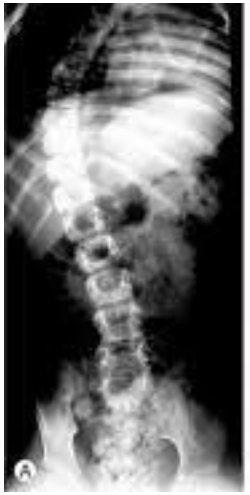
COLLABORATIVE
TRAJECTORY
ANALYSIS
PROJECT

Enabling the right trial design, the first time

Supporting new therapies to patients sooner

Duchenne muscular dystrophy

"A thousand little deaths"



Prescient capture of natural history

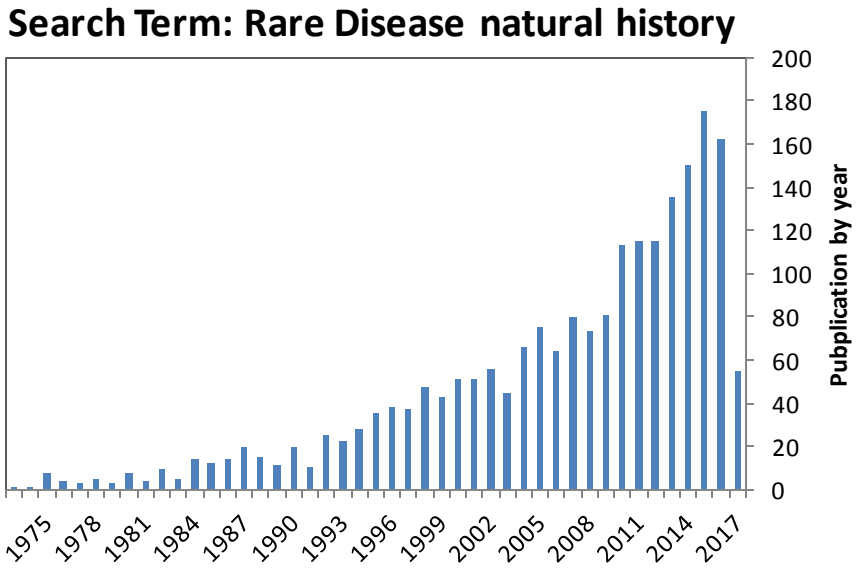
The Promise of Natural History in Rare Disease Drug Development

Natural History
Pathophysiology
MOA

INFORMS

Design of efficacy studies
Early phase clinical
Endpoint identification

"lack of natural history is the #1 reason for clinical trial failures in rare disease"
(C Austin, 2013)



Duchenne Community: an exemplar in rare disease

- Dystrophin Gene identified as causal in 1980's
- Many known mutations
- Reading frame rule in rare disease
- Astute patient advocacy
- Early start on natural history
- Robust Funding
- Exploration of outcome measures
- Pipeline of drug candidates by 2005

The Problem (2010-2015)

TRIAL	PHASE	PATIENTS**	Met Primary endpoint
DEMAND III	Ph 3*	186	no
PTC 007	Ph 2*	174	no
DMD-ACT	Ph 3*	228	no
Tadalafil	Ph 3*	331	2016

- Is the drug ineffective?
- Or effective only in a subset of patients?
- Was the study underpowered?

FAILED TRIAL OR FAILED DRUG?

** Pivotal trial*

***Total # patients =1719 patients; ~ 400 randomized to placebo*

Unexpectedly High Unexplained Variance

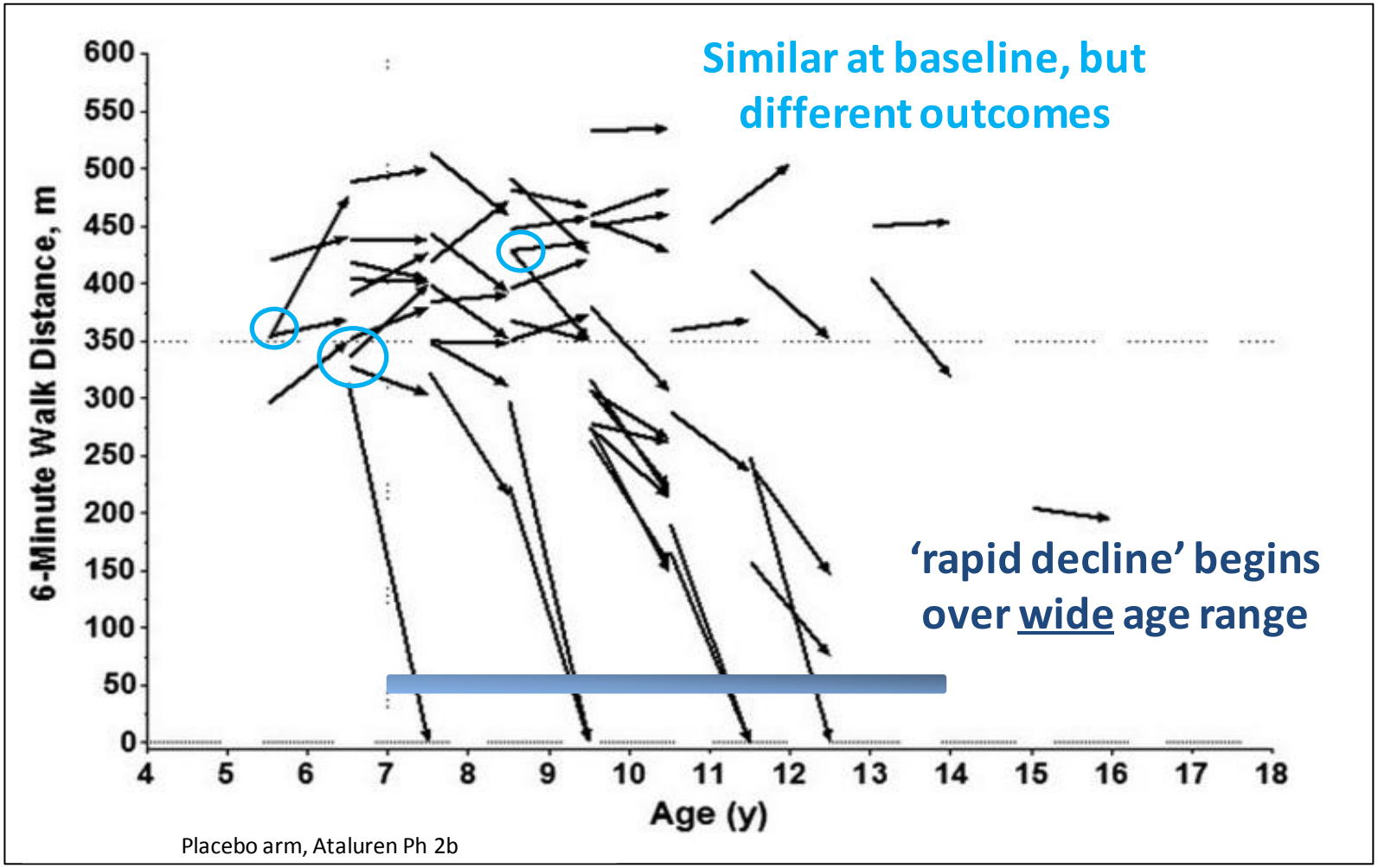
DMD patients lose approximately **40-60 meters** in 6MWD per year

Study	Design	Δ 6MWT (m)	SD (m)	Study (weeks)	n
McDonald 2010*	Natural History	-57	104	52	18
Ataluren 2010*	Placebo arm	-42	90	48	57
Mazzone 2011**	Natural History	-42	74	52	71
Goemans 2012*	Natural History	-38	96	52	19
McDonald 2013**	Natural History	-59	82	48	33
Drisapersen 2014	Placebo Arm	-53	78	48	61

Hindsight: poor Signal to noise, underpowered

Summary from Prosensa Investor presentation, 2014

The Root Cause



Risk - more trial failures

Approaches to overcoming heterogeneity-driven variance in clinical trials

- Run a bigger trial!
- Outcomes Solutions
- Associate with Genetic diversity
- Develop biomarkers

And in the meantime??

cTAP

collaborative **T**rajectory **A**nalysis **P**roject

Collaborate to learn from patient data

Leverage successful approaches from other fields

Create tools and insights for drug development

Share broadly

Deliver near-term impact

PRE-COMPETITIVE COALITION

SHARED BENEFITS/SHARED COSTS

***ALL* DUCHENNE STAKEHOLDERS**

cTAP Members and Collaborators

Clinical experts

Eugenio Mercuri

Nathalie Goemans

Francesco Muntoni

Brenda Wong

Registries, Trials

Drug developers

Patient advocates

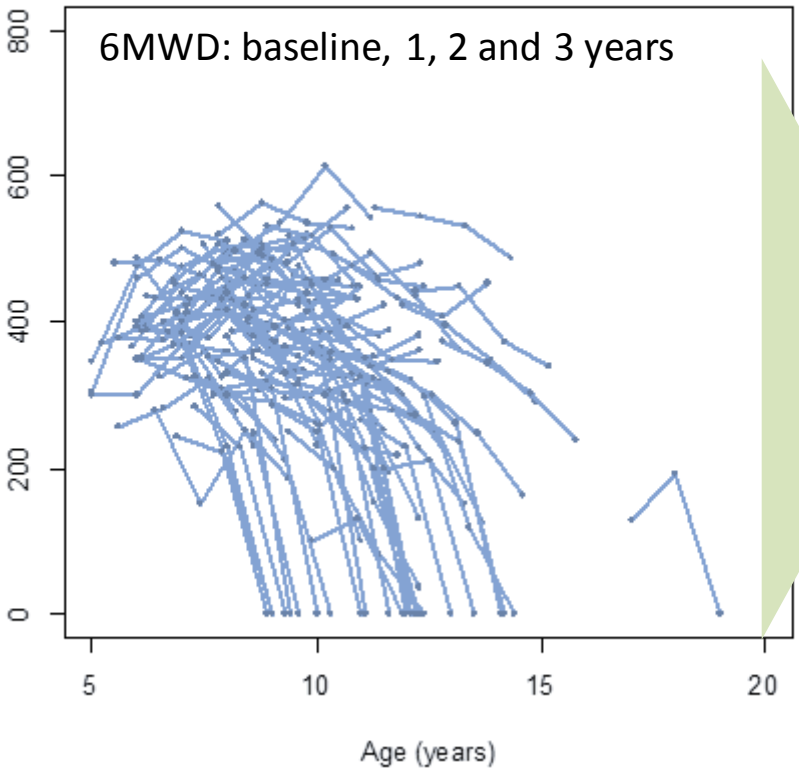
Collaboration

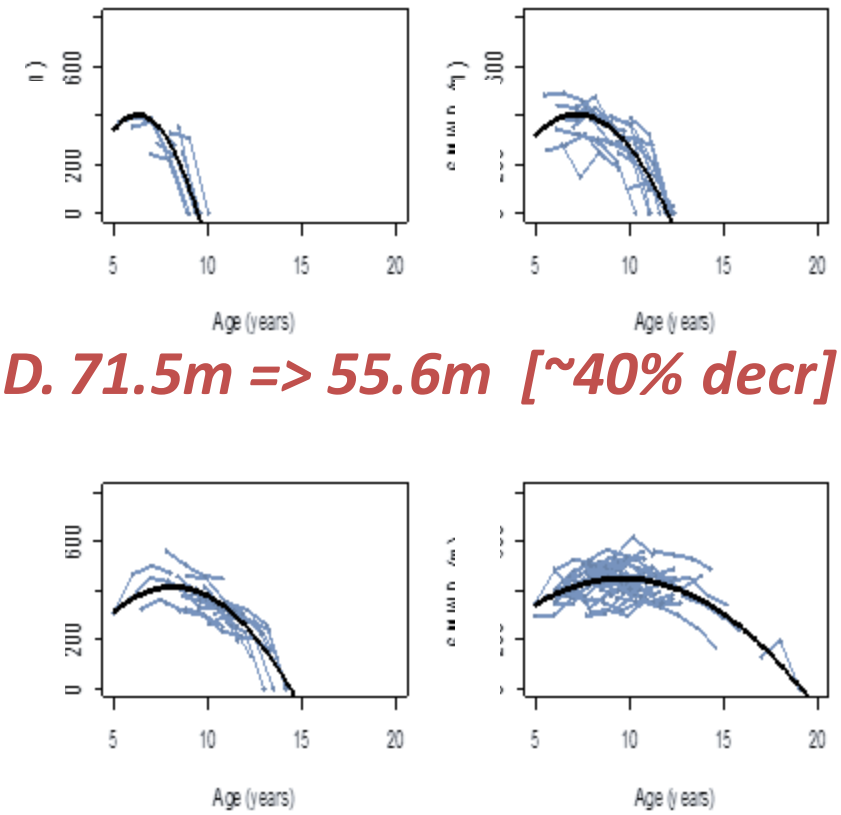
Susan J. Ward, PhD

Data science

James Signorovitch, PhD

Latent Class Trajectory Analysis of natural history



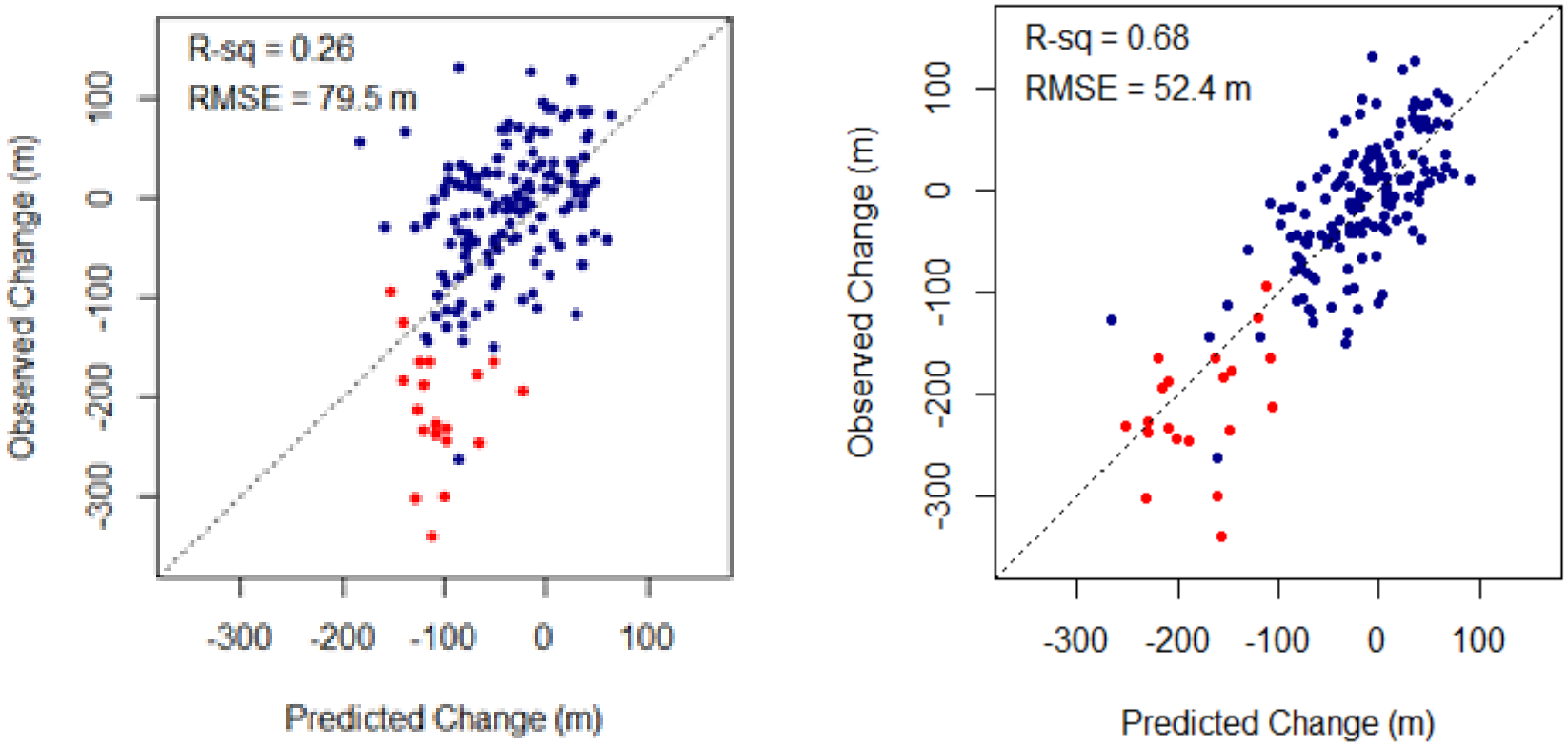


S.D. 71.5m => 55.6m [~40% decr]

Underlying structure, marked reduction in variance

Eugenio Mercuri, et al., 2016. Categorizing natural history trajectories of ambulatory function measured by the 6-minute walk distance in patients with Duchenne muscular dystrophy. Neuromuscular Disorders 26 (2016) 576–583 *doi: 10.1016/j.nmd.2016.05.016*

Multivariable Prognostic Model



Prognostic accuracy more than doubled

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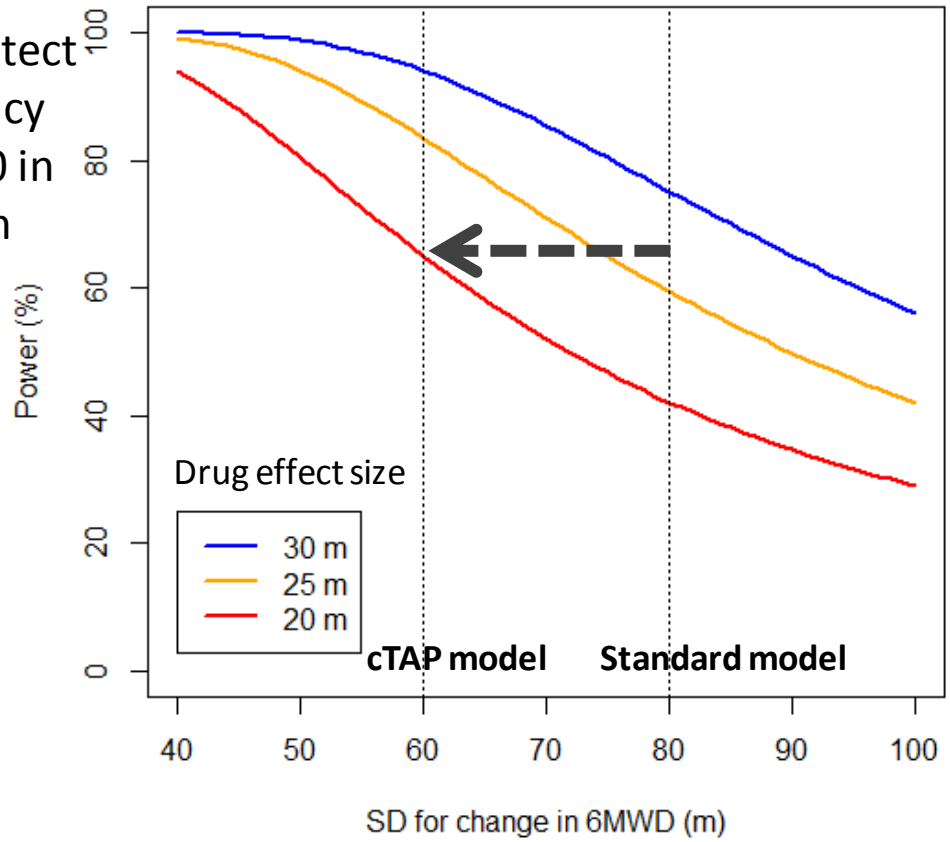
Nathalie Goemans et al., 2016. Individualized prediction of changes in 6-minute walk distance for patients with Duchenne muscular dystrophy. PLoS One. 0164684 . doi.org/10.1371

Impact of Reducing Variability

Power to detect drug efficacy with n=100 in each arm



Decreasing the SD from 80 to 60 meters increases power by 20 percentage points

More power = more definitive results, smaller trials

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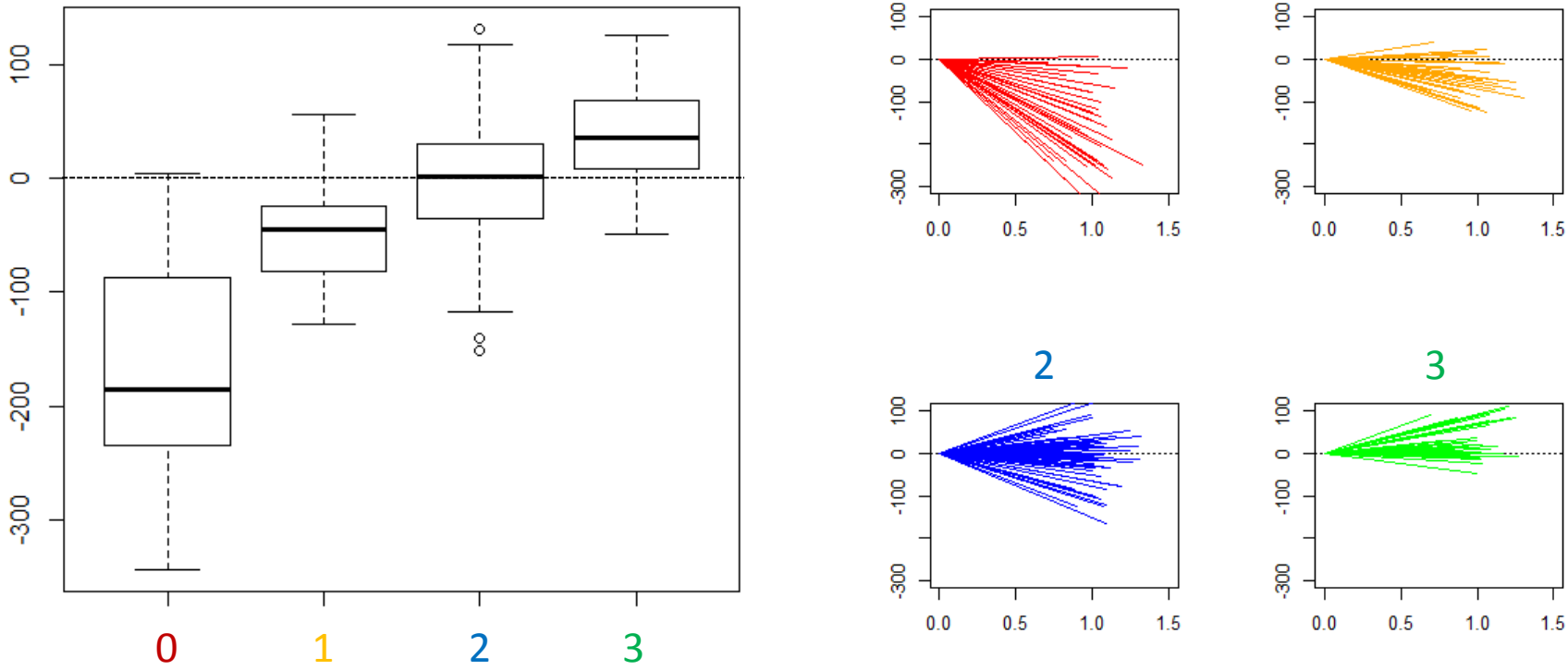
Why it matters: enrich for modifiable trajectories

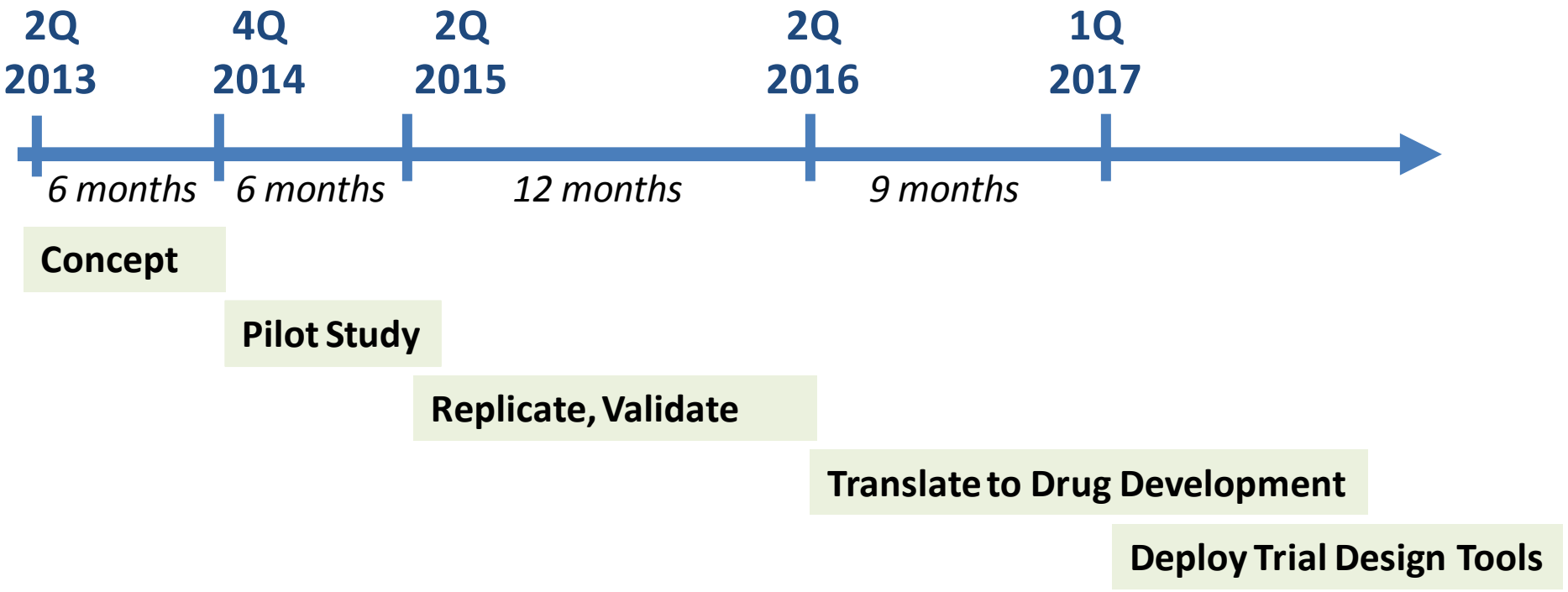
These groups are identifiable at baseline

Which are most modifiable with your MOA?



Goemans N, Vanden Hauwe M, Signorovitch J, Swallow E, Song J; Collaborative Trajectory Analysis Project (cTAP).. Individualized Prediction of Changes in 6-Minute Walk Distance for Patients with Duchenne Muscular Dystrophy. PLoS One. 2016 Oct 13;11(10):e0164684.

Rapid Progress



Only feasible because multiple academic leaders and clinical registries shared curated data

cTAP Duchenne Clinical Data Access

1300+ boys

30+ care centers

10,000 + clinic visits

Functional Assessments

Ambulation **> 4000**

Pulmonary, Cardiac **>350**

boys ≥ 3 yrs follow-up **> 400**

Patient Characteristics

steroid status, history

dystrophin genotype

body composition (incl. fat)

- Largest clinical database in Duchenne, and growing
- Harmonized, Traceable, Dictionaries
- Semi-annual updates
- Majority of data previously never shared
- Uniquely positioned to address regulator concerns

Natural History Landscape 2013/14

- Trial design based on thought-leader input
- No direct access to natural history data
  - Arduous learning curve for who has what data
  - Lengthy cycle-time for requested analytics
  - Significant duplication of effort to access the basics
- The first publication to show individual patient trajectories did not appear until late 2013

Tools: Duchenne Discovery portal

- Real-time, flexible, dynamic analytics
- User defined
  - outcome measure
  - segmentation parameters
- Computes
  - Patient characteristics at baseline
  - 1 year change in outcome measure
- Modularized additions
  - Correlations between outcome measures
  - Interactive per patient trajectory

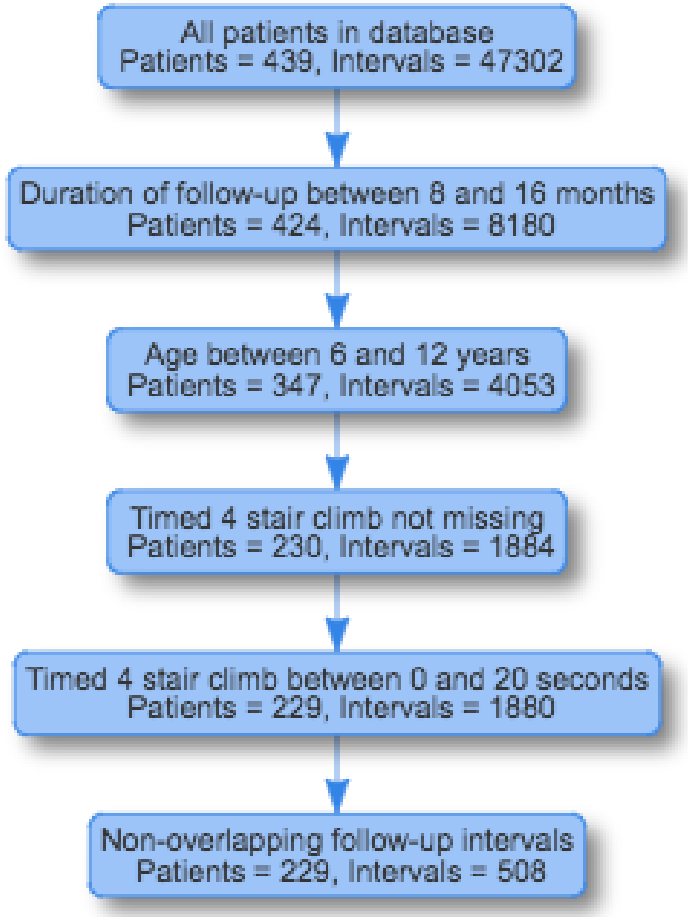
Portal

May variance be small, your drugs be approved, and your patients be well.

Discovery Portal Report: CCHMC

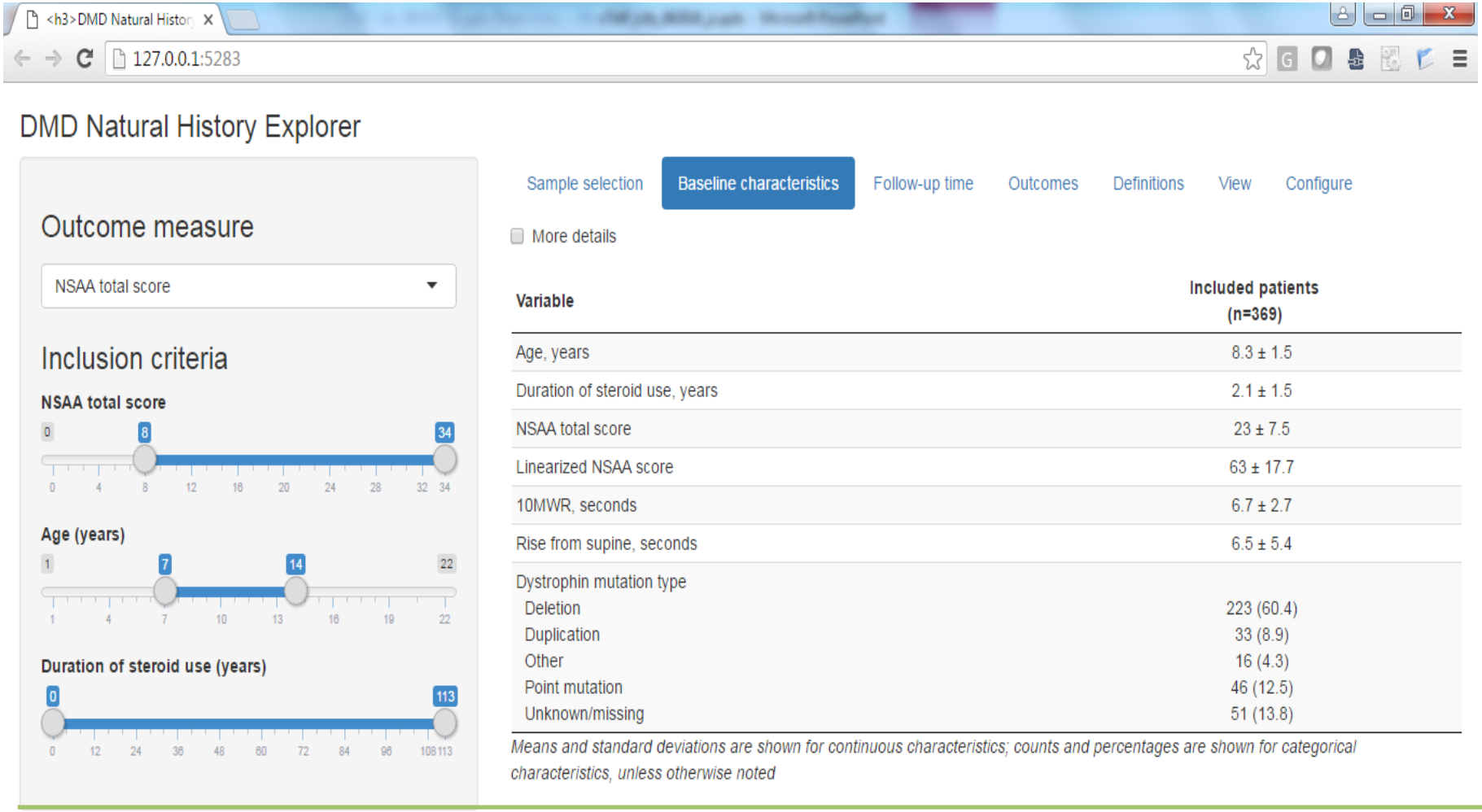
Sample selection | Baseline characteristics | Outcomes | Dictionary

Harmonized Data
Dynamic Analytics
User defined, in real time



Portal

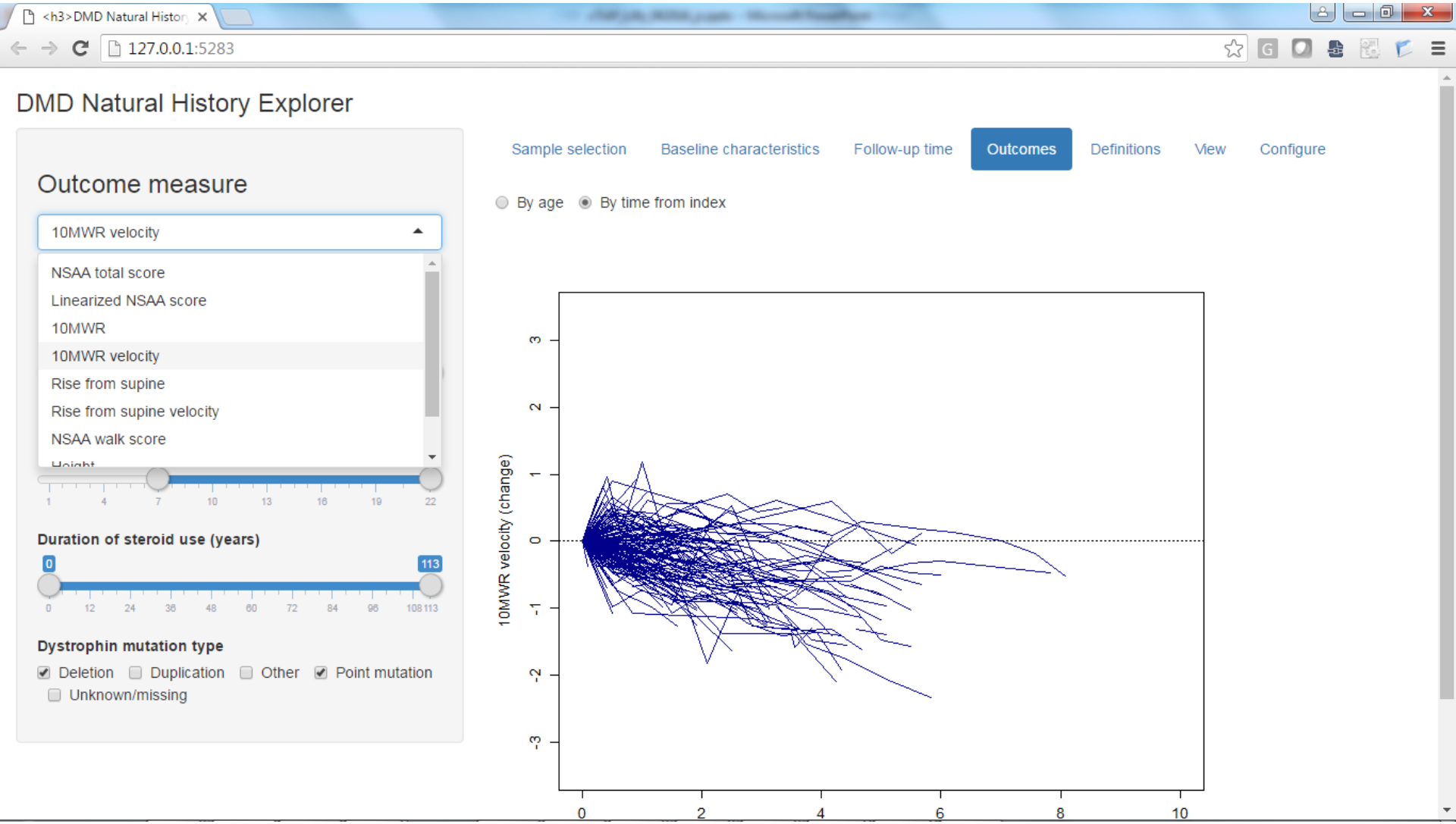
Summarize Patient Characteristics



Variable	Included patients (n=369)
Age, years	8.3 ± 1.5
Duration of steroid use, years	2.1 ± 1.5
NSAA total score	23 ± 7.5
Linearized NSAA score	63 ± 17.7
10MWR, seconds	6.7 ± 2.7
Rise from supine, seconds	6.5 ± 5.4
Dystrophin mutation type	
Deletion	223 (60.4)
Duplication	33 (8.9)
Other	16 (4.3)
Point mutation	46 (12.5)
Unknown/missing	51 (13.8)

Means and standard deviations are shown for continuous characteristics; counts and percentages are shown for categorical characteristics, unless otherwise noted

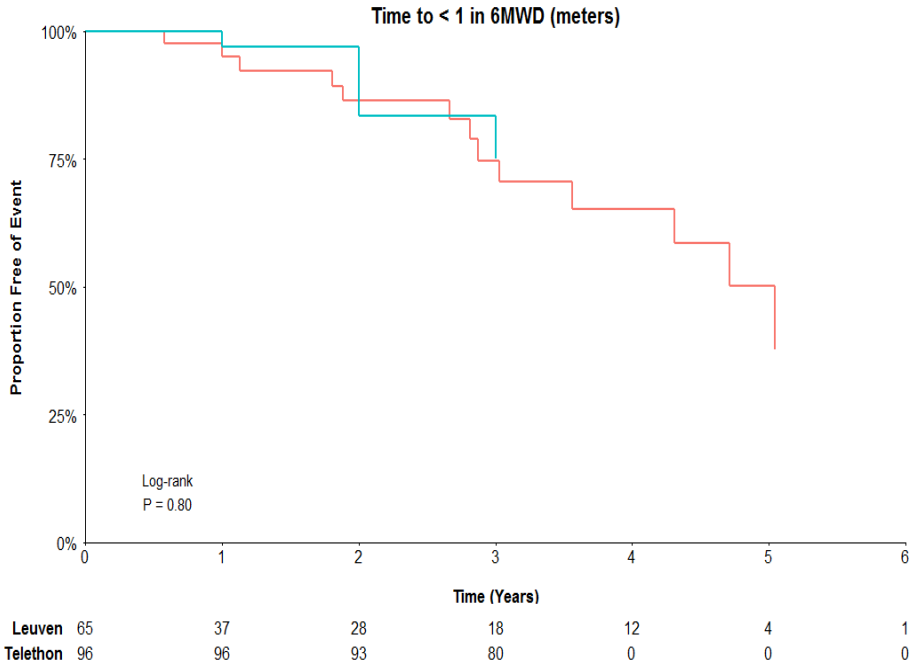
Investigate multiple outcome measures

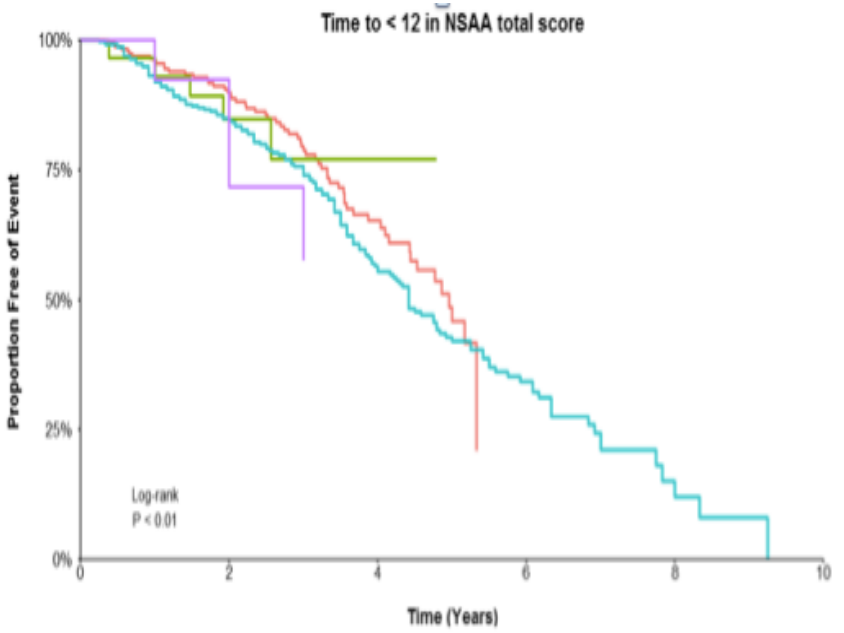


2015 ….. Regulator Concerns

- How **consistent** is natural history across centres, countries?
- Do boys in the placebo arm of studies do better than in a natural history setting?
- Does 6MWD align with other measures of ambulation? Is NSAA a better outcome measure?
- Will efficacy measured on ambulatory decline translate into efficacy downstream (e.g. pulmonary)?

Time-to-event comparative natural history





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Translation to Drug Development

Describe, Predict, Simulate

- Inform trial design and analysis
- Enable natural history controls
- Inform biomarker evaluation
- Establish value of endpoints for regulators and payers

The cTAP experience demonstrates…

The challenge of trial design in the face of phenotypic heterogeneity is too big for any one group to solve

- Cultural shift to data-sharing => critical mass
- Value in learning from other fields, disciplines
- Functional factors can deliver big gains in power
- Radical acceleration of the data enquiry process takes trial design to a new level

Enabling the right trial design, the first time

Supporting new therapies to patients sooner

Collaborators

Clinical Experts

- Eugenio Mercuri
- Nathalie Goemans
- Francesco Muntoni
- Valeria Ricotti
- Adnan Manzur
- Brenda Wong

Analysis Group

- James Signorovitch
- Elaine Swallow
- Li Ping Song

Patient Advocates

- Debra Miller
- Mike Kelly
- Pat Furlong
- Sharon Hesterlee

Drug Developers

- Malaz AbuTarif
- Paolo Bettica
- Michael Binks
- Katherine Beaverson
- Giles Campion
- Lawrence Charnas
- Csaba Csiffel
- Joanne Donovan
- Leslie Jacobsen
- Ed Kaye
- Dana Martin
- Carl Morris
- Rick Munchauser
- Dallan Murray
- Tuyen Ong
- Jorge Quiroz
- Bob Spiegal
- Marcio Souza
- Ed Xiou

And their teams

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