A Concisely Recorded Ambulatory Assessment for Enhancing Real-World Outcomes Research in Duchenne Muscular Dystrophy

Development and Validation

Anna Mayhew, James Signorovitch,* Volker Straub, Chiara Marini Bettolo, Robert Muni Lofra, Adnan Manzur, Vandana Gupta, Victoria Selby, Francesco Muntoni and the North Star Clinical Network

*James.Signorovitch@analysisgroup.com

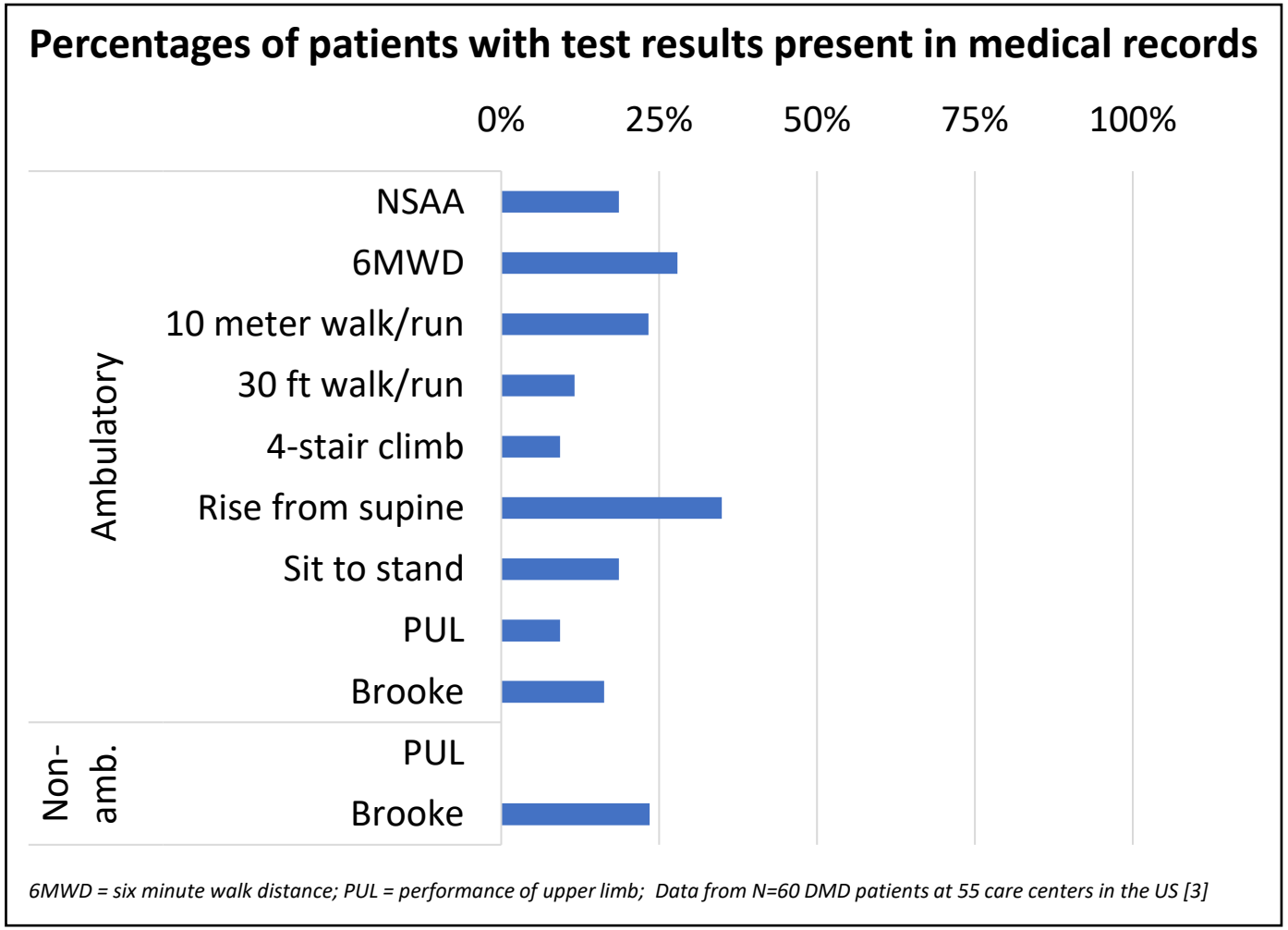
AAN 2022

Background and motivation

- The North Star Ambulatory Assessment (NSAA) is foundational for ambulatory care in Duchenne muscular dystrophy (DMD)[1,2]
- NSAA is regularly conducted per care guidelines and recorded in medical records throughout the United Kingdom, Europe and elsewhere
- At too many centers and practices, however, recording of standardized motor function assessments in DMD medical records is limited or inconsistent
- While optimal clinical management relies on the totality of motor function tasks represented in the NSAA, we aimed to identify a concise subset of motor function tasks that, if consistently recorded in medical records, would adequately proxy for the NSAA total summary score

Background and motivation

- No functional measure was consistently recorded for a majority of patients, for example, in a recent retrospective review of DMD medical records in the US (**Figure**)
- This hinders retrospective learning from real-word data in this rare, progressive and life-limiting disease



Objective

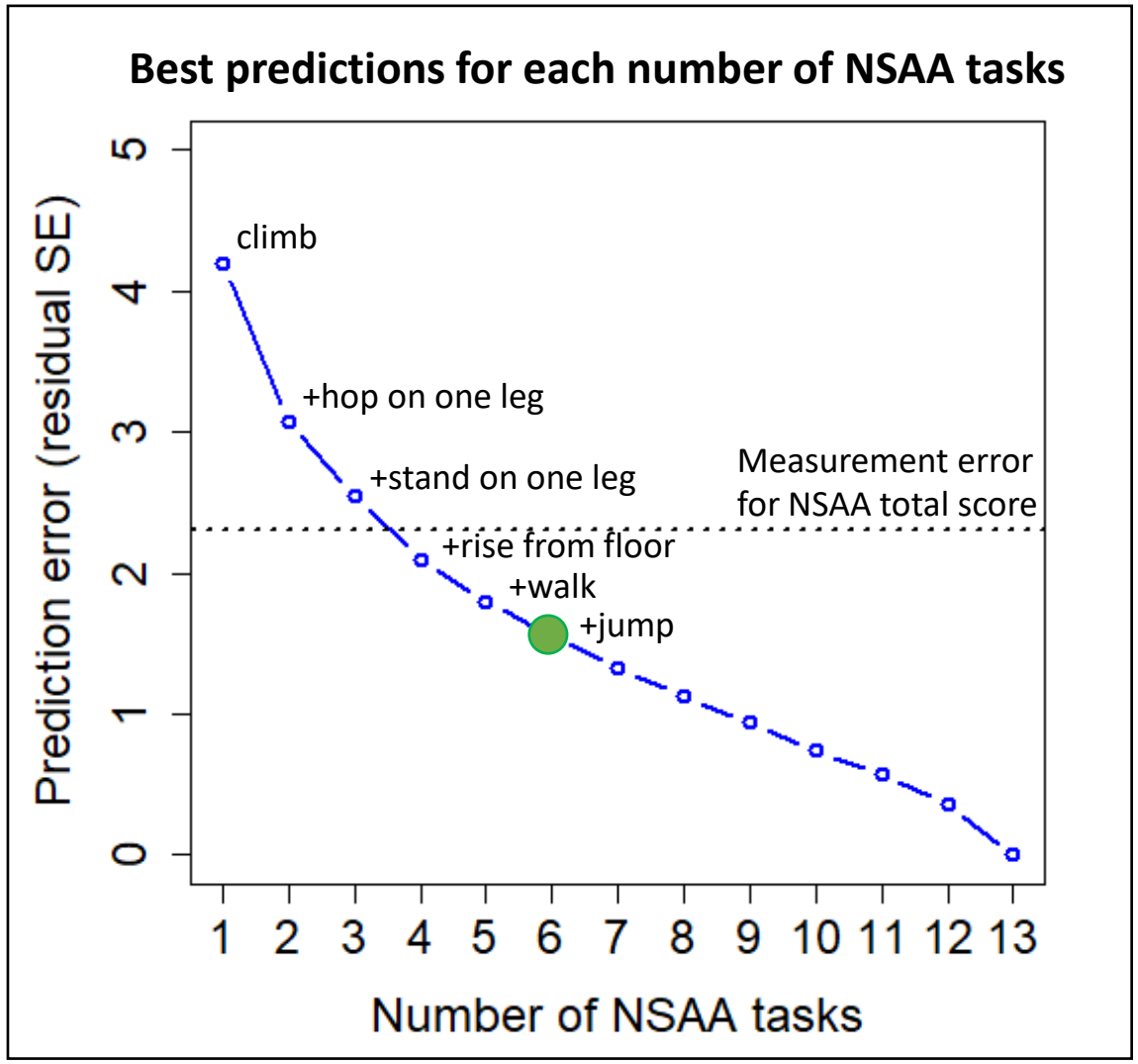
To identify a concise subset of ambulatory assessments for DMD – conducted as part of a complete assessment per care guidelines – that can

- Be easily recorded in medical records
- Accurately quantify real-world disease progression

Study approach

- **Data**
  - 1,828 complete NSAA assessments among 323 patients in the North Star Clinical Network database
- **Methods**
  - Machine learning (lasso[4]) was used to identify NSAA task subsets that best predicted the NSAA total score in a training sample of n=220 patients; tasks represented all 17 NSAA items using best scores for bilateral item pairs
  - Predictions were evaluated in a held-out sample of n=100 patients
  - The standard error of measurement (SEM) of the NSAA total score (previously estimated at 2.3 units[5]) served as a benchmark for prediction accuracy

Main finding: the NSAA total score was well-approximated by as few as 4 tasks



- A proxy based on the best 6 tasks had a prediction error of 1.6 NSAA units in the training data

Proxy for NSAA total score

NSAA ≈ 2.7 + 2.00 x (walk + rise from floor)
+ 2.50 x (stand on one leg + hop on one leg)
+ 1.75 x jump + 4.0 x climb

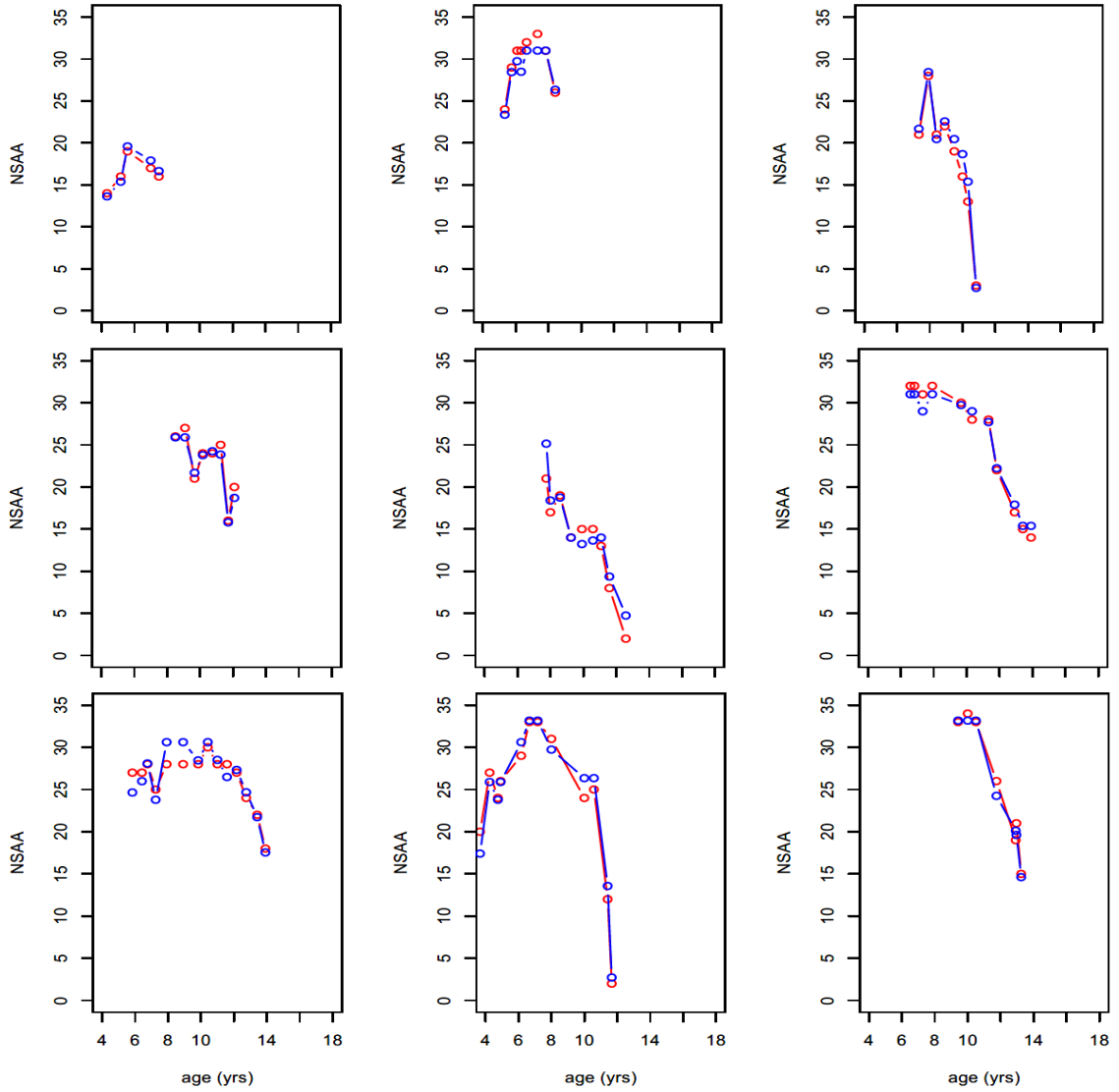
- In a sensitivity analysis replacing *stand on one leg* with *stand on both legs*, prediction error increased to 1.9 units
- Findings were similar when the average, best, worst or random choice of the left and right sides was used for bilateral tasks; results presented are for the best side

Excellent performance in held-out validation data

The 6-task proxy for NSAA total score…

- Explained **95%** of variation in NSAA total scores
- Had correlation **0.97** with the NSAA total score
- Predicted NSAA total score within ± **1.8 units**, better than the measurement error of NSAA total score itself (SEM = 2.3 units[5])
- Showed similar predictive performance by subgroups of age and NSAA

Consistency of observed and proxied NSAA total score trajectories vs. age for nine example patients



Conclusions

- The full NSAA should be conducted by trained assessors, consistent with care guidelines, so that disease management is not divorced from measurement
- When entry of all NSAA items into the medical record is not possible, consistently prioritizing entry of the six items identified here would significantly broaden the foundation for real-world outcomes research in ambulatory DMD

References

1. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, Case LE, Clemens PR, Hadjiyannakis S, Pandya S, Street N, Tomezsko J, Wagner KR, Ward LM, Weber DR; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018 Mar;17(3):251-267.
2. Scott E, Eagle M, Mayhew A, Freeman J, Main M, Sheehan J, Manzur A, Muntoni F; North Star Clinical Network for Paediatric Neuromuscular Disease. Development of a functional assessment scale for ambulatory boys with Duchenne muscular dystrophy. Physiother Res Int. 2012 Jun;17(2):101-9.
3. Marden JR, Santos C, Pfister B, Able R, Lane H, Somma M, Zhao J, Signorovitch J, Parsons J, Apkon S. Steroid switching in dystrophinopathy treatment: a US chart review of patient characteristics and clinical outcomes. J Comp Eff Res. 2021 Oct;10(14):1065-1078.
4. Tibshirani R. The lasso method for variable selection in the Cox model. Stat Med. 1997 Feb 28;16(4):385-95.
5. Muntoni F, Signorovitch J, Sajeev G, Done N, Yao Z, Goemans N, McDonald C, Mercuri E, Niks E, Wong B, Servais L, Straub V, de Groot I, Tian C, Manzur A, Vandenborne K, Dieye I, Lane H, Ward S and the Collaborative Trajectory Analysis Project. Minimal Detectable Changes in Functional Measures in Duchenne Muscular Dystrophy: A Study of Multiple Centers, Networks and Trial Arms. Presented at the Muscular Dystrophy Association Virtual Clinical & Scientific Conference, March 15th –18th, 2021.