporation of additional natural history data and validation, will further improve the utility of this model for benchmarking the outcomes of new treatments

Disclosures
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[2] De Wel, Bram, et al. "Lessons for future clinical trials in adults with Becker muscular dystrophy: Disease progression detected by muscle magnetic resonance imaging, clinical and patient reported outcome measures." *European journal of neurology* (2024): e16282.

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