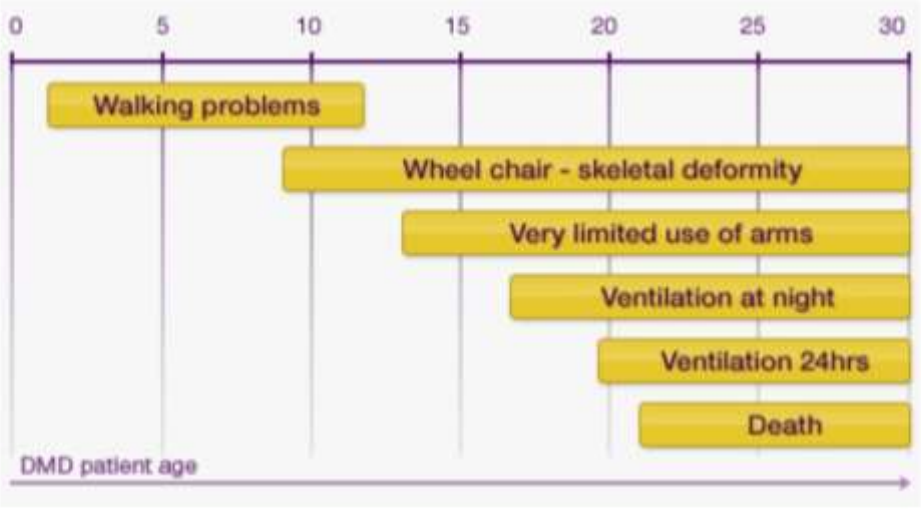
Ambulatory function in Duchenne muscular dystrophy

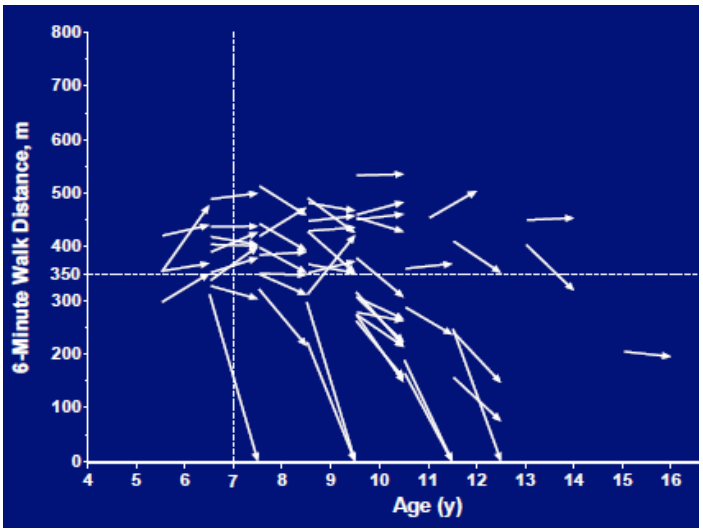
The characteristic trajectory and variation across individuals

James Signorovitch, Francesco Muntoni, Gautam Sajeev, Zhiwen Yao, Susan J. Ward, and Keith R. Abrams

Duchene muscular dystrophy: progressive muscle wasting leads to weakness, loss of motor function and early death



Heterogeneity in rates of disease progression -- a challenge for drug development



Placebo arm from PTC trial 007

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The Collaborative Trajectory Analysis Project

Clinical experts and registries

Eugenio Mercuri
Nathalie Goemans
Francesco Muntoni
Brenda Wong
Hank Meyer
Craig McDonald
Krista Vandenborne

Drug Developers

PTC, Sarepta, catabasis, Shire, Pfizer, SOLID, Lilly, mitobridge, astellas, Roche, ITALFARMACO, WAVE, FibroGen, BIOMARIN, MARATHON, summit

Patient Groups

Cure Duchenne, Parent Project Muscular Dystrophy, Charley's Fund

Collaboration

Susan J. Ward, PhD

Data Science

James Signorovitch, PhD

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Mission

- Learn from patient data to inform all stages of Duchenne drug development
- Make insights and tools available to everyone
- Deliver near-term impact

Research objectives discussed today

- Describe common patterns of disease progression
- Quantify variation across individuals
- Explore relationships across different functional measures

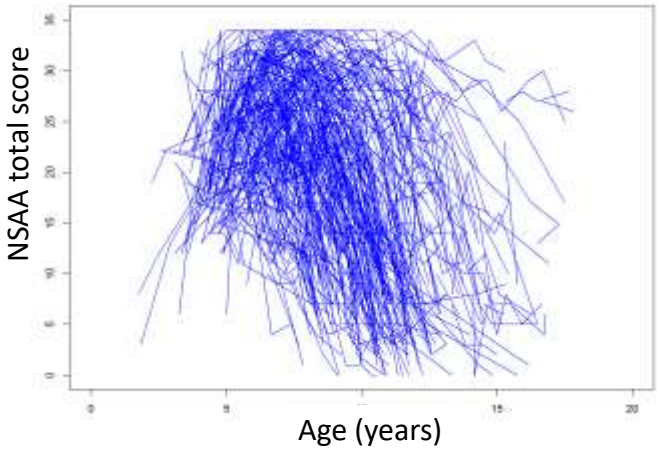
Data

North Star Ambulatory Assessment (NSAA)

(17 items scores 0,1 or 2; e.g., walk, run, jump, climb step…)

Patients

- NorthStar UK Clinical Network database
- 323 boys
- 2,007 assessments
- 3.3 yrs median follow-up



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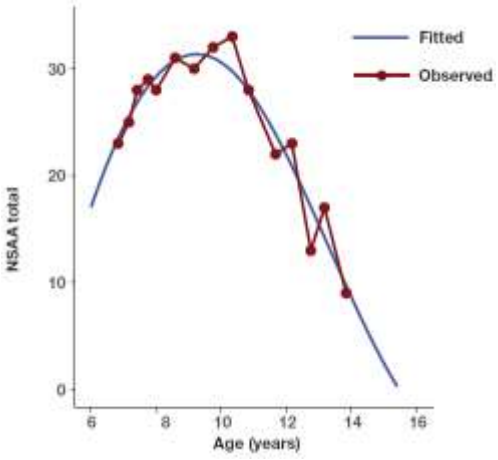
Methods

- **Linear mixed effects (LME) models**
  - Function vs. age
  - Patient-specific random splines
  - Autocorrelation
- **Superimposition by Translation and Rotation (SITAR)**
  - Parameterize characteristic trajectory (spline)
  - Model individual variation as transformations of the time scale (shift + velocity) as well as vertical translation of the outcome scale



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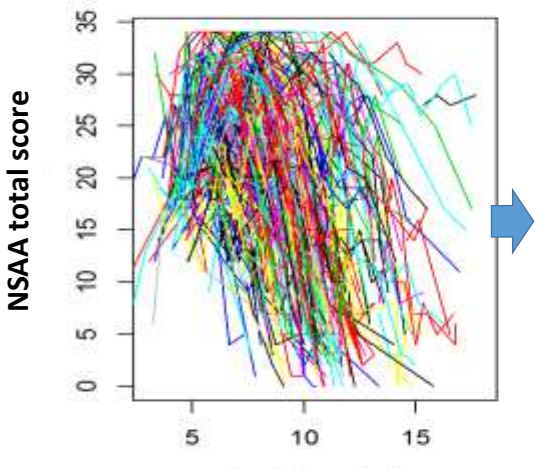
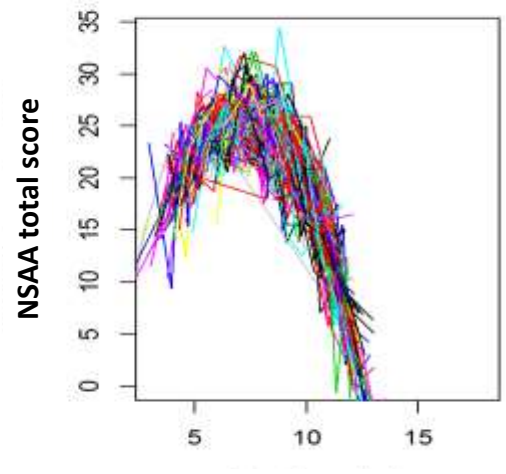
Results – NSAA total score

Observed trajectories



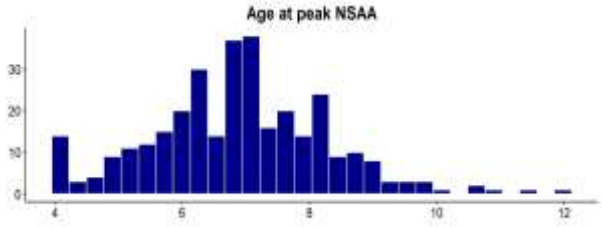
Re-scaled trajectories based on LME

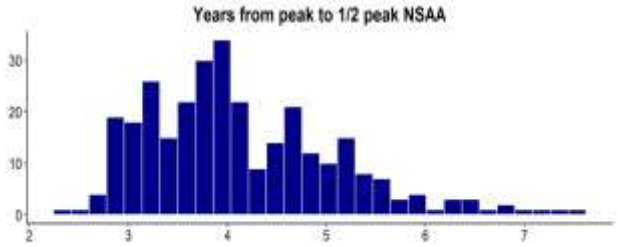


Model explained 92% of variability in NSAA scores

Results – NSAA total score

Feature	Median (IQR)
Age at peak function (years)	6.8 (5.9 to 7.8)
Years from peak to 50% loss	4.0 (3.6 to 4.6)





Relationships between features

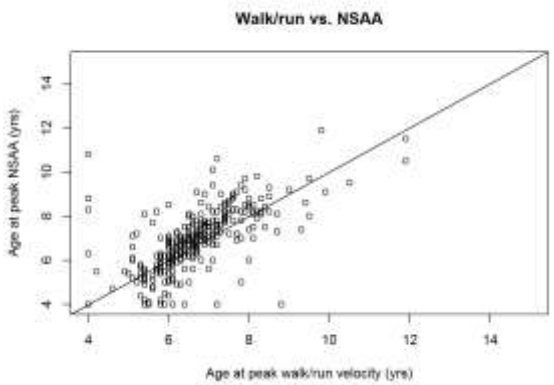
Pearson correlations

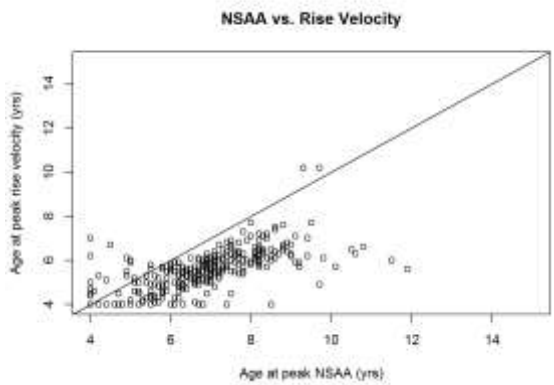
	Age at peak	Years to 50% loss	Height of peak
Age at peak		0.60	0.30
Years to 50% loss	0.60		0.06
Height of peak	0.30	0.06	

- Later age at peak is associated with slower subsequent progression
- Later age at peak is modestly associated with higher peak function
- Height of peak is not strongly associated with the rate of subsequent decline

Associations across measures

- Age at peak NSAA and age at peak 10 meter walk/run speed were **similar**
- Age at peak rise from floor speed was **earlier** by 1.3 (0.7 to 1.8) years compared with peak NSAA





Conclusions

- Despite variability across individuals, ambulatory progression in DMD follows common patterns
- The large majority of cross-patient variation in progression can be explained by differences in age at peak function, peak level achieved and subsequent rates of decline
- Different functional abilities peak at different ages, but with a predictable ordering, suggesting that they reflect different aspects of a consistent underlying disease process
- The SITAR approach was appealing but faced convergence issues in these data; Bayesian versions of SITAR are of interest
- Characterization of progression can help inform the design and interpretation of clinical studies (e.g., by enrichment for certain disease stages), and serve as a reference point for further research in DMD disease modeling

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Acknowledgments and disclosures

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- Investigators and staff from the North Star UK network
- Members of cTAP for contributions to the conceptualization and interpretation of this research

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  - Parent Project Muscular Dystrophy, Charley's Fund, and CureDuchenne, a founding patient advocacy partner and provider of initial seed funding to cTAP

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Extra slides

Data accessed by cTAP

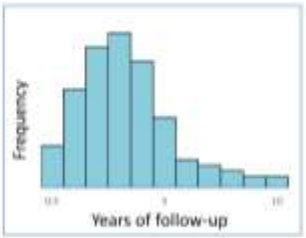
>2,500 boys

LARGE & REPRESENTATIVE

>16,000 clinic visits

RELEASE & COMPREHENSIVE

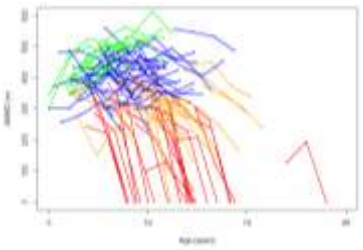
>5,000 patient-years

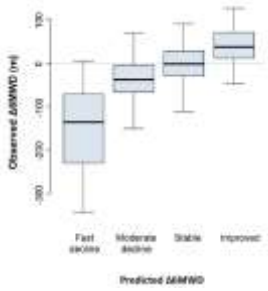


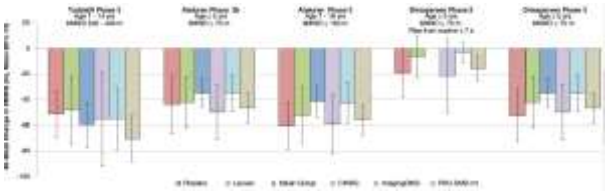
DISEASE PROGRESSION

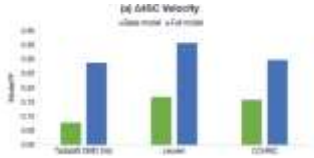
Other cTAP research

- Trajectories of change in clinical endpoints
- Consistency between real-world and clinical trial settings
- Prognostic models
- Minimal clinically important differences in endpoints









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